IMPORTANT INFORMATION ON THE RELEASE OF PSAP 2014 BOOK 2 CHRONIC ILLNESSES

TESTING

BCPS test deadline: 11:59 p.m. (Central) on November 17, 2014.
ACPE test deadline: 11:59 p.m. (Central) on July 14, 2017.

Online errata: Go to www.accp.com/docs/products/psap1315/errata.pdf. Be sure to check the online errata before submitting a posttest.

For information on passing levels, assignment of credits, and credit reporting, see Continuing Pharmacy Education and Recertification Instructions on page v.

IMPORTANT NOTICE ON BCPS RECERTIFICATION

Submitting the required posttest for BCPS recertification attests that you have completed the test as an individual effort and not in collaboration with any other individual or group. Failure to complete this test as an individual effort may jeopardize your ability to use PSAP for BCPS recertification.

BOOK FORMATS

Online book: All purchasers have access to the online book (interactive PDFs). To access, go to your My Account page on www.accp.com and sign in using your e-mail address and password (technical assistance is available). You will find your book and the required posttests under My Online Products.

Print books: If you have purchased a print version of this book, it will be delivered on or near the release date to the address of record on your ACCP account. If you have not received the print book within 1 week of the release date, contact customer service by e-mailing accp@accp.com.

E-Media Package: If you have purchased this package, follow these instructions to load the text and self-assessment questions in this book onto your e-reader, tablet, or Android phone. This package includes the PSAP Audio Companion: follow these instructions to download these files onto a listening device or burn them onto an audio CD.

BOOK CONTENT

Electronic annotation: The online book can be saved to the desktop or printed. The latest version of Adobe Reader (available free) offers functionality such as highlighting or adding “sticky notes” to the text.

Hyperlinks: This book contains both internal and external hypertext links (visible as underlined text in the print book). Clicking on the intra-document/internal links in the Table of Contents will take you to the page containing the selected content. Clicking on external hyperlinks will take you away from the ACCP Web site to the outside resource, guidelines, tools, or other information you have selected.

NOTE: To facilitate further learning and research, this publication incorporates print and live hyperlinks to Web sites administered by other organizations. The URLs provided are those of third parties not affiliated in any way with ACCP. ACCP assumes no liability for material downloaded from or accessed on these Web sites. It is the responsibility of the reader to examine the copyright and licensing restrictions of linked pages and to secure all necessary permissions.

Laboratory Reference Values: The last page of this book contains a table with reference ranges and abbreviations for many common laboratory tests. Use this table as a resource in completing the required posttest.

NOTE: The editors and publisher of PSAP recognize that the development of this volume of material offers many opportunities for error. Despite our best efforts, some errors may persist into print. Drug dosage schedules are, we believe, accurate and in accordance with current standards. Readers are advised, however, to check package inserts for the recommended dosages and contraindications. This is especially important for new, infrequently used, and highly toxic drugs.
## Table of Contents

Preface .......................................................... iii
Disclosure of Potential Conflicts of Interest ................................ iv
Continuing Pharmacy Education and Recertification Instructions ...... v

Chronic Illnesses I .............................................. 1
Faculty Panel .................................................... 3

### Antirheumatic Drugs

By Rachel A. Burke, Pharm.D., BCACP; and Nicole D. White, Pharm.D.

Learning Objectives ........................................... 9
Introduction ...................................................... 9
Epidemiology .................................................... 9
Baseline Knowledge Statements ................................ 9
Additional Readings .......................................... 9
Nonbiologic DMARDs .......................................... 10
Biologic DMARDs ............................................ 10
RA Treatment .................................................. 15
Safety Considerations of Biologic DMARDs ...................... 18
Biologic DMARDs in High-Risk Patients ........................ 20
Patient Education ............................................. 23
References ....................................................... 24
Self-Assessment Questions .................................... 29

### Osteoarthritis

By Jennifer N. Clements, Pharm.D., BCPS, BCACP, CDE

Learning Objectives ........................................... 33
Introduction ...................................................... 33
Baseline Knowledge Statements ................................ 33
Additional Readings .......................................... 33
Etiology .......................................................... 34
Pathophysiology .............................................. 34
Clinical Features ............................................. 34
Treatment Guidelines ....................................... 37
Other Issues ..................................................... 48
References ....................................................... 49
Self-Assessment Questions .................................... 53

### Overweight and Obesity

By Kaelen C. Dunican, Pharm.D.; and Courtney Jarvis, Pharm.D.

Learning Objectives ........................................... 57
Introduction ...................................................... 57
Baseline Knowledge Statements ................................ 57
Additional Readings .......................................... 57
Pathophysiology .............................................. 58
Treatment ....................................................... 62
References ....................................................... 74
Self-Assessment Questions .................................... 76

### Transitions of Care

By Sheryl J. Herner, Pharm.D., BCPS, CPPS; and Valerie S. Ganetsy, Pharm.D., BCPS

Learning Objectives ........................................... 79
Introduction ...................................................... 79
Baseline Knowledge Statements ................................ 79
Additional Readings .......................................... 79
Defining TOC ................................................... 80
TOC Interventions and Outcomes in Primary Literature ............ 84
Established TOC Models ...................................... 84
National Initiatives and Resources ................................ 89
Performance Metrics .......................................... 91
Reimbursement ................................................. 93
References ....................................................... 94
Self-Assessment Questions .................................... 97

Chronic Illnesses II ............................................. 101
Faculty Panel .................................................... 103

### Myelodysplastic Syndromes

By Kristen B. McCulloch, Pharm.D., BCPS, BCOP; and Julianna Merten, Pharm.D., BCPS, BCOP

Learning Objectives ........................................... 109
Introduction ...................................................... 109
Baseline Knowledge Statements ................................ 109
Additional Readings .......................................... 109
Pathophysiology .............................................. 111
Clinical Presentation and Diagnosis ............................. 113
Prognosis ........................................................ 113
Treatment ....................................................... 113
Emerging Therapies .......................................... 123
Treatment approach ........................................... 123
References ....................................................... 124
Self-Assessment Questions .................................... 128

### Chronic Myeloid Leukemia

By Marc A. Earl, Pharm.D., BCOP

Learning Objectives ........................................... 131
Introduction ...................................................... 131
Baseline Knowledge Statements ................................ 131
Additional Readings .......................................... 131
Presentation and Diagnosis .................................... 132
Treatment Response Goals and Criteria ........................ 133
Resistance or Intolerance to Initial Therapy ...................... 135
Hematopoietic Stem Cell Transplantation ......................... 136
Monitoring ....................................................... 136
References ....................................................... 139
Self-Assessment Questions .................................... 141

### Pharmacology of New Targeted Therapies

By Salvatore M. Bottiglieri, Pharm.D., BCOP

Learning Objectives ........................................... 145
Introduction ...................................................... 145
Preface

The start of a new edition of the Pharmacotherapy Self-Assessment Program (PSAP) is truly an exciting time. Our mission remains the same today as for the first edition – to provide evidence-based updates that will improve clinical pharmacy practice and patient outcomes. However, to accomplish this, PSAP must reflect the changes in practice models, patient populations, and the overall health care environment. This new edition introduces features and formats designed to enhance information access while accommodating individual learning styles.

PSAP remains a labor of love for the faculty panel chairs, authors, and expert and professional reviewers, as well as for us, the series editors. We contribute to this endeavor because we are committed to the board certification process and the national recognition of the expertise of clinical pharmacists. We are also dedicated to sharing the most up-to-date knowledge with our colleagues, and we are driven to create opportunities for board-certified clinicians to participate in scholarly activity. The PSAP 2013–2015 releases are each carefully developed to identify clinically relevant content, solid case-based examples, and fair but challenging self-assessment questions that allow the tester to demonstrate mastery of this important material.

For individual chapters, the focus continues to be on significant new information rather than a review of common knowledge about a topic. Authors incorporate the latest national or international guidelines for management, landmark clinical trials, and content, which integrate concepts of biostatistics, epidemiology, and health systems to cover all identified domains for the pharmacotherapy specialist. In response to feedback from PSAP users, many authors have included case-based examples demonstrating the application of concepts, a treatment algorithm or decision tree, and a summative box with practice points or pearls. On the first page of each chapter is listed the baseline knowledge presumed on the part of the reader as well as open-access literature resources that can provide this knowledge, if needed. The process for developing self-assessment questions has been revised by carefully tying the questions to objectives and material presented in the books and incorporating a field-test process using panels of specialists. It is our hope that these efforts will build on and improve PSAP’s reputation as a quality professional development tool for Board Certified Pharmacotherapy Specialists.

We extend our heartfelt appreciation to all the faculty panel chairs, authors, and reviewers for lending their time and expertise to this new series and to ACCP Publications staff members for their ever-present willingness to help and guide the development of this new series.

John E. Murphy and Mary W. Lee, series editors
ROLE OF BPS: The Board of Pharmacy Specialties (BPS) is an autonomous division of the American Pharmacists Association (APhA). BPS is totally separate and distinct from ACCP. The Board, through its specialty councils, is responsible for specialty examination content, administration, scoring, and all other aspects of its certification programs. PSAP has been approved by BPS for use in BCPS recertification. Information about the BPS recertification process is available at www.bpsweb.org/recertification/general.cfm.

Other questions regarding recertification should be directed to:

Board of Pharmacy Specialties  
2215 Constitution Avenue NW  
Washington, DC 20037  
(202) 429-7591  
www.bpsweb.org

Disclosure of Potential Conflicts of Interest

Consultancies: Marc Earl (Amgen); Jessica Farrell (American College of Rheumatology/Association of Rheumatology Health Professionals, Scleroderma Foundation, Consortium of Rheumatology Researchers of North America); Sheryl J. Henner (American Society of Professionals in Patient Safety, Colorado Pharmacists Society, American College of Clinical Pharmacy, Pharmacy Quality Alliance); Julianna A. Merten (American Society of Health-System Pharmacists, American College of Clinical Pharmacy); Amy Barton Pai (National Kidney Disease Education Program, American Society of Nephrology Dialysis Advisory Group, New York State Chronic Kidney Disease Coalition), Judith A. Smith (Advocare's Scientific & Medical Advisory Board); Sarah A. Spindler (Bristol-Myers Squibb, Merck, Boehringer Ingelheim, The Medicines Company); Neeta B. O'Mara (Celgene [spouse or significant other]);

Royalties:

Grants: Judith A. Smith (BioNumerik Pharmaceuticals, ProStrakan Inc., UT System, Merck Medical Co., AMIPurdue, Amino Up Chemical, U.S. Department of Defense, Amino Up Chemical, Janssen Pharmaceutical Companies, NIH); Abigail M. Yancey (American Society of Health-System Pharmacists);

Honoraria: Marc Earl (Sigma Tau Pharmaceuticals Inc.);

Other: Neeta B. O’Mara (Celgene [spouse or significant other]);


Grants: Eric Boyce (Wyeth Ayerst); Katherine Hale (State of Montana Department of Public Health and Human Services [two grants]); Dawn Havrda (Pfizer); Michael Kane (Amylin Pharmaceuticals); Julia Nguyen (Kaiser Permanente); Daniel Riche (Chromadex, Inc., USHBC); Justin Sherman (CDC); Matthew Strum (NACDS Foundation, Pharmacy Quality Alliance [spouse or significant other]); Andrea Traina (Eli Lilly and Co., Abbott Diabetes Care)

Honoraria: Jessica Bellone (Auburn University Harrison School of Pharmacy); Michael Kane (Eli Lilly and Co.); Beth Resman-Targoff - Honoraria (APhA); Daniel Riche (Janssen, Boehringer Ingelheim, Merck); Matthew Strum (Abbott); Bobbie Williamson (Sanofi Pharmaceuticals)

Other:

Nothing to Disclose: Katherine Anderson; Miranda Andrus; Susan P. Bruce; Mary C. Byrne; Lisa Chastain; Jennifer Clements; Christopher Dennis; Marissa Dunham; Kaelen Dunican; Krystal Edwards; Michelle Garoff; Benjamin Gross; Ashley Gunter; Kathryn Hurren; Kellie Knight; Janene Madras; Marianne Miller; Stefanie Nigro; Jessica O’Neill; Steven M. Smith; Dominick Trombetta
CONTINUING PHARMACY EDUCATION AND
RECERTIFICATION INSTRUCTIONS

Continuing Pharmacy Education Credit: The American College of Clinical Pharmacy is accredited by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmacy education (CPE).

Available CPE credits: Purchasers who successfully complete all posttests for PSAP 2014 Book 2 (Chronic Illnesses) can earn 25.5 contact hours of CPE credit. The universal activity numbers are as follows: Chronic Illnesses I – 0217-0000-14-004-H01-P, 9.0 contact hours; Chronic Illnesses II – 0217-0000-14-005-H01-P, 8.5 contact hours; and Chronic Illnesses III – 0217-0000-14-006-H01-P, 8.0 contact hours. You may complete one or all three modules for credit. Tests may not be submitted more than one time.

BCPS test deadline: 11:59 p.m. (Central) on November 15, 2014.
ACPE test deadline: 11:59 p.m. (Central) on July 14, 2017.

Posttest access: Go to www.accp.com and sign in with your e-mail address and password. Technical support is available from 8 a.m. to 5 p.m. (Central) weekdays by calling (913) 492-3311. PSAP products are listed under My Online Products on your My Account page.

BCPS Recertification Credit: To receive BCPS recertification CPE credit, a PSAP posttest must be submitted within the 4-month period after the book’s release. The first page of each print and online book lists the deadline to submit a required posttest for BCPS recertification credit. Only completed tests are eligible for credit; no partial or incomplete tests will be processed. Tests may not be submitted more than once. The passing point for BCPS recertification is based on a statistical analysis of the answers submitted for each posttest module.

ACPE CPE Credit: To receive ACPE CPE credit for a PSAP module, a posttest must be submitted within 3 years after the book’s release. The appropriate CPE credit will be awarded for test scores of 50% and greater.

Credit Assignment and Reporting: All required posttests that meet the 50% score standard will be immediately awarded the appropriate ACPE CPE credit. Earned credits will be transmitted within 24 hours to www.mycpemonitor.net and should appear on statements of credit within 3 business days.

Required posttests that are submitted before the BCPS test deadline and that meet the passing point set by statistical analysis will earn BCPS recertification credits. These credits will be posted within 30 days after the BCPS test deadline. For statements of CPE credit, visit www.mycpemonitor.net.

All BCPS recertification credits are forwarded by ACCP to the Board of Pharmacy Specialties (BPS). Questions regarding the number of hours required for BCPS recertification should be directed to BPS at (202) 429-7591 or www.bpsweb.org. The ACCP Recertification Dashboard is a free online tool that can track recertification credits as they are earned through ACCP and schedule new opportunities for credits from upcoming ACCP professional development programs.

Posttest answers: The explained answers – with rationale and supporting references – will be posted 1 week after the BCPS test deadline and will be available to anyone who has submitted a posttest or waived his or her right to receive credit (see below) from a posttest. Go to www.accp.com and sign in with your e-mail address and password. Click the PSAP book on your My Account page and you will see a link to the explained answers.

Test Waivers: To access the explained answers without submitting a posttest, sign in to your My Account page, select the PSAP book, and click on the waiver link for that module. By completing the waiver form for a module, you waive the opportunity to receive CPE credit for that module. After you submit a waiver, you will see a link to the PDF file that contains the answers for the module you waived. Answers will be available starting 1 week after the BCPS test deadline.
Chronic Illnesses I
Chronic Illnesses I

Series Editors:

John E. Murphy, Pharm.D., FCCP, FASHP
Professor of Pharmacy Practice and Science
Associate Dean for Academic and Professional Affairs
University of Arizona College of Pharmacy
Tucson, Arizona

Mary Wun-Len Lee, Pharm.D., FCCP, BCPS
Vice President and Chief Academic Officer
Pharmacy and Health Sciences Education
Midwestern University
Professor of Pharmacy Practice
Midwestern University
Chicago College of Pharmacy
Downers Grove, Illinois

Faculty Panel Chair

Susan P. Bruce, Pharm.D., BCPS
Chair and Professor
Department of Pharmacy Practice
Northeast Ohio Medical University
Rootstown, Ohio

Biologic Disease-Modifying Antirheumatic Drugs

Authors

Rachel A. Burke, Pharm.D., BCACP
Clinical Pharmacist
Department of Pharmacy
VA Nebraska–Western Iowa Health Care System
Omaha, Nebraska

Nicole D. White, Pharm.D.
Assistant Professor
Department of Pharmacy Practice
Creighton University School of Pharmacy and Health Professions
Omaha, Nebraska

Reviewers

Jessica F. Farrell, Pharm.D.
Assistant Professor
Department of Pharmacy Practice
Albany College of Pharmacy and Health Sciences
Rheumatology Clinical Pharmacy Specialist
The Center for Rheumatology, LLP
Albany, New York

Benita E. Galloway, Pharm.D., BCPS
Clinical Pharmacy Specialist
Department of Pharmacy
V.A. Medical Center
Atlanta, Georgia

Heather Minger, Pharm.D., BCPS
Clinical Pharmacy Specialist
Department of Pharmacy
NorthShore University HealthSystem
Glenview, Illinois

Osteoarthritis

Author

Jennifer N. Clements, Pharm.D., BCPS, BCACP, CDE
Interim Chair and Associate Professor
Department of Pharmacy Practice
Presbyterian College School of Pharmacy
Clinton, South Carolina

Reviewers

Steven M. Smith, Pharm.D., MPH, BCPS
Assistant Professor
Pharmacotherapy and Translational Research
College of Pharmacy
Community Health and Family Medicine
College of Medicine
University of Florida
Gainesville, Florida

Tara Whetsel, Pharm.D., BCACP, BC-ADM
Clinical Associate Professor
Department of Clinical Pharmacy
West Virginia University School of Pharmacy
Morgantown, West Virginia

Tina M. Hamilton, Pharm.D., BCPS
Clinical Pharmacy Specialist
Department of Pharmacy
Cincinnati Veterans Affairs
Cincinnati, Ohio
Overweight and Obesity

Authors

Kaelen C. Dunican, Pharm.D.
Associate Professor
Department of Pharmacy Practice
MCPHS University
Worcester, Massachusetts

Courtney Jarvis, Pharm.D.
Associate Professor
Department of Pharmacy Practice
MCPHS University
Worcester, Massachusetts

Reviewers

Cameron C. Lindsey, Pharm.D., BCACP, BC-ADM, CDE
Professor
Department of Pharmacy Practice and Administration
University of Missouri-Kansas City
Kansas City, Missouri

Mary Elizabeth Briand, Pharm.D., BCPS, CGP, AE-C
Clinical Pharmacy Practitioner
Department of Inpatient Pharmacy
Wolfson Children’s Hospital/Baptist Health
Jacksonville, Florida

Leah Frantzen, Pharm.D., BCPS
PGY1 Residency Program Director
Clinical Pharmacist – Cardiology and Neuroscience Critical Care
Department of Pharmacy
St. Joseph’s Hospital
St. Paul, Minnesota

Transitions of Care

Authors

Sheryl J. Herner, Pharm.D., BCACP, CPPS
Clinical Pharmacy Specialist in Medication Safety
Department of Pharmacy
Kaiser Permanente Colorado
Clinical Assistant Professor
Skaggs School of Pharmacy and Pharmaceutical Sciences
University of Colorado
Aurora, Colorado

Valerie S. Ganetsky, Pharm.D., BCPS
Assistant Professor of Clinical Pharmacy
Department of Pharmacy Practice
Philadelphia College of Pharmacy
University of the Sciences
Philadelphia, Pennsylvania

Sarah A. Spinler, Pharm.D., FCCP, BCPS (AQ Cardiology)
Professor of Clinical Pharmacy
Department of Pharmacy Practice and Pharmacy Administration
Philadelphia College of Pharmacy
University of the Sciences
Philadelphia, Pennsylvania

Daniel C. Johnson, Pharm.D., BCPS (AQ Cardiology)
Clinical Pharmacist – Cardiology and Cardiac Surgery
Department of Pharmacy Services
Vanderbilt University Medical Center
Nashville, Tennessee

The American College of Clinical Pharmacy and the authors thank the following individuals for their careful review of the Chronic Illnesses I chapters:

H. Gwen Bartlett, Pharm.D., BCPS
Assistant Professor of Pharmacy Practice
School of Pharmacy
Husson University
Bangor, Maine

Anne L. Hume, Pharm.D., FCCP, BCPS
Professor of Pharmacy
Department of Pharmacy Practice
University of Rhode Island
Kingston, Rhode Island

Emilie L. Karpiuk, Pharm.D., BCPS, BCOP
Oncology Pharmacist
Department of Pharmacy
Froedtert Hospital
Milwaukee, Wisconsin

Marianne McCollum, Ph.D., BSPharm, BCPS
Assistant Dean for Assessment
School of Pharmacy
Rueckert-Hartman College for Health Professions
Regis University
Denver, Colorado
Learner Chapter Evaluation: Biologic Disease-Modifying Antirheumatic Drugs.

As you take the posttest for this chapter, also evaluate the material’s quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

1. The content of the chapter met my educational needs.
2. The content of the chapter satisfied my expectations.
3. The author presented the chapter content effectively.
4. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
5. The content of the chapter was objective and balanced.
6. The content of the chapter is free of bias, promotion, or advertisement of commercial products.
7. The content of the chapter was useful to me.
8. The teaching and learning methods used in the chapter were effective.
9. The active learning methods used in the chapter were effective.
10. The learning assessment activities used in the chapter were effective.
11. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

12. Assess the differences between classes of biologic disease-modifying antirheumatic drug (DMARD) therapy.
14. Based on individual patient characteristics, construct a treatment and monitoring plan for a patient with RA and, when appropriate, include biologic DMARD therapy.
15. Justify switching agents or the use of combination therapy with nonbiologic DMARDs when treatment with DMARD monotherapy fails.
16. Evaluate the need for tuberculosis screening and vaccinations in patients either starting or currently receiving biologic DMARDs.
17. Evaluate the precautions, contraindications, and warnings involving the use of biologic DMARDs in high-risk patients (e.g., those with hepatitis, heart failure, and malignancy).
18. Please provide any specific comments relating to any perceptions of bias, promotion, or advertisement of commercial products.
19. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter:
Learner Chapter Evaluation: Osteoarthritis.

As you take the posttest for this chapter, also evaluate the material’s quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

1. The content of the chapter met my educational needs.
2. The content of the chapter satisfied my expectations.
3. The author presented the chapter content effectively.
4. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
5. The content of the chapter was objective and balanced.
6. The content of the chapter is free of bias, promotion, or advertisement of commercial products.
7. The content of the chapter was useful to me.
8. The teaching and learning methods used in the chapter were effective.
9. The active learning methods used in the chapter were effective.
10. The learning assessment activities used in the chapter were effective.
11. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

12. Distinguish the probable etiology for a patient with osteoarthritis (OA).
13. For a given patient, classify OA according to the criteria of the hands, hip, or knee.
14. Evaluate the role of evidence-based therapeutic approaches to OA.
15. Design an effective treatment plan, including goals of therapy, nonpharmacologic and pharmacologic therapy, and a monitoring plan, for a patient with OA.

16. Please provide any specific comments relating to any perceptions of bias, promotion, or advertisement of commercial products.
17. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter:
Learner Chapter Evaluation: Overweight and Obesity.

As you take the posttest for this chapter, also evaluate the material’s quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

1. The content of the chapter met my educational needs.
2. The content of the chapter satisfied my expectations.
3. The author presented the chapter content effectively.
4. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
5. The content of the chapter was objective and balanced.
6. The content of the chapter is free of bias, promotion, or advertisement of commercial products.
7. The content of the chapter was useful to me.
8. The teaching and learning methods used in the chapter were effective.
9. The active learning methods used in the chapter were effective.
10. The learning assessment activities used in the chapter were effective.
11. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

12. Classify overweight and obesity and develop patient-specific weight-loss goals.
14. Analyze a patient profile to identify potential drug-induced weight gain and suggest alternatives that are weight neutral or associated with weight loss.
15. Devise a patient-specific treatment plan, including evidence-based comprehensive lifestyle recommendations, for a patient who is overweight or obese.
17. Distinguish between the types, expected benefits, and risks of bariatric surgery.
18. Devise a nutritional plan for a patient after bariatric surgery and evaluate the need for changes in the individual’s drug regimen.
19. Please provide any specific comments relating to any perceptions of bias, promotion, or advertisement of commercial products.
20. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter:
**Learner Chapter Evaluation: Quality Indicators in Transitions of Care.**

As you take the posttest for this chapter, also evaluate the material’s quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

1. The content of the chapter met my educational needs.
2. The content of the chapter satisfied my expectations.
3. The author presented the chapter content effectively.
4. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
5. The content of the chapter was objective and balanced.
6. The content of the chapter is free of bias, promotion, or advertisement of commercial products.
7. The content of the chapter was useful to me.
8. The teaching and learning methods used in the chapter were effective.
9. The active learning methods used in the chapter were effective.
10. The learning assessment activities used in the chapter were effective.
11. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

12. Distinguish between the types of care transitions and the relevant challenges patients may experience in the health care system.
13. Assess patients for risk factors associated with adverse events during care transitions.
14. Design a plan to improve the transitions of care process using established care transitions models and the primary literature.
15. Apply existing quality metrics endorsed by health care quality-sponsoring organizations to improve care transitions.
16. Develop an individualized patient plan to improve the care transitions process.
17. Please provide any specific comments relating to any perceptions of bias, promotion, or advertisement of commercial products.
18. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter:

Questions 19–21 apply to the entire Chronic Illnesses I learning module.

19. How long did it take you to read the instructional materials in this module?
20. How long did it take you to read and answer the assessment questions in this module?
21. Please provide any additional comments you may have regarding this module:
Learning Objectives

1. Distinguish between biologic DMARD use and non-biologic DMARD use in the treatment of rheumatoid arthritis (RA).
2. Assess the differences between classes of biologic disease-modifying antirheumatic drug (DMARD) therapy.
3. Based on individual patient characteristics, construct a treatment and monitoring plan for a patient with RA and, when appropriate, include biologic DMARD therapy.
4. Justify switching agents or using combination therapy with nonbiologic DMARDs when treatment with DMARD monotherapy fails.
5. Evaluate the need for tuberculosis screening and vaccinations in patients either starting or currently receiving biologic DMARDs.
6. Evaluate the precautions, contraindications, and warnings involving the use of biologic DMARDs in high-risk patients.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease that may result in significant disability. The management of RA has seen significant advances during the past 2 decades. Although some patients with RA experience mild illness with minimal joint destruction, disease progression can lead to significant deformity of the affected joints.

Rheumatoid arthritis is systemic in nature and often affects joints in a symmetric manner. The primary symptoms of RA include joint pain or stiffness, weakness, and muscle aches. Joint deformity typically occurs late in disease progression. Extra-articular manifestations of RA may also be present.

Epidemiology

Rheumatoid arthritis affects about 1% of the world’s population with relatively low variation in incidence among countries. When matched for age, 2–3 times more
The ACR criteria have become widely used in clinical trials, methotrexate significantly decreases symptoms of RA and slows joint destruction on radiography. Methotrexate may require dose reduction in patients with liver disease, and it must be used with caution in renal dysfunction, with literature suggesting a 50% dose reduction when the CrCl is below 50 mL/minute (Aronoff 2007). When oral methotrexate is titrated past the starting dose of 7.5 mg, bioavailability decreases by about 30%, which may be caused by a saturation effect (Hamilton 1997). The weekly dosage of oral methotrexate may be given in two doses separated by 12 hours to allow for absorption of higher doses. Subcutaneous administration of methotrexate may improve bioavailability and also avoid gastrointestinal toxicity. Methotrexate is often used in combination with biologic DMARDs, which are discussed later.

**Biologic DMARDs**

Several classes of biologic DMARDs are available for the treatment of RA. Biologic agents are targeted to alter a specific step in the pathogenesis of the inflammatory response associated with RA. Specifically, these agents inhibit proinflammatory cytokines such as tumor necrosis factor (TNF) or interleukin (IL) molecules, among other mechanisms. These agents carry specific safety warnings. Table 1-2 provides a summary of the available biologic DMARDs and tofacitinib.

The ACR criteria have become widely used in clinical trials as a marker for efficacy for the treatment of RA.
Trials commonly cite ACR 20, ACR 50, and ACR 70 response when discussing clinical efficacy. For example, an ACR 20 response is defined as a 20% improvement in specific clinical variables such as tender and swollen joint counts, patient or physician global assessments, and laboratory acute phase reactants. The Disease Activity Score (DAS) is also commonly referenced in RA trials; this composite index quantifies RA disease activity.

**TNF Inhibitors**

Tumor necrosis factor is a pleiotropic cytokine that plays a key role in the inflammatory process of RA. The TNF inhibitors work by binding to TNF-α and blocking its activity on cell surface receptors. The U.S. Food and Drug Administration (FDA) has given five TNF inhibitors label approval for the treatment of RA: etanercept, infliximab, adalimumab, golimumab, and certolizumab. Each agent has shown efficacy in improving clinical response, reducing damage assessed on radiography, and improving quality of life while decreasing disability. Several TNF inhibitors are approved for use as monotherapy, although combination with methotrexate improves response in both early and established RA (Scott 2006).

Limited head-to-head trials of the anti-TNF agents have been performed. A recent meta-analysis found an overall greater ACR 50 response to TNF inhibitors than placebo at 6 months; however, this significant improvement was seen only with adalimumab, etanercept, and certolizumab. Although there were no significant differences in discontinuation rates between each TNF inhibitor versus placebo, this meta-analysis found that

<table>
<thead>
<tr>
<th>Table 1-1. Nonbiologic Agents to Treat RA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Agent</strong></td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Leflunomide</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Minocycline</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Sulfasalazine</td>
</tr>
</tbody>
</table>

DMARD = disease-modifying antirheumatic drug; GI = gastrointestinal; IM = intramuscular; LFT = liver function tests; RA = rheumatoid arthritis; SC = subcutaneous.
adalimumab, certolizumab, and infliximab had a higher rate of discontinuation than etanercept (Aaltonen 2012).

The adverse effect profile of the TNF inhibitors is fairly consistent across the class. One of the most common adverse effects is either injection site or infusion reactions, depending on route of administration. Because the anti-TNF agents modulate immune response, serious infections are also a concern. To reduce the risk of infection, vaccines should be administered before anti-TNF agent initiation. Patients should also be screened for tuberculosis. Live vaccines should not be administered during treatment. Tumor necrosis factor inhibitors may induce or exacerbate multiple sclerosis and reactivate hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. Heart failure exacerbation and increased risk of cancer are described in anti-TNF prescribing information; however, new insights on these risks, developed on the basis of new data, are discussed in the following.

**Etanercept**

Etanercept is a dimeric fusion protein that consists of an extracellular portion of human p75 TNF receptor linked to an Fc fragment of human IgG. Etanercept is self-administered by subcutaneous injection and can be used as either monotherapy or in combination with methotrexate. Etanercept efficacy has been demonstrated in patients whose disease previously failed to respond to methotrexate (Moreland 1999). At 24 weeks, ACR-20

| Table 1-2. Biologic Agents to Treat Rheumatoid Arthritis |
|-------------|----------------|----------------|----------------|
| **Agent**   | **Class**       | **Dose**       | **Frequency**  |
| Abatacept   | T-cell costimulation modulator | IV: < 60 kg: 500 mg, 60–100 kg: 750 mg, > 100 kg: 1000 mg SC: 125 mg | Weeks 0, 2, 4, then monthly |
| Adalimumab  | TNF-α inhibitor | 40 mg SC       | Every 14 days May increase dose to 40 mg every week in patients not taking methotrexate |
| Anakinra    | IL-1 receptor antagonist | 100 mg SC      | Daily |
| Certolizumab| TNF-α inhibitor | 400 mg SC, followed by 200 mg SC | 400 mg SC weeks 0, 2, and 4, followed by 200 mg SC every 2 weeks |
| Etanercept  | TNF-α inhibitor | 50 mg SC; 25 mg SC | Weekly; twice weekly |
| Golimumab   | TNF-α inhibitor | 50 mg SC       | Monthly Combine with methotrexate* |
| Infliximab  | TNF-α inhibitor | 3 mg/kg IV infusion | Weeks 0, 2 and 6; then every 8 weeks* Combine with methotrexate* |
| Rituximab   | Anti–CD 20     | 1000 mg IV plus | Days 1 and 15 may retreat every 24 weeks (no sooner than every 16 weeks) Combine with methotrexate* |
| Tocilizumab | IL-6 receptor antagonist | IV: 4 mg/kg; may increase to 8 mg/kg SC: 162 mg | Every 4 weeks < 100 kg: every other week; increase to every week based on clinical response ≥ 100 kg: every week |
| Tofacitinib | Janus kinase enzyme inhibitor | 5 mg PO        |

*Dose of infliximab may be increased up to 10 mg/kg or administered as often as every 4 weeks in patients with disease that does not respond to lower doses.

IL = interleukin; IV = intravenously; PO = by mouth; SC = subcutaneously; TNF = tumor necrosis factor.
response rates were 51% in the etanercept 10-mg twice-weekly group, 59% in the etanercept 25-mg twice-weekly group and 11% in the placebo group. Etanercept efficacy has also been demonstrated in the treatment of early RA in methotrexate-naive patients (Bathon 2000). In the ERA trial, patients at risk of rapidly progressive joint damage were randomized to either twice-weekly etanercept monotherapy or weekly oral methotrexate for at least 1 year (Genovese 2002). The study showed etanercept more rapidly decreased symptoms and joint damage, but after 12 months of therapy, clinical response was similar to the methotrexate group. Etanercept can be given subcutaneously once weekly (50-mg injection) or twice weekly (two 25-mg injections given 3–4 days apart).

**Infliximab**

Infliximab is a chimeric antibody that combines murine and human IgG. Infliximab is approved in combination with methotrexate to reduce signs and symptoms, stall progression of joint damage, and improve physical functioning in patients with moderate to severe RA. To prevent the formation of antibodies to this foreign protein, methotrexate must be administered concomitantly with infliximab for the duration of treatment. Infliximab is administered by intravenous infusion by a healthcare professional.

The efficacy of infliximab was demonstrated in the pivotal phase III ATTRACTION trial. In this randomized controlled trial, patients with inadequate response to methotrexate were randomized to receive infliximab or placebo add-on therapy to methotrexate. After 30 weeks, the cohort receiving infliximab achieved an ACR 20 response rate of 51.8% versus only 17% from methotrexate plus placebo (Maini 1999). Infliximab efficacy has also been demonstrated in the treatment of early RA and methotrexate-naïve patients. In the ASPIRE trial, infliximab plus methotrexate provided significantly greater clinical, radiologic, and functional improvement than methotrexate alone (St. Clair 2004).

**Adalimumab**

Adalimumab is a fully human monoclonal antibody specific to TNF and is produced using recombinant DNA technology. Adalimumab is self-administered as a subcutaneous injection and is approved for use as monotherapy or in combination with methotrexate.

The efficacy of adalimumab was demonstrated in the ARMADA trial in patients with an inadequate disease response to methotrexate (Weinblatt 2003). At 24 weeks, ACR 20 responses were 47.8%, 67.2%, and 65.8% in the adalimumab 20 mg, 40 mg, and 80 mg groups, respectively, versus 14.5% in the placebo group. Methotrexate background therapy was continued in each of the treatment arms. The efficacy of adalimumab in early methotrexate-naïve RA patients was demonstrated in the Premier study (Breedveld 2006). Patients were assigned to adalimumab or methotrexate monotherapy or adalimumab plus methotrexate combination therapy. The study had a 2-year follow-up and found that combination therapy was more effective than monotherapy, but no difference was found between adalimumab and methotrexate monotherapy.

**Golimumab**

Golimumab is a fully human anti-TNF IgG monoclonal antibody produced using recombinant DNA technology. The agent binds to both soluble and transmembrane TNF, which allows for both receptor binding and inhibition of cytokine activity (Nam 2010). Golimumab is also indicated for use in combination with methotrexate.

The efficacy of golimumab was demonstrated in the phase III GO-FORWARD trial (Keystone 2009). In this study, 444 patients with active RA (despite stable dose methotrexate) were randomized to either continue methotrexate monotherapy, receive golimumab monotherapy, or receive golimumab plus methotrexate therapy. At 24 weeks, significantly more patients in the combination therapy group reached ACR 20 than the methotrexate group (59.6% vs. 27.8%). Golimumab efficacy has also been demonstrated in the treatment of early RA for methotrexate-naïve patients (Emery 2009). In the phase III GO-BEFORE trial, a modified intention-to-treat analysis showed golimumab plus methotrexate therapy achieved a statistically significant disease improvement over methotrexate alone. Additionally, golimumab has been shown to be efficacious in patients who have not responded to other anti-TNF agents (e.g., etanercept, adalimumab, infliximab) (Smolen 2009). At 24 weeks, ACR 20 was achieved in 43.8% of patients receiving golimumab therapy versus 16.8% in the placebo group.

**Certolizumab**

Certolizumab is a pegylated Fab fragment of humanized anti-TNF monoclonal antibody and can be administered with or without methotrexate. Efficacy of certolizumab was demonstrated in methotrexate nonresponders in the RAPID-1 and RAPID-2 trials (Keystone 2009; Smolen 2009). In the RAPID-1 trial, ACR 20 was achieved in a significantly greater number of patients than those in the placebo group (all patients received methotrexate). In the RAPID-2 trial, certolizumab demonstrated inhibition in radiographic progression. Efficacy of certolizumab monotherapy in patients whose previous DMARD therapy had failed was demonstrated in the FAST4WARD trial (Fleischmann 2009). At 24 weeks, ACR 20 rates were 45.5% in the certolizumab arm versus 9.3% in the placebo group (p<0.001).

**Costimulation Modulators (Abatacept)**

Abatacept is a selective T-cell costimulation modulator approved for the treatment of moderate to severe RA. To become activated, T cells (specifically, the CD20 receptor)
require costimulation with CD 80/86 on antigen-presenting cells (APCs). Abatacept inhibits inflammation associated with RA by preventing the interaction between APCs and T cells.

The efficacy of abatacept has been demonstrated in several clinical studies. In one trial, abatacept given in combination with methotrexate improved remission rates and reduced radiographic progression of early RA versus methotrexate monotherapy (Westhovens 2009). Abatacept in combination with methotrexate was also effective in increasing ACR 20, 50, and 70 responses (compared with placebo) when given to patients with an inadequate response to methotrexate monotherapy (Kremer 2006). In addition, in patients with an inadequate disease response to anti-TNF therapy, 50% treated with abatacept experienced ACR 20 response versus 20% treated with placebo (Genovese 2005). Similarly, abatacept demonstrated a greater reduction in RA disease activity than infliximab in a 12-month trial (Schiff 2008). Initially, abatacept was approved only for monthly intravenous administration according to a weight-based dosing regimen. Recently, subcutaneous administration of abatacept proved noninferior to intravenous therapy (Genovese 2011). As a result, the subcutaneous administration of abatacept is now also approved for the treatment of RA.

Abatacept can be given in combination with nonbiologic agents such as methotrexate, but combination with biologic agents (especially anti-TNF agents) should be avoided. In a clinical trial, adverse events, serious adverse events, and discontinuations were higher when abatacept was combined with other biologic DMARDs but not nonbiologic DMARDs. Patients with underlying chronic obstructive pulmonary disease (COPD) developed adverse effects related to the respiratory system (e.g., COPD exacerbations, cough, rhonchi, dyspnea) more often than patients who received placebo (Weinblatt 2006). Common adverse effects with abatacept include infections, infusion-related events, headache, and dizziness.

**Anti-CD 20 Agents (Rituximab)**

Rituximab is a genetically engineered chimeric monoclonal antibody that treats RA by depleting peripheral B cells. Originally approved for the treatment of certain types of cancer, rituximab is approved in combination with methotrexate for moderate to severe RA in patients whose disease has failed to respond to anti-TNF therapy. The role of B cells in the inflammatory process of RA is multifaceted and includes the production of proinflammatory cytokines (e.g., TNF-α, IL-1, IL-6) and disrupting antigen presentation by T cells. Plasma cells, which are derived from B cells, produce antibodies (e.g., rheumatoid factor, ACPA) that promote the autoimmune process of RA.

Rituximab is given as two 1000-mg intravenous infusions separated by 2 weeks. Although this dosing has not been directly compared with other biologic DMARDs in a randomized controlled trial, there is evidence to support its use when anti-TNF agents have failed. In this patient population, one course of rituximab improved ACR 20, 50, and 70 response compared with placebo, and also improved the Disease Activity Score in 28 Joints (DAS28), a validated instrument for the assessment of disease activity in RA (Cohen 2006). An extension of this trial showed that rituximab decreased radiographic structural joint damage for up to 5 years (Keystone 2012). A longitudinal cohort study assessed patients treated with either rituximab or an alternative anti-TNF agent after initial treatment with an anti-TNF agent. Rituximab was more effective than the alternative anti-TNF agent if the patient switched drug classes because of ineffectiveness but not if the switch was because of adverse effects (Finchkh 2010). Additionally, in an observational study of patients with an inadequate response to an initial anti-TNF agent (SWITCH-RA), rituximab was better at reducing RA symptoms than an alternative anti-TNF agent (Emery 2014).

As a result of B cell depletion, rituximab could theoretically decrease the concentration of circulating Ig (e.g., IgG, IgM, IgA); however, concentrations generally remained within normal limits in clinical trials (Cohen 2006). After the initial treatment, patients can be retreated with rituximab after 24 weeks (or no sooner than 16 weeks), which is consistent with clinical trials and generally coincides with the return of peripheral B cells (Cohen 2006).

Infusion reactions (e.g., pruritus, fever, urticaria/rash, chills, hypotension, hypertension) are common with rituximab, and patients should be pretreated with a corticosteroid, acetaminophen, and an antihistamine. Rituximab may increase the rate of infections compared with placebo. However, most infections in clinical trials were mild and included upper respiratory tract infections, nasopharyngitis, and sinusitis. In clinical trials, retreatment with rituximab did not increase the incidence of infusion-related events and did not pose additional safety concerns (Mease 2010).

**IL-6 Receptor Antagonists (Tocilizumab)**

In RA, chronic joint inflammation increases the production of IL-6, which furthers the inflammatory response by stimulating B- and T-cell development. Tocilizumab is a humanized monoclonal antibody that binds to IL-6 and inhibits its anti-inflammatory effects. Tocilizumab is approved as an intravenous formulation to be given as 4 mg/kg or 8 mg/kg every 4 weeks and as a subcutaneous formulation given as 162 mg every week or every other week based on patient weight. Notable adverse effects of tocilizumab include increased liver enzymes, increased cholesterol, and decreased neutrophil and platelet counts. Tocilizumab induces cytochrome P450 (CYP) 3A4 and may decrease the serum concentration of drugs metabolized by this enzyme. Patients treated with tocilizumab were at increased risk of infections, which increased the discontinuation rate of tocilizumab over placebo in clinical trials.
Tocilizumab is indicated for treatment of RA in patients who have not responded to at least one DMARD. Tocilizumab has been effective as monotherapy in clinical trials in patients whose disease failed to respond to nonbiologic DMARDs (Dougados 2013; Jones 2010). Tocilizumab is approved for use without concomitant methotrexate; however, it has been used in combination with methotrexate in clinical practice, a practice supported by data from randomized controlled trials (Emery 2008). Because many biologic DMARDs are used in combination with methotrexate, tocilizumab may be an alternative for patients who cannot tolerate methotrexate or for whom methotrexate use is inappropriate.

Although clinical use of tocilizumab typically follows treatment failure with an anti-TNF agent, there is evidence to suggest that tocilizumab is superior to adalimumab, a commonly used anti-TNF agent (Gabay 2013). This randomized controlled trial compared tocilizumab monotherapy (8 mg/kg every 4 weeks) with adalimumab (40 mg subcutaneously every 2 weeks). Patients treated with tocilizumab had a greater decrease in DAS28 and ACR response rates. However, more patients treated with tocilizumab required dose modification or interruption because of adverse effects.

IL-1 Receptor Antagonists (Anakinra)

Of agents in the IL-1 receptor antagonist class, only anakinra has label approval for use in RA; it is approved for patients whose disease has failed to respond to other DMARDs. Interleukin-1 is a cytokine that is increased in response to inflammation and contributes to cartilage degradation and bone resorption. The daily dosage of anakinra is 100 mg given as a subcutaneous injection. For patients with renal impairment (i.e., CrCl less than 30 mL/minute), the recommended dosage is 100 mg every other day.

Anakinra may be used as monotherapy or in combination with other DMARDs with the exception of anti-TNF drugs. In a clinical trial, the combination of anakinra plus etanercept increased the rate of adverse effects (Genovese 2004). In addition, the combination produced no benefit in clinical outcomes as measured by ACR20 after 24 weeks of therapy. The risk of this combination is deemed to outweigh any benefit.

Anakinra is not included in the most recent ACR recommendations because of its infrequent use compared with other biologics and because there is a lack of strong data to support its use (Singh 2012). Although a significant number of patients in clinical trials achieved symptomatic relief with anakinra versus placebo, the benefit was modest compared with other biologics (i.e., the anti-TNF agents adalimumab, infliximab, and etanercept) (Mertens 2009). In a systematic review of biologic agents, anakinra's lack of efficacy resulted in treatment discontinuation rates higher than those of most other biologics (Desai 2012). Additional adverse effects with anakinra include injection site reactions (up to 71% of patients), serious infections, and decreased neutrophil counts.

Janus Kinase Enzyme Inhibitors

Tofacitinib is a member of the newest class of agents approved to treat RA, the Janus kinase (JAK) enzyme inhibitors. Inhibition of JAK modulates the inflammatory process by interrupting cytokine signaling and immune cell function, specifically by preventing the phosphorylation and activation of signal transducers and activators of transcription. In contrast to biologic agents, the small size of the tofacitinib molecule allows for oral administration and intracellular action. The typical dosage of tofacitinib is 5 mg twice daily. However, this should be reduced to 5 mg daily in patients who have moderate to severe renal insufficiency, moderate hepatic impairment, or who are taking potent inhibitors of CYP3A4, which extensively metabolizes tofacitinib.

Clinical studies support the use of tofacitinib both as monotherapy and in combination with other DMARDs such as methotrexate, but not with other biologic agents. At approved doses, tofacitinib improved symptoms of RA according to ACR response and also improved physical function according to the Health Assessment Questionnaire-Disability Index, but improvements in remission and radiographic changes were variable at 3 and 6 months. In one trial comparing tofacitinib monotherapy with placebo, tofacitinib improved ACR response rates and physical function but did not improve disease remission, although more patients met criteria for low disease activity (Fleischmann 2012). In another trial, tofacitinib showed improvements in ACR 20 criteria, physical function, and disease remission in combination with methotrexate in patients who had experienced treatment failure with an anti-TNF agent (Burmester 2013). When given in combination with methotrexate, tofacitinib was similar to adalimumab in efficacy, physical function, and disease remission, although formal noninferiority analysis was not completed because of study design (Van Vollenhoven 2012). Twelve-month data from a 24-month study showed that tofacitinib improved signs and symptoms of RA and physical function more than placebo; however, it did not decrease radiographic progression of the disease at the approved dosage of 5 mg twice daily (Van der Heijde 2013).

The most common adverse effects in clinical trials were headache, diarrhea, nasopharyngitis, upper respiratory infection, and hypertension (Burmester 2013; Van der Heijde 2013; Van Fleischmann 2012; Vollenhoven 2012). Tofacitinib may contribute to neutropenia and may also increase liver enzymes and lipid parameters. As with other biologics, infections, including serious infections, were increased with tofacitinib.

RA Treatment

Goals and Principles

Principles for the treatment of RA are rapidly changing as new agents are approved and additional trials are conducted. In addition, the course of RA and resulting disability,
Joint damage, and inflammation are highly variable for each patient. In general, the 2012 ACR recommendations support early and aggressive treatment of RA based on individual patient circumstances. Treatment for RA with DMARDs may reverse joint damage and preserve physical function and health-related quality of life (Singh 2012).

The goal of RA treatment is complete remission, although low disease activity may be a more acceptable target for some patients (Singh 2012). According to a recent consensus provided by the ACR and European League Against Rheumatism (EULAR), RA remission can be defined as no more than one tender or swollen joint, C-reactive protein less than 1 mg/dL, and positive patient global assessment. Alternatively, remission may be defined by a Simplified Disease Activity Index score of 3.3 or less (Felson 2011). In clinical trials, remission is commonly defined as a score of less than 2.6 on the DAS28. Low, moderate, or high disease activity may also be determined by use of these validated scales.

Clinical recommendations may be based on the length of time that a patient has had RA. A disease duration of less than 6 months is termed early RA, whereas RA of at least 6 months is considered established RA. Of note, although the ACR/EULAR changed the RA classification criteria in 2010, these terms remain in the current guidelines because clinical data are based on the old criteria. Another important distinction when choosing treatment is the presence or absence of poor prognostic features. Features of poor prognosis include functional limitation, extra-articular disease, positive rheumatoid factor or ACPA, or bony erosions on radiography (Singh 2012).

**Early RA**

Options for treating early RA are based on the level of disease activity and the presence or absence of poor prognostic features (Table 1-3). The panel of experts that created the ACR guidelines for RA treatment recommend the use of nonbiologic DMARD monotherapy in early RA for patients without poor prognostic factors for any degree of RA disease activity (i.e., low, moderate, or high). Monotherapy with DMARDs includes methotrexate, leflunomide, hydroxychloroquine, sulfasalazine, and minocycline. In patients with high disease activity and absence of poor prognostic features, the panel recommends the use of methotrexate plus hydroxychloroquine as initial therapy. Combination therapy with methotrexate plus either hydroxychloroquine, leflunomide, or sulfasalazine is recommended for patients with moderately or highly active disease and poor prognostic features. Triple therapy with methotrexate, hydroxychloroquine, and sulfasalazine may also be used in these patients. There is a role for the use of anti-TNF agents with or without methotrexate as initial therapy for patients with early RA. This approach is appropriate for patients with high disease activity and poor prognostic features. Infliximab, however, should be used with methotrexate and not as monotherapy (Singh 2012).

**Established RA**

The guidelines for treating established RA address the concepts of switching among nonbiologic DMARDs, switching from nonbiologic DMARDs to the biologic agents, and switching among biologic agents. For a patient with established RA who is taking DMARD monotherapy, therapy should be reassessed after 3 months of treatment. At that point, the patient may benefit from either adding a nonbiologic agent to current therapy or switching to another nonbiologic DMARD, based on prognosis and disease activity. Patients with moderate to high disease activity after 3 months of treatment with methotrexate monotherapy or DMARD combination therapy can add or switch to an anti-TNF biologic agent. Other candidates for adding or switching to an anti-TNF biologic agent include patients with moderate to high disease activity who have already been treated with intensified DMARD combination therapy or after a second DMARD.

When treatment with a biologic agent is necessary, anti-TNF agents are typically selected before other biologic agents.

---

**Table 1-3. Treatment of Early RA**

<table>
<thead>
<tr>
<th>Disease Activity</th>
<th>Absence of Poor Prognosis</th>
<th>Presence of Poor Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>DMARD monotherapy</td>
<td>Not addressed</td>
</tr>
<tr>
<td>Moderate</td>
<td>DMARD monotherapy</td>
<td>DMARD combination therapy</td>
</tr>
<tr>
<td>High</td>
<td>DMARD monotherapy or MTX + HCQ</td>
<td>DMARD combination therapy or anti-TNF agent with or without MTX</td>
</tr>
</tbody>
</table>

*Early RA = disease duration less than 6 months.

*DMARD monotherapy includes methotrexate, minocycline, hydroxychloroquine, sulfasalazine, and leflunomide.

*DMARD combination therapy includes methotrexate plus hydroxychloroquine, methotrexate plus leflunomide, methotrexate plus sulfasalazine, sulfasalazine plus hydroxychloroquine, and sulfasalazine plus hydroxychloroquine plus methotrexate.

*Options include etanercept with or without methotrexate, infliximab with methotrexate, adalimumab with or without methotrexate, golimumab with or without methotrexate, and certolizumab with or without methotrexate.

Anti-TNF = anti-tumor necrosis factor; DMARD = disease-modifying antirheumatic drug; HCQ = hydroxychloroquine; MTX = methotrexate; RA = rheumatoid arthritis.
because of their high efficacy and the preference given to them in the guidelines and in clinical practice. Patients taking an anti-TNF agent may benefit from switching to a non-TNF agent if disease activity remains moderate to high after 3 months or if adverse events occur. If the adverse event experienced with an anti-TNF agent is not considered serious, the patient may want to try a different anti-TNF agent. Because of the variability in the role of proinflammatory cytokines (e.g., TNF-α, IL-1, IL-6) that mediate the RA disease process among patients, those who have tried anti-TNF agents without achieving adequate disease control may benefit from switching to another class of biologics that target a different aspect of the inflammatory cascade.

In clinical practice, patients commonly are switched between anti-TNF agents because of a lack of complete remission. This is supported by the guidelines, although only limited controlled clinical trials have investigated the concept. Patients may respond to one anti-TNF agent and not another because of drug resistance, which is linked to the development of antibodies to the drug (Emery 2012).

Additional time may be necessary to determine the success of treatment of RA with non-TNF biologic agents. Compared with anti-TNF agents, a 6-month trial of non-TNF agents should be considered before reassessing therapy and providing adjustments (Singh 2012). If a patient experiences inadequate disease response or adverse effects after 6 months of treatment with a non-TNF agent, a switch to a different class of drugs is recommended. Options include either another non-TNF agent or an anti-TNF agent, if appropriate. Non-TNF agents specifically included in the latest ACR guidelines include abatacept, rituximab, and tocilizumab. Anakinra is not included because of low clinical use and little perceived clinical benefit. Tofacitinib was not approved at the time the guidelines were published; however, on the basis of clinical trial data and pharmacodynamics, a 6-month trial is appropriate to determine if tofacitinib will be efficacious for a particular patient. Figure 1-1 describes recommendations for switching among biologic agents in the treatment of established RA.
**Safety Considerations of Biologic DMARDs**

**Tuberculosis Screening**

Tuberculosis (TB) infections were documented in patients with RA even before the biologic DMARDs were on the market. An increased number of cases occurred after the release of anti-TNF agents (Gardam 2003).

Because TNF-α regulates host defense against mycobacterial infections, inhibition of this cytokine increases the risk of new-onset TB infection and reactivation of latent tuberculosis infection (LTBI). Tuberculosis infection has been documented with all of the anti-TNF agents, although some studies suggest the risk is lower with etanercept (Tubach 2009; Gomez-Reino 2003). In contrast to the anti-TNF agents, no causal link has been

---

**Figure 1-1.** Recommendations for switching among biologic agents for the treatment of established rheumatoid arthritis.

Anti-TNF = anti-tumor necrosis factor.

established between anakinra, abatacept, rituximab, or tocilizumab and either new-onset TB infection or reactivation of LTBI, although experience with tocilizumab in patients with LTBI is limited (Rubbert-Roth 2012).

Screening for LTBI has been shown to reduce the risk of reactivation. The ACR guidelines recommend screening for LTBI with a thorough assessment of the patient’s medical history and with either the tuberculin skin test or interferon-gamma-release assay (IGRA). This screening should take place before initiation of any biologic DMARD therapy (not just the anti-TNF agents) regardless of a patient’s risk factors for LTBI. Risk factors for TB infection include intravenous drug use, prison or health care occupation, homelessness, and a history of travel or residence in an area with high prevalence of the infection.

The optimal test for TB screening is unclear. The tuberculin skin test may be limited by the potential for false-negative results in patients with RA receiving immunosuppressant therapy or with immunocompromising comorbidities (Smith 2011). The IGRA has similar sensitivity but improved specificity over the tuberculin skin test in patients with a history of Bacille Calmette-Guerin vaccine or past infection with a non-TB mycobacterium. The IGRA is more costly than the tuberculin skin test and may have reduced sensitivity in patients without intact immune systems (Smith 2011). The ACR endorses use of the IGRA in patients with a history of Bacille Calmette-Guerin vaccination. The guidelines caution that a negative TB screen should not be interpreted as excluding the possibility of infection, especially when clinical suspicion exists because of concomitant risk factors. A second screening can be considered 1–3 weeks after the initial negative screen to confirm results.

The 2012 ACR guidelines recommend a step-wise approach to TB screening. Any positive tuberculin skin test (induration of greater than 5 mm in the immunocompromised patient) or IGRA should be followed by chest radiography. If chest radiography is suggestive of active TB, a subsequent sputum examination is indicated to check for active TB infection. Anti-TB therapy should be started in any patient with RA having active TB, and prophylactic therapy should be initiated in a patient with LTBI. According to the ACR guidelines, biologic therapy can begin or resume after complete treatment of active TB and after 1 month of anti-TB prophylaxis in a patient with LTBI.

The value of repeated TB screening in patients treated with long-term biologic therapy is unknown (Fuchs 2009). However, the 2012 ACR guidelines recommend annual screening for patients receiving long-term biologic therapy who live, work, or travel where TB exposure is likely to occur.

Vaccination Recommendations

Patients with RA are more susceptible to vaccine-preventable infections. One study estimated the risk of infectious complications to be 2-fold higher in patients with RA than in the general population (Gluck 2008). This increased susceptibility is not likely dependent on treatment with immunomodulating biologic therapies alone. Other factors that may contribute to an increased risk of infection in patients with RA include immune system dysfunction attributable to the disease itself, comorbidities, nonbiologic immunosuppressive RA therapies, and RA disease activity (Au 2011; Kapetanovic 2006). Biologic therapy clearly plays a role in increased risk of infection. Specifically, the anti-TNF drugs block important signaling processes in the immune response, leading to greater susceptibility to bacterial and fungal pathogens.

Regardless of cause, the morbidity and mortality in patients with RA make vaccination screening and administration important. Unfortunately, vaccination status in the population with RA is low. A study of Irish patients with RA found that only 42% were up to date on their influenza vaccination, and just 19% had received a pneumococcal vaccination (McCarthy 2011).

The ACR guidelines recommend that before biologic therapy initiation, the inactivated influenza vaccine, recombinant pneumococcal vaccine, recombinant human papillomavirus vaccine, and live attenuated herpes zoster vaccine be administered to patients deemed appropriate by the current Center for Disease Control and Prevention (CDC) vaccination schedule. Additionally, the HBV vaccination should be considered before biologic therapy for any patient with risk factors for the disease. Risk factors for HBV include intravenous drug abuse, multiple sexual partners in the previous 6 months, and occupational settings such as health care or the prison system.

The 2013 CDC schedule recommends annual influenza vaccinations in adults, a three-dose series of the human papillomavirus vaccine in men and women 19–26 years of age, herpes zoster vaccination once after age 60, and a three-dose series of HBV vaccination in at-risk individuals. The pneumococcal polysaccharide (PPSV23) vaccination should be given to adults (older than 19 years) with RA followed by a one-time revaccination 5 years after the first dose. The CDC also recommends that individuals at least 65 years of age receive a one-time revaccination if they were vaccinated more than 5 years previously and the primary vaccination was given before age 65 (CDC 2013).

According to the ACR guidelines, live vaccines are contraindicated during biologic therapy; however, the guidelines do not address the minimum interval to wait after administration of a live vaccine before biologic therapy initiation. Guidelines from three countries (i.e., Great Britain, India, and Canada) recommend waiting 4 weeks between administration of a live vaccine and initiation of biologic therapy (Bombardier 2012; Misra 2008; Devlin 2005; Ledingham 2005).

Inactivated vaccines are generally considered acceptable for patients taking immunosuppressive drugs. The ACR guidelines recommend concomitant administration
of biologic therapy with the inactivated influenza vaccine, pneumococcal vaccine, human papillomavirus vaccine, and HBV vaccine for appropriate patients. Although not discussed in the ACR guidelines, data suggest the risk of infection is higher in patients with high RA disease activity (Au 2011). Based on this information, it may be prudent to vaccinate patients when their maximal immune response is anticipated, which is just before initiation of biologic therapy or during a time of stable disease (Van Assen 2011).

Immunosuppression and Opportunistic Infections
In addition to increased risk of vaccine-preventable infections, biologic agents pose an increased risk of opportunistic bacterial and fungal infections. A boxed warning about the risk of serious, sometimes fatal Legionella and Listeria infections was recently added to the label of each of the TNF inhibitors. The FDA adverse effect reporting system contained 80 cases of Legionella pneumonia in patients receiving TNF inhibitors between 1999 and 2010 (FDA 2011). Of the 80 cases, 65% were receiving their respective anti-TNF agent for RA for a median of 10.4 months. All TNF inhibitors except certolizumab were linked with the incidence of Legionnaire’s disease. The FDA has also received reports of Listeria monocytogenes in patients taking TNF inhibitors and identified 26 published cases of Listeria infections in anti-TNF treated patients (FDA 2011). Data from the French registry RATIO report the annual incidence rate of nontuberculosis opportunistic infections including Legionella and Listeria to be 151.6 per 100,000 patient years (Salmon-Ceron 2011). The same study found that monoclonal anti-TNF antibodies (specifically infliximab and adalimumab) rather than soluble TNF receptor therapy (specifically etanercept) and steroid use greater than 10 mg per day are independently associated with increased risk of opportunistic infection.

Opportunistic fungal infections, particularly histoplasmosis, have been identified in patients treated with adalimumab, etanercept, infliximab, and certolizumab pegol. In 2008, the FDA required a strengthened label warning for opportunistic fungal infections on these drugs (FDA 2008). This was prompted by several cases of histoplasmosis that were not initially recognized by health care professionals, thereby delaying treatment. Twelve of 21 of these cases were fatal (FDA 2008). Unfortunately, histoplasmosis infections often present atypically in anti–TNF treated patients. Once acquired, this population is at greater risk of more severe or disseminated disease (Smith 2009). Special care should be taken in assessing for and recognizing these infections in patients taking biologic agents.

Cardiovascular Disease
Inflammatory diseases such as RA increase cardiovascular risk. The increased risk of cardiovascular disease (CVD) morbidity is estimated to be 2-fold higher than that of the general population (Avina-Zubieta 2012). In addition to a higher prevalence of traditional CVD risk factors in patients with RA, the disease itself seems to confer additional risk factors (Barbhayiya 2013). These disease-specific risk factors include immune dysregulation, plaque instability, elevated thrombotic markers (fibrinogen, D-dimer), systemic inflammation, and impaired coronary reserve (Barbhayiya 2013).

An array of human and animal studies have suggested an association between TNF inhibitors with vascular instability, progression of atherosclerosis, and negative inotropic and cardiac remodeling effects on the myocardium (Barbhayiya 2013; Danila 2008). Because of the presumed deleterious effects of TNF-a within the cardiovascular system, it has been postulated that treatment with anti-TNF agents actually confers a cardioprotective effect; however, data are conflicting.

**Biologic DMARDs in High-Risk Patients**

**Heart Failure**
Concern with the use of anti-TNF agents in heart failure stems from several randomized clinical trials as well as postmarketing case reports. A 2001 report from the American College of Cardiology identified several large-scale clinical trials that were stopped early because etanercept treatment failed to demonstrate a benefit on heart failure or mortality (Louis 2001). In addition, a study of 150 patients with New York Heart Association (NYHA) class III and IV heart failure found treatment with infliximab increased mortality and hospitalization from heart failure exacerbation after just 28 weeks of treatment (Chung 2003). Postmarketing case reports of new and worsening heart failure in patients receiving anti-TNF therapy have also been documented. In 2003, a study from the FDA MedWatch program reported 38 new cases of heart failure and nine cases of heart failure exacerbation in patients receiving anti-TNF therapy (Kwon 2003). Thirty-eight of these cases were in patients with RA; of the incident heart failure cases, 50% occurred in patients with no identifiable risk factors. Ten of the 38 cases occurred in patients younger than 50 years.

This worrisome clinical data influenced the ACR guidelines for use of anti-TNF agents in patients with heart failure. The guidelines recommend avoiding any anti-TNF biologic in patients with NYHA class III or IV heart failure or in those with an ejection fraction of 50% or less. New York Heart Association class III patients have marked limitation of physical activity because of their heart condition but are comfortable at rest. New York Heart Association class IV patients are unable to carry out any physical activity without discomfort and may experience discomfort at rest. The ACR guidelines do not address the use of non-TNF biologics in the patient with RA and concomitant heart failure.

Not all data regarding anti-TNF biologics and heart disease are unfavorable. A recent study of more than 20,000 U.S. veterans with RA found that use of TNF
Biologic DMARDs inhibitors was not associated with increased risk of heart failure and was associated with a decreased risk of stroke (Al-Aly 2011). This study is further supported by a second study of patients with RA that found the use of anti-TNF agents was not associated with a greater risk of hospitalization for heart failure than nonbiologic DMARD use (Solomon 2012). Lastly, a review and meta-analysis found that anti-TNF therapy is associated with a reduced risk of all cardiovascular events, myocardial infarction, and stroke (Barnabe 2011). The study did not look at the risks of anti-TNF agents in heart failure specifically. Because of conflicting evidence in this high-risk population, more research is needed to determine best practices for use of anti-TNF biologics in heart failure.

Hepatitis

It is well established that immunosuppression increases viral replication, although much of the existing data come from patients receiving chemotherapy for malignancy or long-term immunosuppression after transplant rather than in the RA setting. Both rituximab and the anti-TNF agents have been implicated in viral replication and reactivation of hepatitis infections, whereas extremely limited data exist in the setting of HBV or HCV with the other biologic agents (Hoofnagle 2009; Koo 2009; Vassilopoulos 2007).

Although the risk of viral replication exists, the current ACR guidelines do not recommend universal HBV or HCV testing at baseline for patients initiating biologic therapy. The guidelines do suggest that if risk factors for hepatitis are present, evaluation may include hepatitis B surface antigen (HBsAG), antibody (anti-HBs), or core antibody (HBcAb) testing and/or HCV antibody testing; however, no formal recommendation for specific screening procedures are made. In contrast, the CDC recommends every patient starting immunosuppressive therapy be screened for HBV with the HBsAG, anti-HBs, and HBcAb tests (Weinbaum 2008). A survey of U.S. rheumatologists found 69% practiced universal HBV screening before initiating immunosuppressive therapy (Stine 2010).

In 2012, the ACR guidelines were updated regarding biologic use in patients with hepatitis; these changes are shown in Table 1-4. In contrast to the 2008 guidelines, which relied predominantly on Child-Pugh classification, the new guidelines include both disease severity and concurrent treatment in therapeutic decision-making. New biologic agents are not recommended in untreated chronic HBV regardless of the Child-Pugh classification. Research shows that the rate of HBV reactivation in patients receiving immunosuppression therapy without antiviral prophylaxis ranges widely from 24%–88%. The risk of liver-related mortality in this population is high at 5%–30%. Specific to anti-TNF agents, the rate of HBV reactivation in HBsAg-positive patients not receiving antiviral prophylaxis is 38% (Vassilopoulos 2011). When chronic HBV is being treated, biologic therapy can be used in mild disease (defined as Child-Pugh class A). Biologic therapy is contraindicated in patients with Child-Pugh class B or C because of HBV, regardless of treatment status.

Current guidelines recommend etanercept as a treatment option for patients with RA having HCV. This is in contrast to the 2008 guidelines, in which biologic therapy is contraindicated in active HBV or HCV infection. Of note, the 2012 guidelines do not distinguish acute HCV from chronic HCV, nor do they discuss HCV Child-Pugh

| Table 1-4. ACR Guidelines on the Use of Biologic Agents to Treat RA in Patients with a History of Hepatitis |
|---------------------------------------------------------------|------------------|------------------|
| **Active hepatitis B**                                         | **2008 Recommendations** | **2012 Recommendations** |
| Contraindicated                                               | Etanercept       |
| **Active hepatitis C**                                        | Contraindicated  | Etanercept       |
| **Chronic hepatitis C (Child-Pugh class A)**                  | Any biologic agent | Etanercept       |
| **Chronic hepatitis C (Child-Pugh class B or C)**             | Contraindicated  | Etanercept       |
| **Untreated chronic HBV (Child-Pugh class A)**                | Any biologic agent | Contraindicated  |
| **Treated chronic HBV (Child-Pugh class A)**                 | Any biologic agent | Any biologic agent |
| **Untreated/treated HBV (Child-Pugh class B or C)**           | Contraindicated  | Contraindicated  |

RA = rheumatoid arthritis.
Only one study to date found the risk of malignancy to be significantly higher in patients with RA who were treated with anti-TNF agents (Bongartz 2006). Of note, doses of anti-TNF agents studied in this review were often higher than those recommended in clinical practice for treatment of RA. Recent meta-analyses and systematic reviews refute this finding (Le Blay 2012; Solomon 2012; Askling 2011; Mariette 2011). A pooled analysis of randomized controlled trials from 2011 found anti-TNF therapy did not significantly increase the risk of short-term malignancy, except for nonmelanoma skin cancer, in which anti-TNF therapy doubled the risk of occurrence (Askling 2011). This finding was supported by two additional studies (Solomon 2012; Mariette 2011).

The labeling for malignancy in most non-TNF biologics is vague, largely because of the lack of postmarketing data to inform the risk in tocilizumab, abatacept, and anakinra (Ruderman 2012). Tofacitinib, however, carries a boxed warning for increased risk of lymphoma and other

---

**Patient Care Scenario**

A 53-year-old woman (weight 84 kg) with medical history of HCV has a new diagnosis of RA. Her allergies include sulfa medications (severe swelling of tongue, lips and throat). She is experiencing a moderate degree of functional limitation as a result of the RA. The rheumatologist notes the presence of rheumatoid nodules and joint erosions on a recent radiograph. She also has a positive rheumatoid factor. Her disease activity is considered high by the rheumatologist, who prefers to use a biologic agent as initial therapy. What would be best to recommend for this patient?

**Answer**

Early treatment in a patient with RA is based on disease severity and the presence or absence of poor prognostic features. The patient has high disease activity based on an assessment by the rheumatologist and features of poor prognosis including functional limitation, extra-articular disease (manifesting as rheumatoid nodules), positive rheumatoid factor, and erosions present on radiography. Therapy options for this patient include traditional DMARD combination therapy or an anti-TNF agent with or without concurrent methotrexate.

Because the patient has a life-threatening allergy to sulfa, she is not a candidate for any DMARD combination therapy that contains sulfasalazine. Additionally, the patient is not a candidate for any combination therapy that includes methotrexate because of her history of HCV. These two factors eliminate each of the traditional combination DMARD therapy options and leave therapy with an anti-TNF inhibitor as first choice. This patient is considered at high risk when taking biologic therapy because anti-TNF agents have been implicated in viral replication and reactivation of HCV infection. Of the anti-TNF agents, etanercept has the greatest amount of evidence supporting its use in the setting of HCV. Etanercept is also the preferred biologic agent in the treatment of RA in patients with HCV according to the 2012 ACR guideline update.

Unlike biologic therapy in patients with HBV, biologic treatment in patients with HCV is not based on Child-Pugh classification or concomitant antiviral therapy. Therefore, no additional hepatic disease assessments need to be completed, and the patient can be considered for biologic therapy. Whereas the guidelines call for anti-TNF therapy with or without methotrexate for early initial RA, this patient has a clear contraindication to methotrexate because of her history of HCV. Etanercept monotherapy should therefore be initiated at a weekly subcutaneous injection of 50 mg.

---

malignancies, especially in patients receiving concomitant immunosuppressive therapies.

The 2012 ACR guidelines recommend rituximab for treatment of RA in patients with any solid or nonmelanoma malignancy treated within the past 5 years and any skin melanoma or lymphoproliferative malignancy history, regardless of time since treatment. Of note, this recommendation is not supported by clinical trial data; however, rituximab is indicated for treatment of lymphoma and other hematologic cancers and may be a safer alternative in patients with a recent history of malignancy. Any biologic therapy, including the anti-TNF agents, can be used in patients with solid malignancy or nonmelanoma skin cancer that was treated more than 5 years previously, according to the guidelines. The guidelines panel rated the level of evidence for these recommendations a “C” based on consensus opinion of experts, case studies, or standards of care. Additionally, the literature search for the 2012 guideline update ended February 26, 2010, and did not include many of the reviews discussed earlier.

**Patient Education**

With the introduction of synthetic DMARDs, and now the biologic DMARDs, treatment goals for RA have shifted from simply treating symptoms to trying to control or halt disease activity. Ensuring the appropriate DMARD is being used with good adherence is important to achieving low disease activity or remission. Inadequate treatment and poor adherence are both issues in patients with RA (Schmajuk 2011).

Several studies have shown that interdisciplinary, patient-centered care in RA produces clinical and functional outcomes superior to the traditional rheumatologist-centered model (Engen 2011; Esselens 2009). One study showed that pharmacists can improve patient medication adherence and quality of life through an RA disease therapy management (DTM) program (Stockl 2010). In the study, patients were flagged for participation in the DTM program by the pharmacy benefits manager if they had a diagnosis of RA and a pharmacy claim for an injectable RA drug. The DTM program offered pharmacist- and nurse-directed patient education and resources to self-manage pharmacotherapy and symptoms. Special attention was given to education on medication adherence. Counseling sessions included information on management of injection site reactions, the consequences of missed doses, patient assistance programs, and financial aid for injectable RA drugs. A proportion of days covered of at least 0.80 is considered high adherence and is the benchmark most commonly reported in the literature (Andrade 2006). The results of the study showed that proportion of days covered was significantly higher for patients enrolled in the DTM program than for patients receiving biologic therapy from a traditional community pharmacy (0.83 vs. 0.60). The patients in the DTM program also showed significantly greater physical health-related quality of life than their community pharmacy comparators.

Another role for pharmacists in the management of RA lies in the importance of vigilant safety monitoring. As discussed earlier, biologic DMARD therapy is not without risks. Although prevention strategies have been developed to minimize or mitigate the adverse reactions of biologic therapy, they are not always incorporated into practice.

**Practice Points**

In considering treatment of RA:

- Medication selection between nonbiologic DMARDs, biologic DMARDs, and tofacitinib is based on RA disease activity, presence or absence of features of poor prognosis, and therapy that has been tried previously.
- The biologic agents are typically tried after trials with other DMARD agents and rarely as initial therapy. When treatment with a biologic agent is necessary, TNF inhibitors are typically selected before other biologic agents because of their high efficacy and preference given in the guidelines and clinical practice.
- Patients taking a TNF inhibitor who experience significant disease activity after 3 months of treatment may consider switching to another TNF inhibitor or a non-TNF agent.
- Patients taking a non-TNF biologic agent who experience significant disease activity after 6 months of treatment may consider switching to another non-TNF agent or an anti-TNF agent.
- Although adalimumab, certolizumab, and etanercept can be used as monotherapy, each of the TNF inhibitors shows improved response when given in combination with methotrexate in early and established RA. Golimumab and infliximab are indicated only in combination with methotrexate.
- Anti-TNF agents should be avoided in patients with NYHA class III-IV heart failure.
- Because anti-TNF agents modulate immune response, serious infection is a concern. Vaccinations and TB screening should occur before initiation of these agents, and live vaccines should be avoided during treatment.
- Any biologic therapy can be used in patients with a history of solid malignancy or nonmelanoma skin cancer treated more than 5 years previously. Rituximab is recommended for solid and nonmelanoma malignancy treated within the past 5 years and any skin melanoma or lymphoproliferative malignancy history, regardless of time since treatment.
- Biologic therapy can be used in mild HBV (Child-Pugh class A) when a prophylactic antiretroviral agent is being used concomitantly. Etanercept is recommended in patients with HCV.
A study team set out to determine whether implementation of system-wide clinical care guidelines for biologic response modifiers increased the rate of compliance with safety monitoring recommendations (Hanson 2013). The guidelines recommended a TB test, HBsAg test, liver function test (LFT), complete blood cell count (CBC), up-to-date vaccination status, cancer assessment, pregnancy test, and evaluation of all other contraindications to therapy occur before initiation of a biologic agent. A process was developed to flag biologic hospital orders or outpatient prescriptions for an assessment of guideline compliance. Guideline compliance was defined as completion of four safety screenings (TB, HBsAg, LFT, and CBC) before initiation of biologic therapy. During this evaluation process, pharmacists assisted clinical staff in ordering laboratory tests before biologic initiation, when necessary.

Before implementation of the clinical care guidelines, only 31% of outpatient biologic prescription orders were preceded by completion of the safety monitoring guidelines. After implementation of the guidelines, a statistically significant improvement occurred in 60% of cases compliant with the guidelines.

**Conclusion**

The increased availability of biologic DMARD agents to treat RA provides expanded drug therapy options for patients. Clinical studies for the biologic DMARDs often enroll patients who have already tried and not responded to methotrexate or other DMARD therapy. In clinical practice, the biologic agents are typically tried after trials with other DMARD agents and rarely as initial therapy. There are limited data comparing biologic DMARD agents. Several classes of biologic agents are available, and patient-specific characteristics and adverse effect profiles of the agents should be considered when selecting among the biologic agents. Additionally, the ACR guidelines provide algorithms to aid the clinician in the decision. The pharmacist plays an important role in patient education and drug selection for these patients with progressing RA.

**References**


Genovese MC, Bathon JM, Martin RW, et al. Eta


Rubbert-Roth A. Assessing the safety of biologic agents in patients with rheumatoid arthritis. Rheumatology 2012;S1:v38-v47.

Ruderman, EM. Overview of safety of nonbiologic and biologic DMARDs. Rheumatology 2012;S1:v37-v43.


**Self-Assessment Questions**

1. A patient with a history of severe chronic obstructive pulmonary disease, depression, and hyperlipidemia presents to the rheumatology clinic for a follow-up visit related to rheumatoid arthritis (RA). The patient has been taking an anti-tumor necrosis factor agent, adalimumab 40 mg subcutaneously, for the past year and has not achieved satisfactory control of RA symptoms. Which one of the following is best to recommend for this patient?
   A. Increase adalimumab to 80 mg subcutaneously weekly.
   B. Stop adalimumab and start abatacept 125 mg subcutaneously weekly.
   C. Stop adalimumab and start etanercept 25 mg subcutaneously weekly.
   D. Stop adalimumab and start golimumab 50 mg subcutaneously monthly plus methotrexate 7.5 mg orally every week.

2. A 46-year-old woman with RA was started on intravenous tocilizumab at her last appointment 3 months ago. Today, she presents for follow-up. She states that her joint pain and stiffness have not improved since starting tocilizumab. Her medical history is significant for hypothyroidism, hypertension, and chronic constipation. Which one of the following is best to recommend for this patient?
   A. Add etanercept 50 mg subcutaneously every week.
   B. Add methotrexate 7.5 mg orally daily.
   C. No change in therapy.
   D. Stop tocilizumab and initiate infliximab.

**Questions 3–5 pertain to the following case.**

L.P. is a 58-year-old woman (height 66 inches, weight 76 kg) with a new diagnosis of RA. Her disease activity is considered high. In addition, L.P. has features of poor prognosis including positive rheumatoid factor and bony erosions by radiography. She lives in a rural area that is a significant distance from the city where her clinic appointments are located. Her laboratory data include BUN 23 mg/dL, SCr 1.4 mg/dL, glucose 148 mg/dL, potassium 5.0 mmol/L, and sodium 139 mmol/L.

3. Which one of the following is the best initial therapy for L.P.?
   A. Anakinra 100 mg subcutaneously daily plus methotrexate 7.5 mg orally weekly.
   B. Adalimumab 40 mg subcutaneously every other week plus methotrexate 7.5 mg orally weekly.
   C. Leflunomide 20 mg orally daily.
   D. Methotrexate 7.5 mg orally weekly.

4. Which one of the following is most likely to pose medication administration challenges for L.P.?
   A. Abatacept.
   B. Certolizumab.
   C. Infliximab.
   D. Tofacitinib.

5. L.P. refuses an injectable medication. Which one of the following is best to recommend for L.P.?
   A. Hydroxychloroquine 200 mg twice a day.
   B. Leflunomide 100 mg for 3 days. Then 20 mg daily plus sulfasalazine 500 mg three times a day.
   C. Methotrexate 7.5 mg weekly plus sulfasalazine 500 mg twice daily.
   D. Tofacitinib 5 mg twice daily.

6. A 23-year-old woman presents to the clinic to initiate biologic therapy for RA. She was vaccinated with the inactivated influenza, recombinant pneumococcal, and human papillomavirus vaccines 2 weeks ago. Which one of the following is best to recommend for this patient?
   A. Start biologic therapy immediately.
   B. Start biologic therapy in 2 weeks.
   C. Start biologic therapy in 4 weeks.
   D. Do not start biologic therapy.

7. A patient was given a diagnosis of RA 3 years ago. Her medical history includes hypothyroidism. Initially, therapy with methotrexate plus sulfasalazine adequately controlled her RA symptoms. However, she has recently experienced an increase in tender and swollen proximal joints of the hands. Today, at the follow-up appointment, a change in therapy is being considered. Which one of the following is best to recommend for this patient?
   A. Anakinra 100 mg subcutaneously daily.
   B. Etanercept 50 mg subcutaneously weekly.
   C. Golimumab 50 mg subcutaneously weekly.
   D. Rituximab 1000 mg intravenous days 1 and 15 plus methotrexate 7.5 mg orally every week.
8. A 32-year-old woman has a new diagnosis of RA. She is planning to become pregnant in the next year and questions whether RA will affect her chances of becoming pregnant. Her medical history includes type 2 diabetes mellitus. Which one of the following is best to recommend for this patient?
A. Adalimumab 40 mg subcutaneously every other week.
B. Golimumab 50 mg subcutaneously every week.
C. Leflunomide 20 mg orally daily.
D. Methotrexate 7.5 mg orally every week.

9. A 56-year-old man (height 70 inches, weight 98 kg) has had RA for 5 years. He is currently taking disease-modifying antirheumatic drug (DMARD) combination therapy with methotrexate 15 mg orally every week plus hydroxychloroquine 400 mg orally daily. In the past year, his disease activity has progressed to moderate despite the combination therapy. His current laboratory values include BUN 22 mg/dL, SCr 2.2 mg/dL, glucose 190 mg/dL, potassium 4.8 mEq/L, and sodium 136 mEq/L. Which one of the following is best to recommend for this patient?
A. Switch to methotrexate intramuscularly and continue hydroxychloroquine.
B. Switch to tocilizumab 4 mg/kg intravenously monthly plus methotrexate 7.5 mg orally daily.
C. Switch to tofacitinib 5 mg orally daily.
D. Switch to etanercept 50 mg subcutaneously weekly.

10. Which one of the following education points is most appropriate for a patient taking tofacitinib for RA?
A. Increased risk of infection while taking the medication.
B. Monitoring for medication-induced myalgia.
C. Need for frequent blood glucose testing.
D. Tofacitinib not to be taken in combination with simvastatin.

Questions 11–13 pertain to the following case.
L.S. is a 62-year-old woman who presents with uncontrolled RA and complaints of fatigue and weight loss. Her rheumatologist would like to convert her therapy from oral methotrexate to etanercept. L.S. has the following vaccination history: tetanus/diphtheria/acellular pertussis (TDaP) vaccine, annual inactivated influenza vaccine, Bacille Calmette-Guerin vaccine, and the recombinant pneumococcal vaccine (with one-time revaccination). She is employed in a correctional facility.

11. Which one of the following would be best option to screen for tuberculosis (TB) in L.S.?
A. Tuberculin skin test at baseline.
B. Interferon-gamma-release assay (IGRA) at baseline.
C. Tuberculin skin test at baseline and annually.
D. IGRA at baseline and annually.

12. L.S. was screened for TB infection and the results returned negative. Which one of the following would be the best next step in the treatment of L.S.’s RA?
A. Begin etanercept therapy.
B. Rescreen for TB.
C. Obtain chest radiography.
D. Collect sputum culture for examination.

13. If L.S. were to start etanercept therapy, which one of the following vaccines would be most appropriate to administer during treatment?
A. Hepatitis B vaccine.
B. Human papillomavirus vaccine.
C. Pneumococcal vaccine.
D. Zoster vaccine.

14. In which one of the following patients with RA would it be most appropriate to recommend biologic therapy?
A. A patient with untreated Child-Pugh class A hepatitis B.
B. A patient with treated Child-Pugh class A hepatitis B.
C. A patient with untreated Child-Pugh class B hepatitis B.
D. A patient with treated Child-Pugh class B hepatitis B.

15. A 43-year-old man has a medical history of RA, heart failure, diabetes, and hyperlipidemia. His current laboratory values are as follows: A1C 7.3%, LDL cholesterol 148 mg/dL, TG 445 mg/dL, and an ejection fraction of 48%. Which one of the following biologic agents would be best to treat this patient’s RA in combination with methotrexate?
A. Adalimumab.
B. Etanercept.
C. Rituximab.
D. Tocilizumab.

16. A 43-year-old man has a medical history of RA, testicular cancer (diagnosed 3 years ago, currently in remission), and New York Heart Association (NYHA) class II heart failure. He presents to initiate
his first biologic DMARD. Which one of the following is best to recommend for this patient?

A. Abatacept.
B. Anakinra.
C. Etanercept.
D. Rituximab.

Questions 17 and 18 pertain to the following case.
T.T. is a 54-year-old man (height 70 inches, weight 86 kg) who has moderate RA disease activity and no features of poor prognosis. T.T. has been taking oral methotrexate 25 mg weekly for 2 years. He feels that his RA symptoms are well controlled on his current regimen, but he has heard of newer injectable biologic DMARDs to treat RA and wants to know if he should switch. He is tolerating methotrexate well and denies adverse effects. Although he does not have a history of renal dysfunction, routine laboratory monitoring now shows moderate renal dysfunction. T.T.’s pertinent laboratory values and vital signs include: sodium 140 mEq/L, potassium 4.2 mEq/L, BUN 18 mg/dL, SCr 1.8 mg/dL, and glucose 178 mg/dL.

17. Which of the following would be most advantageous when switching T.T from oral methotrexate to a biologic DMARD?
A. Ease of administration.
B. Slowing joint destruction on radiography.
C. Increased bioavailability.
D. Minimizes risk of reactivation of tuberculosis.

18. Which one of the following is best to recommend for T.T.?
A. Make no change in therapy.
B. Reduce methotrexate to 15 mg orally.
C. Stop methotrexate and initiate etanercept 50 mg subcutaneously weekly.
D. Switch to methotrexate 30 mg intramuscularly weekly.

Questions 19 and 20 pertain to the following case.
A 2006 meta-analysis by Bongartz et al. assessed the risk of malignancy from the anti-TNF agents. Data from the nine randomized controlled trials showed 29 cases of malignancy in patients treated with at least one dose of anti-TNF therapy (n=3493) and three cases of malignancy in the control group (n=1512).

19. Based on the results from the meta-analysis, which one of the following best represents the number needed to harm, for malignancy in patients treated with anti-TNF inhibitors?
A. 120.
B. 159.
C. 196.
D. 380.

20. Based on the results from the meta-analysis, which one of the following best represents the odds ratio for developing malignancy from therapy with an anti-TNF agent?
A. 2.3.
B. 4.2.
C. 6.4.
D. 9.6.
Learning Objectives

1. Distinguish the probable etiology for a patient with osteoarthritis (OA).
2. For a given patient, classify OA according to the criteria of the hands, hip, or knee.
3. Evaluate the role of evidence-based therapeutic approaches to OA.
4. Design an effective treatment plan, including goals of therapy, nonpharmacologic and pharmacologic therapy, and a monitoring plan, for a patient with OA.

Introduction

Osteoarthritis (OA) is a common type of arthritis known to affect weight-bearing and other moveable joints. In the United States, an estimated 27 million people (12.1%) older than 25 years have clinical OA, as defined by symptoms and physical examination findings. The prevalence of OA may have increased in recent years because of obesity rates and an aging patient population (Lawrence 2008). Osteoarthritis is the leading cause of disability in American adults, often resulting in a diminished health-related quality of life (HRQOL) and increased use of health care resources. Worldwide estimates of OA burden vary with the definition of the condition. For individuals older than 60 years, OA affects an estimated 9.8% of men and 18% of women worldwide (Woolf 2003). In the 2010 Global Burden of Disease Study, musculoskeletal disorders accounted for 6.8% of disability-adjusted life-years (Murray 2012). Osteoarthritis was 10% of this total and was common in all populations. It is estimated that OA has a medical cost of $128 billion per year (Arthritis Foundation 2013).

Baseline Knowledge Statements

Readers of this chapter are presumed to be familiar with the following:
- Basic anatomy and physiology of joints and their structural components
- Role of bone, articular cartilage, and synovium in joints
- Basic pathophysiology of OA
- General understanding of the clinical presentation for OA
- Understanding of potential complications from OA
- Selectivity of nonsteroidal anti-inflammatory drugs (NSAIDs)

Additional Readings

The following free resources are available for readers wishing additional background information on this topic.
- American Academy of Orthopaedic Surgeons (AAOS). Treatment of Osteoarthritis of the Knee. Evidence-Based Guidelines, 2nd ed. [homepage on the Internet].
guidelines for OA of the hand by the American College of Rheumatology (ACR) in 2012. In 2013, the American Academy of Orthopaedic Surgeons (AAOS) released the second edition of guidance on the treatment of knee OA. This chapter focuses on treatment recommendations from the current guidelines and the role of various agents in the management of OA.

**Etiology**

Osteoarthritis is not an inherent part of the normal aging process but a multifactorial condition for which increasing age is a major risk factor. In particular, age greater than 50 years is a strong risk factor for developing OA, and above this age the incidence of OA rises precipitously (Murphy 2008). Obesity is another risk factor, particularly for OA of the weight-bearing joints (i.e., knee). The prevalence of knee OA is 30.6% among those individuals with a normal body mass index (BMI), with increased prevalence among individuals who are overweight (46.9%) or obese (60.5%) (Pereira 2009).

The link between exercise and the development of OA remains somewhat controversial; mechanical loading has been empirically linked with a greater prevalence of knee OA in the elderly. However, exercise can reduce the risk of OA in the absence of injury to the knee (Hunter 2009). Occupational habits (e.g., heavy lifting), physical stress to the hip, and major injuries have been identified as risk factors for OA of the hip (Juhakoski 2009). In most cases, several factors converge to cause joint degradation over time. Other individuals may develop OA as the result of a congenital or developmental condition such as acromegaly or calcium crystal deposition in the tissue.

**Pathophysiology**

Several factors imbalance the degradation and synthesis of cartilage, leading to damage of the bone and synovium (Samuels 2008). These factors include genetic, metabolic, biochemical, and biomechanical influences on the joint. No single factor is the direct cause of abnormalities with chondrocytes. A person with greater vulnerability to joint degradation from systemic or local factors is more likely to develop OA with minimal joint impact forces. In contrast, other individuals with minimal vulnerability to joint degradation are more likely to need much greater joint impact forces to begin developing OA.

Osteoarthritis can be classified as primary (i.e., idiopathic) or secondary depending on the absence or presence of identifiable causes, respectively. Primary OA has two subclasses: (1) localized, involving one or two joints; and (2) generalized, involving three or more joints. Secondary
OA is less common and is the result of an identifiable cause such as joint trauma or metabolic, congenital, or developmental disorder. A patient with secondary OA may have an atypical presentation, particularly as it pertains to age at symptom onset. Table 2-1 summarizes the classification criteria of OA of the hip, knee, and hands.

**Diagnosis and Prognosis**

The diagnosis of OA includes a review of the patient’s medical history and a comprehensive physical examination to distinguish OA from conditions such as rheumatoid arthritis, gout, or septic arthritis. A thorough history of clinical features should be obtained, including the type, duration, frequency, and intensity of pain. Stiffness and joint swelling should also be assessed. Risk factors and potential causes of the patient’s symptoms should be identified.

The pharmacist can assist in obtaining a medication history regarding the use of any over-the-counter (OTC) agents or complementary/alternative agents, together with a prescription drug history, history of allergies, medication-associated adverse events, and potential drug-drug interactions. Joint abnormalities may be absent early in the disease process, but joint deformity or misalignment may be visible in severe cases. In patients with knee or hip OA, gait should be observed to determine the need for referrals to physical and/or occupational therapy. Activities of daily living should be assessed to determine the need for joint protection techniques, assistive devices, or splints. Box 2-2 lists suggested questions for interviewing the patient with OA.

Laboratory tests generally are not useful in confirming a diagnosis of OA. Erythrocyte sedimentation rate and rheumatoid factor may be obtained to distinguish OA from rheumatoid arthritis; results of the former test may be normal or slightly elevated, whereas the latter test may be undetectable in OA. An elevated WBC may aid in identifying infectious etiologies of osteoarthritic symptoms (e.g., septic arthritis). However, a normal WBC does not necessarily rule out joint sepsis, and a subsequent synovial fluid analysis may be necessary. For OA, such tests should show clear synovial fluid with normal viscosity and a WBC of less than 2 x 10^3 cells/mm^3. Joint aspiration of synovial fluid also may be useful to rule out other potential causes such as gout.

Biomarkers for bone turnover in OA have no clearly defined role in clinical practice (Punzi 2005). Radiographic imaging may be indicated for patients with severe OA or suspected secondary OA (i.e., caused by trauma). Radiographic abnormalities include joint space narrowing, osteophytes, and subchondral cysts.

Typically, the prognosis of OA is slowly progressive. As mentioned earlier, OA is the most common cause of disability in the United States. Activities of daily living and other related activity should be assessed to determine the impact of OA on the patient’s HRQOL. Of importance, patients should be screened for psychosocial issues (e.g., anxiety, depression, insomnia) at each visit or as clinically indicated. These psychosocial issues can develop or worsen as the severity of OA worsens (Katon 2007).

### Assessment Scales

Once the diagnosis of OA has been confirmed, several assessment scales can be used to determine symptom severity. The Western Ontario and McMaster Universities Arthritis Index (WOMAC) is often used in clinical trials and has been used to evaluate other conditions related to pain and joint involvement (e.g., rheumatoid arthritis, systemic lupus, fibromyalgia). This scale, which is

<table>
<thead>
<tr>
<th>Box 2-1. Risk Factors, Pathophysiologic Features, and Complications of Osteoarthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk Factors</strong></td>
</tr>
<tr>
<td>Excess weight</td>
</tr>
<tr>
<td>Family history</td>
</tr>
<tr>
<td>Female sex</td>
</tr>
<tr>
<td>Estrogen deficiency</td>
</tr>
<tr>
<td>Joint immobilization</td>
</tr>
<tr>
<td>Joint misalignment</td>
</tr>
<tr>
<td>Joint trauma / injury</td>
</tr>
<tr>
<td>Occupation</td>
</tr>
<tr>
<td>Older age</td>
</tr>
<tr>
<td>Playing sports</td>
</tr>
<tr>
<td><strong>Pathophysiologic Features</strong></td>
</tr>
<tr>
<td>Reduction in proteoglycan synthesis</td>
</tr>
<tr>
<td>Destruction of chondrocytes</td>
</tr>
<tr>
<td>Inflammation of synovium</td>
</tr>
<tr>
<td>Reduction in viscosity of fluid</td>
</tr>
<tr>
<td>Destruction of cartilage</td>
</tr>
<tr>
<td>Growth of bones (i.e., spurs)</td>
</tr>
<tr>
<td>Thickening of capsule</td>
</tr>
<tr>
<td>Angiogenesis</td>
</tr>
<tr>
<td>Activation of nociceptors</td>
</tr>
<tr>
<td><strong>Complications</strong></td>
</tr>
<tr>
<td>Development of clinical features</td>
</tr>
<tr>
<td>Reduction in range of motion</td>
</tr>
<tr>
<td>Decrease in quality of life</td>
</tr>
<tr>
<td>Development of depression</td>
</tr>
<tr>
<td>Rise in medical costs</td>
</tr>
</tbody>
</table>

recommended by the ACR, assesses 5 items for pain, 2 items for stiffness, and 17 items for physical function of hip or knee involvement on a Likert scale or a 100-mm visual analog scale. On the Likert scale version, the maximum score is 68 and is based on the following descriptors: none (0), slight (1), moderate (2), very (3), and extremely (4). On the visual analog scale, a ruler is used to measure the patient’s marker to the left end of the scale; it is based on symptoms – from 0 (no pain/stiffness/difficulty) to 100 (extreme pain/stiffness/difficulty).

Specific HRQOL tools can also be used to evaluate patients with OA. Osteoarthritis-specific HRQOL instruments such as the Arthritis Impact Measurement Scale evaluate mobility, physical activity, dexterity, household activity, social activities, activities of daily living, pain, depression, and anxiety. A second version of the Arthritis Impact Measurement Scale evaluates measures of arm function, social support, and work. This tool was specifically developed to assess physical, social, and emotional well-being from OA on health care outcomes. Short Form 36 is another tool to evaluate a patient’s quality of life over time and with treatment. This tool evaluates eight domains: physical functioning, social functioning, pain, vitality, mental health, general health perception, emotional functioning, and physical role functioning. Each domain is scored from 0 (more disability) to 100 (less disability).

The McGill Pain Questionnaire can be a useful tool for initial evaluation because the patient can rate his or her pain by choosing descriptor words. The Brief Pain Inventory (BPI) can be useful for an ongoing assessment at each follow-up visit because the patient shows on a diagram where he or she experiences pain. In addition, patients can rate the severity of the pain and relief attributable to treatment. The BPI allows a physician to assess the severity and impact of the patient’s pain on daily functions. Patients must have a high reading level to complete the McGill Pain Questionnaire and BPI.

Treatment Goals

Realistic treatment goals should be individualized for each patient. Global goals include resolution of current symptoms, prevention or reduction in disease progression, and maintenance or improvement of functional ability and HRQOL. An example of a patient-specific goal could be the prevention of fatigue and atrophy with an adequate balance of exercise and rest, or weight loss if the patient is overweight or obese. Treatment goals are best accomplished by implementing nonpharmacologic interventions and initiating pharmacologic agents. In advanced or severe cases of OA, surgical treatment may be necessary to restore joint mobility and function.

### Table 2-1. Classification of Osteoarthritis

<table>
<thead>
<tr>
<th>Joint</th>
<th>Criteria</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee</td>
<td>Presence of knee pain PLUS three of the following:</td>
<td>95</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>• Age &gt; 50 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Morning stiffness lasting &lt; 30 minutes</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Crepitus on active motion</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Bony tenderness</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Bony enlargement</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• No palpable warmth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hands</td>
<td>Presence of painful, aching, or stiff hands PLUS three of the following:</td>
<td>94</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td>• Hard tissue enlargement of ≥ 2 of 10 selected joints</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Hard tissue enlargement of ≥ 2 distal interphalangeal joints</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Swelling of &lt; 3 metacarpophalangeal joints</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Deformity of 1 of 10 selected joints</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip</td>
<td>Presence of hip pain PLUS two of the following:</td>
<td>89</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td>• Erythrocyte sedimentation rate &lt; 20 mm/hour</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Radiographic evidence of femoral or acetabular osteophytes</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Joint space narrowing</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TREATMENT GUIDELINES

The 2008 AAOS guidelines for symptomatic knee OA were updated in 2013. The new guidelines incorporate strong, moderate, limited, or consensus recommendations based on the strength of available evidence. The ACR published guidelines in early 2012 using GRADE (Grades of Recommendations, Assessment, Development, and Evaluation) to provide updated recommendations for hip and knee OA, together with new recommendations for hand OA. Table 2-2 and Table 2-3 summarize the ACR nonpharmacologic and pharmacologic recommendations, respectively, for OA of the hands, hip, and knee. Health care professionals involved in the management of OA should be familiar with guidelines from the AAOS, ACR, and European League Against Rheumatism (EULAR).

In addition to the guidelines, quality measures should be followed in the management of OA. The Physician Quality Reporting System Quality Measures contain two quality measures related to OA in patients older than 21 years. Quality measure No. 109 pertains to the assessment of function and pain; the percentage of patient visits should be evaluated for assessment of function and pain. Quality measure No. 142 pertains to the percentage of patient visits in which use of an OTC NSAID or analgesic agent was assessed.

Nonpharmacologic Interventions

Nonpharmacologic interventions are an integral part of the comprehensive treatment plan. The pharmacist can counseling each patient on the importance of implementing and adhering to individualized nonpharmacologic interventions. The specific interventions depend on the joint involved. The ACR provides more extensive recommendations for nonpharmacologic interventions than does the AAOS (AAOS 2013; Hochberg 2012).

For OA of the hands, limited evidence supports a small to moderate benefit from nonpharmacologic modalities. For OA of the knee and hip, patients should be encouraged to do aerobic and/or resistance exercises, do aquatic exercises, and achieve weight loss, when appropriate. Specific exercises depend on the patient’s preference and ability to do the exercise. Patients should be encouraged to increase exercise intensity, frequency, and duration slowly and as tolerated. Weight-loss goals should be tailored to the individual patient, but 5%–10% is a reasonable minimum goal for most overweight or obese patients. For OA of the knee, assistive devices, patellar taping, tai chi, and thermotherapy may be tried for patients unable to do aerobic, resistance, or aquatic exercises. For OA of the hip, the same nonpharmacologic therapy is recommended, with the exception of tai chi, which has not been adequately studied in patients with this type of OA.

Acupuncture has been associated with functional improvements, but this finding may simply reflect a placebo effect (Manheimer 2007). Manual therapy can include massage, joint manipulation, or chiropractic treatment. According to limited and somewhat conflicting evidence, manual therapy may be modestly more effective than placebo, but not pharmacologic therapy (French 2011). Total joint replacement can vastly improve function in patients with severe OA and may be indicated for refractory pain and substantial disability unrelieved by optimal pharmacologic and nonpharmacologic therapies.

Pharmacologic Therapy

Currently, consensus recommendations are lacking regarding the order for initiating pharmacologic agents for OA. Figure 2-1 provides a treatment algorithm for the pharmacologic agents commonly used in OA. Table

| Box 2-2. Selected Interview Questions for the Patient with Suspected Osteoarthritis |
|--------------------------------|-------------------------------------------------|
| Please describe your pain. Intensity? Morning vs. throughout the day? Duration? Type? | • What medications have you used to alleviate the pain? |
| • What was the dose? Frequency? Timing? | • Did you experience any adverse events with the medication? |
| • Did you have concerns about medications used for osteoarthritis? | • What other medical conditions do you have? How long have you had these conditions? |
| • Does osteoarthritis affect your current conditions? | • Have you ever been injured? |
| • Have you ever been injured? | • What is your occupation? |
| • Are you able to perform your job? | • Because of your symptoms, have you needed to make any adjustments at home or work? |
| • Because of your symptoms, have you needed to make any adjustments at home or work? | • What is your current social history? |
| • How do you complete activities of daily living? | • How well are you able to complete your hobbies? |
| • How do you complete activities of daily living? | • Do you exercise? Does exercise alleviate or worsen your symptoms? |
| • How well are you able to complete your hobbies? | • What type of exercise? Frequency per week? Duration per day? |
| • How do you complete activities of daily living? | Do you have a history of depression? |
| • How has your mood been recently? | • How has your mood been recently? |
| • How have you been sleeping? Do you feel rested in the morning? | • How have you been sleeping? Do you feel rested in the morning? |
| • What was the dose? Frequency? Timing? | What do you know about osteoarthritis? |
| • What was the dose? Frequency? Timing? | • Do you have concerns about osteoarthritis? |
| • What medications have you used to alleviate the pain? | • What are your expectations for treatment? |

Table 2-2. Selected Nonpharmacologic Interventions for Osteoarthritis

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Level of Evidence from AAOS&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Level of Evidence from ACR&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KNEE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aerobic exercise (class-based, home-based)</td>
<td>Strong</td>
<td>Strong</td>
</tr>
<tr>
<td>Assistive devices (walking aids)</td>
<td>None</td>
<td>Conditional</td>
</tr>
<tr>
<td>Land-based exercises (nonaquatic)</td>
<td>Strong</td>
<td>Strong</td>
</tr>
<tr>
<td>Manual therapy and supervised exercise</td>
<td>Inconclusive</td>
<td>Conditional</td>
</tr>
<tr>
<td>Neuromuscular education</td>
<td>Strong</td>
<td>None</td>
</tr>
<tr>
<td>Patellar taping</td>
<td>Inconclusive</td>
<td>Conditional (medially) None (laterally)</td>
</tr>
<tr>
<td>Self-management programs</td>
<td>Strong</td>
<td>Conditional</td>
</tr>
<tr>
<td>Proprioception/strength/resistance training</td>
<td>Strong</td>
<td>Strong</td>
</tr>
<tr>
<td>Tai chi</td>
<td>None</td>
<td>Conditional</td>
</tr>
<tr>
<td>Thermotherapy</td>
<td>None</td>
<td>Conditional</td>
</tr>
<tr>
<td>Water-based exercise (hydrotherapy)</td>
<td>Strong</td>
<td>Strong</td>
</tr>
<tr>
<td>Weight reduction</td>
<td>Moderate</td>
<td>Strong</td>
</tr>
<tr>
<td><strong>HIP</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aerobic exercise (class based, home based)</td>
<td>—</td>
<td>Strong</td>
</tr>
<tr>
<td>Assistive devices (walking aids)</td>
<td>—</td>
<td>Conditional</td>
</tr>
<tr>
<td>Land-based exercises (nonaquatic)</td>
<td>—</td>
<td>Strong</td>
</tr>
<tr>
<td>Manual therapy and supervised exercise</td>
<td>—</td>
<td>Conditional</td>
</tr>
<tr>
<td>Neuromuscular education</td>
<td>—</td>
<td>None</td>
</tr>
<tr>
<td>Self-management programs</td>
<td>—</td>
<td>Conditional</td>
</tr>
<tr>
<td>Proprioception/strength/resistance training</td>
<td>—</td>
<td>Strong</td>
</tr>
<tr>
<td>Tai chi</td>
<td>—</td>
<td>None</td>
</tr>
<tr>
<td>Thermotherapy</td>
<td>—</td>
<td>Conditional</td>
</tr>
<tr>
<td>Water-based exercise (hydrotherapy)</td>
<td>—</td>
<td>Strong</td>
</tr>
<tr>
<td>Weight reduction</td>
<td>—</td>
<td>Strong</td>
</tr>
</tbody>
</table>

<sup>a</sup>The American Academy of Orthopaedic Surgeons does not provide recommendations for nonpharmacologic interventions for osteoarthritis of the hip, nor does this organization recommend a specific order for nonpharmacologic interventions; interventions are encouraged on an individual basis.

<sup>b</sup>The American College of Rheumatology provides recommendations with nonpharmacologic interventions for osteoarthritis of the hands. There are no strong recommendations for this classification; however, there is a small to moderate benefit with assistive aids, thermal modalities, and splints, which are conditional recommendations. There is no specific order for these nonpharmacologic interventions from this organization; interventions are encouraged on an individual basis.

2-4 describes specific dosing and adverse events of pharmacologic agents indicated for OA.

**Topical Agents**

**Topical Salicylate**

According to the ACR guidelines, trolamine can be considered for OA of the hand. However, there are no rigorous trials of this agent in patients with OA, and existing evidence on salicylate use dates from several decades ago. In one trial, trolamine 10% was administered as a single application (Rothacker 1998). The sum of pain and stiffness intensity was evaluated at baseline and at 30, 45, and 120 minutes after the application. Compared with placebo, trolamine salicylate was more effective in reducing the intensity of pain (p=0.0492) and stiffness (p=0.0283). In general, topical salicylate may modestly improve the pain of superficial joints in patients with OA. However, few patients will receive adequate symptom control from these agents alone; thus, topical salicylate is typically considered an adjunctive therapy. The product’s effectiveness should be assessed at each visit. If symptom relief is inadequate, additional pharmacologic management should be initiated.

**Topical Capsaicin**

Derived from chili peppers, topical capsaicin has modest analgesic efficacy. Capsaicin can be initiated at a low dose and titrated according to patient response and tolerability; at least 1 month of regular use typically is required to deplete substance P and alleviate pain for effectiveness. In several trials, capsaicin 0.015%, 0.025%, or 0.075% administered once or four times daily has been more effective than placebo in improving pain over 4–12 weeks (Gemmell 2003; McCleane 2000; Altman 1994; McCarthy 1992; Deal 1991). In clinical practice, this agent is typically reserved as an adjunct to more effective therapies. Unfortunately, comparative data are lacking between topical capsaicin and other topical or systemic agents. The EULAR recommends topical capsaicin as a safe and effective option, but this suggestion is based on only one randomized trial (Jordan 2003). The ACR does not recommend topical capsaicin for osteoarthritis of the hips and knee (Hochberg 2012). Finally, capsaicin has a high discontinuation rate because of adverse events (e.g., redness and burning sensations) and frequent daily dosing.

**Topical Nonsteroidal Anti-inflammatory Drugs**

Topical nonsteroidal anti-inflammatory drugs (NSAIDs) may be useful for acute or chronic pain associated with OA of superficial joints and are an alternative to oral NSAIDs for patients at high risk of gastrointestinal (GI), cardiovascular (CV), or nephrotoxic adverse events. In 2007, diclofenac gel and solution received a U.S. Food and Drug Administration (FDA)-approved indication for OA; the diclofenac patch does not have the same indication. Guidelines for topical NSAIDs vary greatly by publication date. The EULAR guidelines recommend topical NSAIDs for OA of the knee. For OA of the hand, EULAR prefers topical NSAIDs to systemic agents, especially if the pain is mild to moderate and few joints are affected.

---

**Table 2-3. Pharmacologic Recommendations by the American College of Rheumatology**

<table>
<thead>
<tr>
<th>Pharmacologic Option</th>
<th>OA of the Hands</th>
<th>OA of the Hip</th>
<th>OA of the Knee</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical capsaicin</td>
<td>Y</td>
<td>-</td>
<td>N</td>
</tr>
<tr>
<td>Topical NSAIDs</td>
<td>Y</td>
<td>-</td>
<td>Y</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>-</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Oral NSAIDs</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Intra-articular corticosteroids</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Intra-articular hyaluronic acid</td>
<td>N</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tramadol</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Opioid analgesics</td>
<td>N</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Glucosamine and chondroitin</td>
<td>-</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>

*The ACR does not provide guidance on the order in which agents are used in clinical practice. (-) = no recommendation provided; N = not recommended; and Y = recommended for the joint involvement; OA = osteoarthritis.
Excellence recommends topical NSAIDs as first-line therapy for localized OA regardless of the risk of GI and/or CV adverse events. Topical NSAIDs also can be an alternative for patients with chronic kidney disease or at risk of nephrotoxic adverse events. Lastly, topical NSAIDs can be adjunctive therapy if full-dose acetaminophen is partly effective relieving pain (Conaghan 2008). The ACR recommends topical NSAIDs for OA of the hand or knee if the patient: (1) has had inadequate response to an OTC product with intermittent dosing, (2) has inadequate pain control with full-dose oral acetaminophen, or (3) is older than 75 years and requires an alternative to oral NSAIDs. The last recommendation is consistent with the American Geriatrics Society recommendations for persistent pain in older patients (AGS 2009). Topical NSAIDs are generally ineffective for OA of the hip. The latest AAOS guidelines strongly encourage the use of topical NSAIDs for symptomatic OA of the knee because of their safety and efficacy data (AAOS 2013).

In a recent meta-analysis of 34 published trials, topical NSAIDs were effective for musculoskeletal pain, including OA of the knee and hands. Most of the trials used the gel and solution formulation (Derry 2012). In 23 trials, topical NSAIDs were more effective than placebo in outcomes such as pain. In 11 trials that compared oral NSAIDs with topical gel and solutions, no difference was found; as expected, topical NSAIDs caused more local reactions but fewer GI adverse events. The evidence suggests that 1 of 6 patients treated with the topical solution and 1 of 11 patients treated with the topical gel will experience a 50% reduction in pain after 8–12 weeks of treatment. Overall, topical NSAIDs are one of the first-line options because of their efficacy. In addition, these agents have a better safety profile because of minimal systemic absorption. However, the cost of the gel and solution may limit their use for some patients.

Lidocaine Patches
Lidocaine blocks nerve impulses by decreasing the permeability to sodium ions at the neuronal membrane. Although lidocaine patches are not currently recommended in any OA guideline, they have been studied as a treatment option for knee OA.

In an open-label parallel-group trial, 100 patients with moderate to severe OA of the knee were administered up to four lidocaine 5% patches as adjunctive therapy (with NSAIDs, acetaminophen, celecoxib, or opioids), or as monotherapy in patients not previously on stable analgesic agents, for 2 weeks (Gammaitoni 2004). Lidocaine patches significantly reduced all four Neuropathic Pain Scales as monotherapy and adjunctive therapy (p<0.001). In another prospective open-label trial, 137 patients were treated with lidocaine 5% patches for 4 weeks, resulting in improved WOMAC scores (p<0.001) (Burch 2004). From baseline to study end, improvements were seen in the pain (36.5%), stiffness (39.6%), function (33.4%), and composite scores (34.6%). This trial concluded that lidocaine 5% patches applied every 24 hours were an adjunctive option to systemic agents.

In a more recent randomized, open-label, parallel study, 12 weeks of therapy with lidocaine 5% patches showed no difference in WOMAC or BPI scores with celecoxib 200 mg once daily in patients with moderate to severe OA of the knee (Kivitz 2008). Of importance, more celecoxib-treated patients than lidocaine-treated patients dropped out because of concern about CV adverse events.

Additional efficacy and safety trials are needed to determine the role of lidocaine 5% patches – probably as adjunctive therapy – in OA of the knee and potentially for hip involvement. This option may be particularly beneficial in patients with neuropathic symptoms. Local site reactions (e.g., irritation, itching) have been associated with the lidocaine patch; these can be lessened if patients cut the patch to better fit the appropriate area and avoid exposing the patch to external heat sources. Because lidocaine does not have an FDA-approved labeling for the treatment of OA, some patients may have difficulty obtaining insurance coverage for this option.

Oral Agents
Oral agents for OA are selected according to preference, tolerability, previous medication trial, and potential adverse events.

Acetaminophen
Acetaminophen is a first-line agent and a potential long-term treatment for mild to moderate pain; however, it may not fully relieve the pain of severe OA. Acetaminophen is strongly recommended for the management of OA in all current guidelines except in the AAOS guidelines, which do not recommend for or against acetaminophen.

A meta-analysis of 15 randomized trials comparing acetaminophen with placebo or oral NSAIDs in around 6000 patients with OA of either the knee or the hip found that, compared with placebo, acetaminophen was more effective and had a similar safety profile (Towheed 2006). However, the authors noted inadequate randomization within these placebo-controlled trials. It is also difficult to determine the clinical significance of acetaminophen’s efficacy because it reduced pain by only 5%, on average, from baseline. Compared with oral NSAIDs, acetaminophen was less effective at reducing pain or improving functional status. However, acetaminophen was associated with fewer GI adverse events than NSAIDs (13% vs. 19%). Similar evidence has been reported in other meta-analyses and systematic reviews (Wegman 2004; Zhang 2004).

Acetaminophen has traditionally been considered a first-line option because of its relative safety profile compared with other oral analgesic agents. Reports of
acetaminophen-induced hepatotoxicity have increased in recent years, generating concern among prescribers and patients. Acetaminophen requires no laboratory monitoring; however, patients should be counseled not to exceed the recommended total daily dose from all sources including OTC combinations. Severe hepatotoxicity has been reported in patients taking more than 4 g/day with or without alcohol consumption. Because of concerns about overdoses and liver failure, the FDA required labeling to include risk of hepatotoxicity, but only requested manufacturers to limit the acetaminophen strength to 325 mg per tablet in combination products (FDA 2011).
Nonsteroidal Anti-inflammatory Drugs

Oral NSAIDs are recommended as initial therapy, particularly in more moderate to severe cases or as an alternative after unsatisfactory response to acetaminophen monotherapy. No data support the efficacy of one NSAID over another. Of importance, efficacy is similar between nonselective and selective NSAIDs. The potential for adverse events among NSAIDs may vary with selectivity for the cyclooxygenase (COX) enzymes; those with COX-2 selectivity can have a lower risk of minor and major GI events than nonselective NSAIDs. However, gastroprotection may persist for 6 months with a selective NSAID, and aspirin could diminish the GI advantages of these agents (Lanza 2009). Although oral NSAIDs are one of the recommended initial agents for OA, the patient’s previous medication use, cost, medical conditions, current medications, and risk of adverse events should be considered. Individual patient responses can vary with different NSAIDs; thus, if a patient does not respond adequately to one NSAID, another may be tried. An adequate trial of any NSAID is 2–4 weeks at the maximal dose. If the patient has a partial response, using adjunctive therapy or changing to a different NSAID is appropriate.

Of importance, patient-related factors should be considered before initiating an oral NSAID. In particular, assessment of GI and CV risks is important in determining the need for a nonselective NSAID versus the COX-2–selective agent celecoxib (Figure 2-2). If an oral NSAID is used long term, concomitant gastroprotection, usually with a proton pump inhibitor (PPI) or alternatively with misoprostol, can reduce the risk of upper GI events. Histamine-2 receptor antagonists are not usually recommended in this setting.

In the CONDOR trial (Celecoxib versus Omeprazole and Diclofenac in Patients with Osteoarthritis and Rheumatoid Arthritis), patients at high GI risk who were treated with diclofenac 75 mg twice daily plus omeprazole 20 mg once daily had a higher incidence of clinically important GI events than those treated with celecoxib 200 mg once daily (3.8% vs. 0.9%, respectively; hazard ratio 4.3; 95% confidence interval, 2.6–7.0, p<0.001) (Chan 2010). These results suggest that monotherapy with celecoxib is associated with a lower risk of GI events than a nonselective NSAID plus a gastroprotective agent in patients with significant baseline risk factors for GI events. Misoprostol’s efficacy in preventing ulceration and bleeding is similar to that of PPIs, but it requires four daily doses and is thus more cumbersome to use. Combination products with an NSAID and gastroprotective agent can lower the pill burden, but none are available in generic form.

For patients needing aspirin for cardioprotection, the least ulcerogenic NSAID can be used at the lowest effective dose with a PPI (Lanza 2009). In these patients at high CV risk, NSAIDs should be avoided when possible; for patients requiring NSAID therapy, the agent of choice is usually naproxen because most data suggest it carries less CV risk than other NSAIDs (Lanza 2009). If the patient has no concurrent disease states (e.g., cardiovascular disease, chronic kidney disease, previous ulcer) and is taking no concurrent drugs (e.g., anticoagulants, antiplatelets), any oral NSAID can be used for the management of OA.

Adverse events associated with oral NSAID use include peripheral edema, elevated blood pressure, weight gain, hypersensitivity, and renal insufficiency. There is also a high likelihood of drug-drug interactions between NSAIDs and other agents (e.g., antiplatelets, anticoagulants, angiotensin-converting enzyme inhibitors, thiazide diuretics). Of particular concern is the increased risk of acute kidney injury when NSAIDs are combined with diuretics and angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (Lapi 2013). If the patient is at high risk of GI events and is receiving NSAID therapy, fecal occult blood screening should be completed annually. Before initiating pharmacologic therapy, baseline tests should include SCR, complete blood cell count, and ALT. These tests should be repeated every year or more often depending on the patient’s comorbid conditions or concomitant drugs.

Tramadol

Tramadol, a partial µ-opioid agonist and serotonin-norepinephrine reuptake inhibitor, plays a role in the management of OA similar to that of other opioid analgesics. Therefore, it is recommended as an alternative – either as monotherapy or in combination therapy – for analgesic relief for those who have contraindications to other oral agents or respond insufficiently to acetaminophen and NSAID therapy. The AAOS guidelines recommend tramadol in a role similar to NSAIDs for symptomatic knee OA. However, potential drug-drug interactions exist with serotonergic agents. Specifically, tramadol should be used cautiously in patients taking other serotonergic agents (e.g., selective serotonin reuptake inhibitors, triptans, selective norepinephrine reuptake inhibitors, monoamine oxidase inhibitors). The tramadol dose should be adjusted for patients with renal impairment: for CrCl less than 30 mL/minute, the immediate-release dose is 50–100 mg every 12 hours and the extended-release formulation cannot be used. Caution is required if the patient has a history of seizures. Table 2-4 describes specific dosing of tramadol and other agents indicated for OA.

Opioids

Opioids are typically a third-line option in patients who have had an inadequate response to NSAIDs and acetaminophen combined with appropriate nonpharmacologic therapy. The EULAR states opioids are an option if NSAIDs are contraindicated, ineffective, or poorly tolerated (Jordan 2003). However, the ACR recommends opioids for patients whose response to combined nonpharmacologic and pharmacologic therapy has been less than optimal or as
an alternative option for patients who do not want surgical intervention (Hochberg 2012).

Each patient should be evaluated for potential abuse and addiction before opioids are initiated. A drug contract should be issued and signed by the patient. Treatment expectations and risk must be clearly discussed with the patient, particularly with this class of drugs.

Current data most strongly support the use of oxycodone in patients with OA; other strong opioids may be equally effective in this setting, but comparative trials are lacking (de Leon-Casasola 2013; Nüesch 2009). If prescribed, opioid therapy should be initiated at a low dose and titrated according to response. Each patient should be monitored frequently for adverse events. These agents should be used cautiously in elderly patients because of an increased risk of sedation, falls, and altered mental status, particularly in patients with OA of the weight-bearing joints who may already have stability issues. Opioids should be avoided or used cautiously in patients with respiratory disorders because of the risk of respiratory depression. Patients should be educated on preventing and managing nausea, drowsiness, and constipation. If the patient has severe OA, a combination of short- and long-acting opioids may be considered, with the short-acting agent used for breakthrough pain as needed. If one opioid does not provide a sufficient response in 2–4 weeks, another opioid can be tried.

**Duloxetine**

Duloxetine is a serotonin-norepinephrine reuptake inhibitor and is indicated for major depression, neuropathic pain, fibromyalgia, generalized anxiety disorder, and, as of 2010, chronic musculoskeletal pain caused by chronic OA or lower back pain. The ACR conditionally recommends duloxetine use for knee OA in patients older than 75 years (Hochberg 2012).

Evidence from three randomized trials suggests that duloxetine significantly reduces pain and improves function in patients with OA of the knee. In one trial, 231 patients with OA of the knee were randomly assigned to duloxetine 60–120 mg once daily or matching placebo for 13 weeks (Chappell 2009). About 75% of patients completed the study. More patients in the duloxetine group achieved 30% or more pain reduction (59.3% vs. 44.5%; p=0.003) and 50% or more pain reduction (47.2% vs. 29.4%; p=0.0006). Duloxetine treatment was also associated with reductions in mean weekly pain scores from baseline to end of the study (13 weeks; p=0.006). Adverse event–related treatment discontinuation was higher in the duloxetine group than with placebo (13.5% vs. 5.8%; p=0.07).

A second trial compared duloxetine 60–120 mg once daily with placebo; 256 patients were enrolled using inclusion and exclusion criteria similar to the previous study. More duloxetine-treated patients achieved 30% or greater pain reduction (65.3% vs. 44.1%, p<0.001) and 50% or more pain reduction (42.8% vs. 32.2%; p=0.07) (Chappell 2011).

A higher discontinuation rate because of adverse events was associated with duloxetine (18.8% vs. 5.5%; p=0.002).

In the most recent trial, duloxetine 60 mg once daily was studied in mainly older women with OA of the knee (Abou-Rayaya 2012). In the intention-to-treat analysis, duloxetine, compared with placebo, improved the mean pain score (6.0 vs. 8.4; p=0.05) and function score (24.0 vs. 30.6, p=0.01) at trial’s end. In addition, more patients had an adequate response (defined as a 20% or more reduction in pain or physical function score) in the duloxetine group than the placebo group (48% vs. 9%, p<0.05).

These trials suggest that one of every five to eight patients experiences a 30% reduction in pain scores during a short time. However, one of every 8–12 patients will experience an adverse event warranting therapy discontinuation. Duloxetine can be an effective agent, but it may be best suited for patients with comorbid depression or neuropathic pain, or as a second-line therapy in patients receiving inadequate pain control with, or who are unable to tolerate, other analogesics. However, a limiting factor for duloxetine may be the cost, despite its generic formulation. If a patient cannot afford duloxetine, it is best to switch to a different class of agent for OA. Duloxetine is well absorbed, but food may decrease the extent of absorption. Duloxetine is metabolized through cytochrome P450 (CYP) 1A2 and 2D6 and can be initiated at 30 mg once daily for 1 week and then increased to 60 mg once daily. Doses above 60 mg are associated with a higher incidence of adverse events (e.g., GI, dizziness, somnolence) and are unlikely to confer additional analgesia relative to lower doses, as shown in the clinical trials.

**Injectable Agents**

**Intra-articular Corticosteroids**

The AAOS guidelines recommend intra-articular corticosteroids for short-term relief of knee pain, whereas the ACR suggests using these agents for initial management or alternative therapy if acetaminophen fails to provide an adequate response for OA of the knee or hip (AAOS 2013; Hochberg 2012). The EULAR publication lists intra-articular corticosteroids as an option for OA of the knee if effusions are present (Jordan 2003). Compared with placebo, intra-articular corticosteroids have been shown to reduce WOMAC scores of pain and stiffness and improve WOMAC scores of function for 1–6 weeks (Bellamy 2006b). In a more recent trial, 79 participants were randomized to either triamcinolone 40 mg or normal saline injection for OA of the knee. After 4 weeks, triamcinolone, compared with placebo, improved the mean WOMAC pain score (-2.1 vs. -0.1; p=0.001), the WOMAC composite score (-8.7 vs. 1; p=0.001), and the visual analog scale score (-1.1 vs. 0.1; p=0.03) (Chao 2010).

Intra-articular corticosteroids can be combined with other systemic agents, but they are often reserved as second- or third-line options before a surgical consultation. The number of injections should be limited to three or
<table>
<thead>
<tr>
<th>Medication/Specific Agents</th>
<th>Typical Dosing</th>
<th>Common Adverse Events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Topical Agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capsaicin</td>
<td>0.025%–0.1% QID</td>
<td>Erythema, pain, burning sensation</td>
<td>Monotherapy or in combination with oral analgesics (not for OA of the knee or hip)</td>
</tr>
<tr>
<td>Diclofenac gel (1%)</td>
<td>2–4 g applied QID (maximal dose = 32 g/day) [16 g for a single joint of lower extremities] [8 g for a single joint of upper extremities]</td>
<td>Local irritation, pruritus, rash, contact dermatitis, dry skin</td>
<td>Monotherapy or in combination with oral analgesics, but may be preferred for a patient &gt; 75 years because of low systemic exposure of 6%</td>
</tr>
<tr>
<td>Diclofenac patch (1%)</td>
<td>Apply twice daily to painful area</td>
<td>Dermatitis, dysgeusia, nausea</td>
<td>Topical treatment of acute musculoskeletal pain (not indicated for OA) and short-term benefit for patients who cannot take oral medications</td>
</tr>
<tr>
<td>Diclofenac topical solution (1.5%)</td>
<td>Apply 40 drops (10 at a time) QID to affected knee</td>
<td>Dry skin</td>
<td>Alternative topical treatment for OA of the knee</td>
</tr>
<tr>
<td><strong>Oral Agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>325–1000 mg PO every 4–6 hours Maximal dose = 4000 mg/day (max 2000 mg/day if patient has liver/renal disease or chronic alcoholism)</td>
<td>Well tolerated, but nephrotoxicity and hepatotoxicity in acute or chronic overdoses</td>
<td>First-line therapy for mild to moderate OA</td>
</tr>
<tr>
<td>Nonselective NSAIDs</td>
<td>Lower doses = analgesic properties (i.e., ibuprofen 200–400 mg QID; naproxen 250–500 mg BID) Higher doses = anti-inflammatory properties (i.e., ibuprofen 400–800 mg TID or QID; naproxen 500–750 mg BID; diclofenac 150-200 mg/day in divided doses, depending on formulation)</td>
<td>Dyspepsia, epigastric pain, constipation</td>
<td>Initiate short-acting agent with around-the-clock dosing Evaluate patient for CVD, GI, and renal risk before initiating and with continuing therapy Maintenance therapy with lowest effective dose</td>
</tr>
<tr>
<td>Celecoxib (COX-2 inhibitor)</td>
<td>200 mg once daily</td>
<td>Peripheral edema, rash, abdominal pain</td>
<td>Reserved for therapeutic failure of acetaminophen and intolerance of nonselective NSAIDs or high risk of developing GI toxicities (i.e., ulceration, bleeding) with nonselective NSAIDs, but has a higher CVD risk compared with nonselective NSAIDs</td>
</tr>
<tr>
<td>Tramadol</td>
<td>50–100 mg PO every 4–6 hours Max dose = 400 mg/day, but 300 mg/day if patient is ≥ 75 years</td>
<td>Dizziness, headache, somnolence, nausea, vomiting</td>
<td>Moderate to severe OA³</td>
</tr>
</tbody>
</table>
four per year per joint to prevent damage to the joint and bone. However, some patients report waning efficacy only a few weeks after injections; thus, these agents are sometimes ineffective for long-term treatment. A pharmacist can educate the patient on the response to expect with an intra-articular corticosteroid and the importance of putting minimal pressure on joint for 1–2 days after the injection. Specific counseling points should include signs of postinjection flare, which are often minor and reversible; if the swelling is extensive or does not resolve 72 hours after injection, aspiration of the joint may be needed. Glucose concentrations can become elevated after corticosteroid injections, though the elevations are predominantly transient and often clinically insignificant. A patient should be directed on an appropriate self-monitoring schedule and methods to manage the 1- to 2-week elevation in glucose levels.

**Viscosupplementation**

Hyaluronic acid acts as a viscous lubricant during low-stress movement and may improve inflammation within the synovium. These injections, which have a long duration, are used for the treatment of osteoarthritis.

---

### Table 2-4. Dosing and Common Adverse Events for Pharmacologic Treatments of OA (continued)

<table>
<thead>
<tr>
<th>Medication/Specific Agents</th>
<th>Typical Dosing</th>
<th>Common Adverse Events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids (i.e., oxycodone)</td>
<td>Depends on the product: short acting for breakthrough pain vs. extended release for chronic pain (i.e., oxycodone 5–15 mg every 4–6 hours PRN or 10 mg every 12 hours)</td>
<td>Somnolence, dizziness, pruritus, constipation, nausea, vomiting</td>
<td>Last-line therapy for moderate to severe OA&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Glucosamine (± chondroitin)</td>
<td>Glucosamine = 1500 mg/day ± chondroitin = 1200 mg/day</td>
<td>Itching, diarrhea, dyspepsia, nausea, vomiting</td>
<td>Alternative option for those with contraindications to or intolerance of preferred therapy, but not recommended for OA of the knee or hip because of the lack of clinically important efficacy</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>30–60 mg once daily</td>
<td>Headache, somnolence, fatigue, nausea, xerostomia</td>
<td>Symptom improvement for chronic pain in patients with OA of the knee</td>
</tr>
<tr>
<td><strong>Injectable Agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intra-articular triamcinolone, methylprednisolone</td>
<td>Varies among agents and size of joint (i.e., methylprednisolone 4–80 mg with limitation of 4 injections per year)</td>
<td>Local site reactions such as redness, swelling, pain, hyperglycemia</td>
<td>Monotherapy for OA of the knees as short-term, palliative relief of painful symptoms if effusions are present or as adjunctive or alternative therapy if systemic therapy is not recommended or has failed</td>
</tr>
<tr>
<td>Intra-articular hyaluronic acid</td>
<td>Varies among agents for a certain therapy duration (i.e., 3–5 consecutive weeks)</td>
<td>Local site reactions such as erythema, tenderness, pain, pruritus</td>
<td>Reserved for patients with moderate to severe OA of the knees whose other therapies have failed; limited evidence of efficacy</td>
</tr>
</tbody>
</table>

<sup>a</sup>Among patients with no response, adverse effects, or contraindications to acetaminophen, NSAIDs, and COX-2 inhibitors. BID = twice daily; OA = osteoarthritis; PO = orally; PRN = as needed; QID = four times daily; TID = three times daily. Information from: Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res 2012;64:465-74.
duration, have been used as an alternative in clinical practice. In the recent AAOS guidelines, viscosupplementation with intra-articular hyaluronic acid is not recommended for patients with symptomatic knee OA because of its lack of efficacy (AAOS 2013). In contrast, the ACR guidelines state that hyaluronic acid may be an option for patients older than 75 years for whom other proven therapies (e.g., topical NSAIDs) have failed (Hochberg 2012).

Studies of hyaluronic acid have varied widely and shown mixed results on efficacy and tolerability. A 2006 Cochrane review evaluated 76 trials with intra-articular hyaluronic acid and found that, compared with NSAIDs in six trials, viscosupplementation was equally effective in patients with OA of the knee. Moreover, compared with intra-articular corticosteroids in 10 trials, viscosupplementation had a benefit on pain, function, and global assessment 5–13 weeks after the injection, with fewer adverse events in patients with OA of the knee (Bellamy 2006a).

After the 2006 Cochrane review – and after publication of the 2012 ACR guidelines – two additional meta-analyses, including one rigorous analysis incorporating several unpublished negative trials, questioned the efficacy and safety of intra-articular hyaluronic acid (Colen 2012; Rutjes 2012). Although a statistically significant benefit in pain and functioning was observed, the effect was generally modest and of questionable clinical significance. Moreover, the most recent meta-analysis suggests that hyaluronic acid is associated with a significantly increased risk of major adverse events. Thus, these agents may not be as benign as previously thought in patients with symptomatic knee OA. In addition, it is difficult to determine the effectiveness of viscosupplementation, partly because of the different products, heterogeneity among clinical trials, and apparent publication bias. Therefore, clinical studies are needed to determine the efficacy and safety of these agents in an identified subgroup of patients and to identify the most efficacious hyaluronic acid product.

Current literature does not support the use of hyaluronic acid for OA of the knee; these agents should be reserved for patients with disease that has not responded to other agents that have been proven effective. A patient should be counseled on the expense of hyaluronic injections, which includes additional physician and administrative costs for each appointment. These agents may be an alternative for patients with symptomatic knee OA that has failed to improve with intra-articular corticosteroid therapy, or for patients with contraindications to systemic agents or intra-articular corticosteroids or who do not wish to undergo surgery.

Dietary Supplements

Glucosamine and Chondroitin

Glucosamine, an amino sugar, and chondroitin, a complex carbohydrate, are both found naturally in healthy joints and have been marketed for decades as dietary supplements for improving joint structure and function. Overall, evidence is conflicting regarding the use and role of glucosamine and/or chondroitin for OA. Although the EULAR guidelines recommend the use of glucosamine in patients with symptomatic OA (Jordan 2003), neither glucosamine nor chondroitin is recommended in the current AOS or ACR guidelines (AAOS 2013; Hochberg 2012).

The landmark GAIT (Glucosamine/Chondroitin Arthritis Intervention Trial) study enrolled around 1500 patients with OA of the knee, with random assignment to one of five arms: placebo, glucosamine alone, chondroitin alone, glucosamine plus chondroitin, or celecoxib (Clegg 2006). Glucosamine, chondroitin, and their combination were no more effective than placebo overall, although the combination of glucosamine and chondroitin did show benefit in an exploratory subgroup analysis of patients with moderate to severe pain according to the WOMAC score.

In a recent meta-analysis, 10 randomized placebo-controlled trials were reviewed to determine whether glucosamine, chondroitin, or the combination had a benefit for OA of the hip or knee (Wandel 2010). A clinically significant pain difference was considered a 9-mm reduction on a 100-mm visual analog scale; no significant difference in scale reduction was found between glucosamine monotherapy (4 mm), chondroitin (3 mm), or the combination (5 mm).

If patients choose to try these products, they should be warned to expect delayed onset of 2–3 months. If symptoms are not improved after 3 months, the supplements should be discontinued. To prevent nausea or GI adverse events, the dose can be divided throughout the day for administration at mealtime.

S-adenosyl-l-methionine

S-adenosyl-l-methionine (SAMe) has been studied for various conditions including OA because this agent is thought to reduce inflammation and restore cartilage synthesis by providing protection from proteolytic enzymes. S-adenosyl-l-methionine has been shown to improve functional limitation compared with placebo (De Silva 2011). One study also suggested that, in patients with OA of the knee, SAMe is as effective as celecoxib at reducing pain, although onset of pain relief is slower (Najm 2004). However, a meta-analysis of four trials of patients with hip or knee OA showed no difference between SAMe and placebo (with a varying treatment period of 3–12 weeks) in patients’ mean pain score, proportion of patients with reduced pain, or function (Rutjes 2009). The meta-analysis noted several limitations in the included trials, most notably inadequate randomization, unblinded methods, and lack of intent-to-treat analysis.

S-adenosyl-l-methionine can cause mild GI adverse events and requires frequent daily dosing. This supplement may also interact with drugs that modulate serotonin levels (e.g., antidepressants, dextromethorphan). No
guidelines recommend or mention the use of SAMe for OA of any joint. Additional rigorous studies showing efficacy are needed before SAMe can be recommended for OA.

**Vitamin D**

Vitamin D is thought to improve the immune system’s ability to protect against bone destruction. In one cohort study, suboptimal vitamin D levels were associated with cartilage loss (Ding 2009). In a recent study, 146 middle-aged patients with symptomatic knee OA were randomly assigned to receive cholecalciferol 2000 units once daily or placebo for 2 years (McAlindon 2013). The cholecalciferol dose could be increased by 2000 units at months 4, 8, and 12 to achieve a target 25-hydroxyvitamin D level of 36–100 ng/mL. After 2 years, there were no statistically significant differences between the groups in WOMAC pain or function score. Patients randomly assigned to receive vitamin D supplementation had a nonsignificant, but higher, average pain score at baseline compared with placebo (6.9 vs. 5.8 on a 20-point Likert scale; p=0.08). In addition, patients who received vitamin D supplementation had a significantly higher average function score (indicating worse functioning) at baseline compared with placebo (22.7 vs. 18.5, respectively, on a 68-point Likert scale; p=0.04). The impact of these apparently spurious differences on study outcomes is unknown.

Additional studies are needed to determine the role of vitamin D in patients with OA, especially regarding whether certain subgroups (e.g., those with low serum vitamin D concentrations) may benefit more from vitamin D supplementation. Related evidence and safety data with dietary supplements and nutraceuticals are available in a review article that focuses on glucosamine, chondroitin, collagen hydrolysates, and avocado-soybean (Ragle 2012).
Emerging Evidence

No disease-modifying agent is currently indicated for the management of OA. However, treatments currently under investigation include growth factor, anakinra, and tanezumab. These are discussed briefly in the following paragraphs and are reviewed elsewhere more extensively (Chevalier 2013; Roubille 2013).

An injection of growth factor has been studied as a regenerative option to stimulate joint repair and thereby improve symptoms and reduce inflammation. In a randomized double-blind trial, 176 patients with symptomatic knee OA received local injections of either plasma rich in growth factor or hyaluronic acid every week for 3 weeks (Sanchez 2012). The primary outcome was a 50% reduction in the WOMAC pain score at 24 weeks. In the intent-to-treat analysis, 38.2% of patients treated with growth factor achieved the primary outcome compared with 24.1% of patients who received hyaluronic acid (p=0.044).

Anakinra is an interleukin-1 (IL-1) antagonist approved for the management of rheumatoid arthritis. Proinflammatory cytokines such as IL-1 are elevated in the synovial fluid of patients with OA of the knee. In a double-blind, randomized, placebo-controlled trial enrolling 170 patients (60% women, 88% white, average age 62.6 years), subcutaneous anakinra 50 mg or 150 mg was compared with placebo. The primary outcome of change in knee symptoms (pain, stiffness, and physical function) using the WOMAC score was assessed 4, 8, and 12 weeks after the anakinra injection (Chevalier 2009). About 94% of subjects completed the study, but no significant difference in the primary outcome was seen between the three groups. Similarly, no significant difference was seen in the occurrence of adverse events.

Nerve growth factors are present in the synovium, causing pain within injured or inflamed tissues. In a phase II trial, 450 patients with moderate to severe pain associated with knee OA were randomly assigned to intra-articular tanezumab, a monoclonal antibody that binds and inhibits nerve growth factor, or placebo administered on days 1 and 56 (Lane 2010). Tanezumab doses given were 10 mcg/kg, 25 mcg/kg, 50 mcg/kg, 100 mcg/kg, or 200 mcg/kg. At week 16, all tanezumab doses significantly lowered pain score from baseline according to a visual analog pain scale (mean relative reduction of 45%–62% for tanezumab vs. 22% for placebo; p<0.001 for each tanezumab dose vs. placebo). There were also statistically significant improvements in the global treatment response score (74%–93% for tanezumab vs. 44% for placebo; p<0.001). The most common adverse events with tanezumab included headache (9%), upper respiratory infection (7%), and paresthesia (7%), which were higher than in the placebo group (2%, 4%, and 1%, respectively). Of importance, acetaminophen and tramadol were considered as “rescue medications” during the trial, but the authors did not report the percentage of patients needing these agents. Similar results were reported in another randomized placebo-controlled trial (Brown 2012).

Although these results are promising, tanezumab has been associated with osteonecrosis and, in some cases, a need for total joint replacement (Balanescu 2013; Brown 2012). Additional studies are needed to determine the role of these and other disease-modifying therapies for OA.

Other Issues

Monitoring

What constitutes an adequate trial varies by agent. For example, an adequate trial of NSAIDs is 2–4 weeks, compared with 4–6 weeks for acetaminophen. Intra-articular corticosteroids can improve symptoms 2–3 days after the injection and last for 4–8 weeks.

A complete response may be validated by an assessment scale; however, a realistic response and goal should be agreed on by the patient and physician before therapy initiation. If a complete response cannot be achieved, the treatment regimen should be modified to an agent or combination to achieve the lowest disease activity with minimal adverse events. There are no specific laboratory tests to determine a response to therapy for a patient with OA. However, baseline and periodic laboratory tests (e.g., liver and kidney function tests) should be obtained to assess the safety of the pharmacologic option (see Table 2-4).

To determine the success of a treatment regimen, pain intensity, type, duration, and timing are assessed (e.g., daytime vs. nighttime, activity related). Pain should be measured using a validated tool (e.g., visual analog scale, WOMAC, BPI). In addition, the patient should be asked about improvement of symptoms and number of affected joints. A physical examination will assess joint range of motion. Additional tests (e.g., grip strength) may be conducted depending on the severity and location of the patient’s OA. Radiographic testing is unlikely to provide information on treatment response or disease progression.

A patient and physician assessment should be completed to determine the global impact of OA on the patient’s life. Activities of daily living and other related activity should be assessed to determine the impact of the OA treatment on the patient’s HRQOL. When possible, family members or caregivers should be queried regarding the effect of OA on the patient. Other screenings (e.g., depression, anxiety, and insomnia) should be performed at each visit or as clinically indicated. Other referrals (e.g., physical therapy, occupational therapy, surgery) may be considered, depending on the severity of disease activity.

Patient Education

Several Web sites offer patient education information on OA to assist patients in learning about the disease. A pharmacist can provide general information about OA, if needed. Both the AAOS and the ACR recommend self-management
programs such as the Arthritis Self-Management Program. Patient-oriented information is available online from the Arthritis Foundation and the ACR.

For patients with OA, realistic goals should be discussed at the visit, especially when initiating a pharmacologic agent, monitoring safety issues, and assessing functional status and pain levels. Relevant information should be provided on the expected effectiveness and time to optimal response of the prescribed treatment regimen. Adverse events and methods to prevent these issues should be addressed with medication initiation. Patients should be educated on reducing the risk of progressive damage on joints. For example, an overweight or obese patient should be encouraged to reduce body weight by at least 5%–10%. Self-management programs improve pain modestly if monthly telephone visits are conducted to review goals and action plans (Allen 2010). In addition, periodic visits or telephone calls for social support can improve pain and functional status without significant cost (Weinberger 1993).

Medication Therapy Management

Clinical trials have not assessed the impact of adding a pharmacist to the osteoarthritic management team. However, as health care evolves, the pharmacist can be an integral member of the health care team and have an expanded role in osteoarthritic management within the patient-centered medical home. Moreover, pharmacists can play an important role in screening or identifying patients with possible OA, providing interventions to ensure adequate prescribing, and educating on the prescribed pharmacologic regimen. Pharmacists can assist with creating a comprehensive medication list to improve patients’ understanding of their regimens. Strategies can be emphasized or developed to help patients understand the importance of adhering to prescribed medications and administering them appropriately (e.g., around-the-clock). All patients should have access to experts in arthritis management or a rheumatologist.

CONCLUSION

Osteoarthritis requires an effective and patient-centered therapeutic plan to improve functional status, reduce OA-associated disabilities, and improve HRQOL. Guidelines have recently been published to guide therapeutic plans for patients with OA, but these guidelines are intended to supplement, not replace, clinical judgment. Individualized nonpharmacologic interventions should be recommended for all patients. Pharmacotherapy is effective in symptom control and improved function in most patients with OA, particularly early in the disease course; however, currently available pharmacologic treatments do not modify disease progression. Patient engagement, together with the involvement of their family members or caregivers when possible, is crucial to achieving optimal outcomes for patients with OA.

Practice Points

- It is important to understand and consider the current guideline recommendations when developing treatment plans for patients with OA of the hip, knee, and/or hands.
- Nonpharmacologic interventions should be individualized and reinforced with each patient. Common recommendations should include self-management programs and weight loss (when appropriate), together with aerobic, aquatic, and/or resistance exercise.
- Several different systemic and topical agents are available for the management of OA to provide a patient-centered therapeutic plan. The guidelines are supplemental information for clinical decision-making with the pharmacologic agents.
- Additional considerations for regimen selection include cost, patient preference, previous therapy response, and comorbid conditions.
- The patient should be informed about expected outcomes and response times with selected agents.
- Patient education is essential in managing OA, together with an emphasis on adherence to nonpharmacologic and pharmacologic interventions.
- Monitoring efficacy and safety outcomes is essential in redesigning therapeutic regimens, if needed.

REFERENCES


Kivitz A, Fairfax M, Sheldon EA, et al. Comparison of the effectiveness and tolerability of lidocaine patch 5% versus celecoxib for osteoarthritis-related knee pain: post hoc analysis of a 12 week, prospective, randomized, active-controlled,


Questions 21–23 pertain to the following case.
P.T. is a 47-year-old man (height 68 inches, weight 104 kg [230 lb]) who presents to the family medicine clinic with the chief concern of right knee pain. His medical history is significant for hypertension and type 2 diabetes mellitus. He was a mechanical engineer for 20 years, walking the plant floor for 8 hours/day, 5 days/week. Recently, he took a senior management position and sits at a desk 6–7 hours/day, 5 days/week. P.T. may drink 2 cans of beer on the weekend while watching football. He walks about 30 minutes every other day and wants to increase the frequency of his walks to 5 days/week. Laboratory values are within normal range, except for hemoglobin A1C 8.9% and SCr 1.8 mg/dL (1.5 mg/dL 6 months ago). Today, his vital signs are as follows: blood pressure 158/92 mm Hg, heart rate 84 beats/minute, temperature 37.2°C (98.9°F), and respiratory rate 18 breaths/minute. On physical examination, crepitus and bony tenderness are noted. His gait is normal. His current drugs are lisinopril 20 mg once daily, aspirin 81 mg once daily, metformin 1000 mg twice daily, and insulin glargine 40 units subcutaneously at bedtime.

21. Which one of the following is most likely to contribute significantly to P.T.’s knee pain?
   A. Age.
   B. Obesity.
   C. Previous occupational activity.
   D. Weekly walking routine.

22. Which one of the following nonpharmacologic interventions would be best as part of a comprehensive plan to alleviate P.T.’s knee pain?
   A. Self-management program.
   B. Assistive devices.
   C. Tai chi exercises.
   D. Acupuncture.

23. Six weeks later, P.T. returns to the family medicine clinic. He has tried a topical diclofenac 1% gel applied to affected knee four times per day but would now prefer another agent because he is still experiencing pain and stiffness. Today, laboratory values are within normal range, except for random glucose level 202 mg/dL and SCr 1.9 mg/dL. His vital signs are as follows: blood pressure 162/90 mm Hg, heart rate 94 beats/minute, temperature 37.2°C (98.9°F), and respiratory rate 19 breaths/minute. Which one of the following is best to recommend for P.T.?
   A. Acetaminophen 1000 mg every 8 hours.
   B. Ibuprofen 800 mg every 8 hours.
   C. Tramadol 100 mg every 6 hours.
   D. Intra-articular triamcinolone 40 mg today.

24. Investigators in an orthopedic office are conducting a randomized controlled trial comparing drug A with placebo for osteoarthritis (OA) of the hip. The primary outcome is a reduction (or improvement) in the Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores for pain, stiffness, and function from baseline to 12 weeks in each group. Which one of the following statistical tests would best assess differences in the primary outcome between the two groups?
   A. Analysis of variance.
   B. Kruskal-Wallis.
   C. Chi-square.
   D. Wilcoxon rank sum test.

25. In a clinical trial, 1786 patients were randomly assigned to drug A or placebo in a 1:1 fashion. The primary outcome was complete response, defined as a 50% or greater reduction in WOMAC pain score after 8 weeks. Of patients receiving drug A, 607 had a complete response. In comparison, 286 patients receiving placebo had a complete response (p<0.001). According to these data, which one of the following best represents the number of patients needed to treat with drug A to have a complete response?
   A. 3
   B. 6
   C. 9
   D. 12

26. A 52-year-old woman presents to the clinic for an annual physical. At today’s visit, she is given a diagnosis of OA of the left knee and right hip with inflammation. She has no significant comorbid conditions except for allergic rhinitis. Her current drugs include a multivitamin by mouth once daily and loratadine 10 mg by mouth once daily. Her primary care provider approaches you for a recommendation. Which one of the following is best to recommend for this patient?
   A. Tramadol.
   B. Oxycodone.
   C. Naproxen.
   D. Duloxetine.
27. A 77-year-old man presents to the clinic with a history of myocardial infarction (2 years ago), seizures (last seizure 5 years ago), and OA. Current drugs include lisinopril 10 mg once daily, metoprolol succinate 50 mg once daily, aspirin 81 mg once daily, and acetaminophen 1000 mg every 8 hours. The physician would like to replace acetaminophen with an NSAID for a short time because the patient is experiencing hip pain and insufficient pain control with acetaminophen. The patient’s primary care provider approaches you for a recommendation. Which one of the following is best to recommend for this patient?
A. Piroxicam.
B. Celecoxib.
C. Ibuprofen.
D. Naproxen plus pantoprazole.

28. A 66-year-old woman presents with hypertension (controlled for 6 months), stage 2 chronic kidney disease (stable for 12 months), atrial fibrillation, and OA of the hip. Her physician prescribes naproxen 250 mg every 12 hours. The physician plans to continue this regimen for 3–6 months to improve the patient’s pain and stiffness. The patient currently takes lisinopril 20 mg once daily, warfarin 5 mg once daily (INR in therapeutic range for five consecutive visits), metoprolol 50 mg once daily, and aspirin 325 mg once daily. Which one of the following adverse events is most concerning in this patient?
A. Elevated blood pressure.
B. GI bleed.
C. Nephrotoxicity.
D. Hepatic dysfunction.

29. A research team is evaluating the efficacy of duloxetine compared with celecoxib using a randomized double-blind study design. The subjects are patients with symptomatic knee OA who are treatment naive for osteoarthritic management. The primary outcome is change in health-related quality of life from drug therapy. Which one of the following tools would provide the most comprehensive assessment?
A. WOMAC.
B. Brief Pain Inventory (BPI).
C. McGill Pain Questionnaire.
D. 36-item Short-Form survey (SF-36).

Questions 30–35 pertain to the following case.
M.Z. is a 71-year-old woman (height 64 inches, weight 56 kg [125 lb]) who presents to the family medicine clinic with the chief concern of left hip pain. The pain has progressively worsened over the past 12 months. She has a medical history of seizures, hypertension, depression, and atrial fibrillation. She has been retired for 6 years as an office worker (“lots of walking and stairs”). M.Z. does not drink alcohol or smoke. She was a marathon runner from her 20s to her 40s, but she slowly decreased her running sessions. About 10 years ago, she dislocated her hip after a fall during a long-distance run. For the past 5 years, she has walked about 30 minutes every other day. Laboratory values are within normal range. Today, the patient’s vital signs are blood pressure 128/72 mm Hg, heart rate 64 beats/minute, temperature 37°C (98.6°F), and respiratory rate 16 breaths/minute. Her current drugs include phenytoin 100 mg three times daily, hydrochlorothiazide 25 mg once daily, metoprolol tartrate 50 mg twice daily, sertraline 50 mg once daily, and warfarin 3 mg once daily. Physical examination reveals crepitus and bony tenderness; radiographic findings include joint space narrowing and osteophytes.

30. Which one of the following is the most likely contributor of M.Z.’s left hip pain?
A. Age.
B. Previous occupation.
C. History of an injury.
D. Obesity.

31. Which one of the following best describes the diagnosis of OA of the hip in M.Z.?
A. Confirmed because she has pain plus two other characteristics.
B. Not confirmed because she needs laboratory tests for confirmation.
C. Confirmed because she has a clear etiology for her pain.
D. Not confirmed because symmetrical involvement is not present.

32. Which one of the following is best to recommend for M.Z.?
A. Ibuprofen.
B. Tramadol.
C. Celecoxib.
D. Oxycodone.

33. M.Z., who does not wish to start a prescription agent at this time, is requesting an OTC supplement. You inform her about inconclusive data with supplements for OA, but she still wants a product to try. Which one of the following is best to recommend for M.Z.?
A. Glucosamine.
B. Chondroitin.
C. Vitamin D.
D. S-adenosyl-L-methionine.
34. Three months later, M.Z. returns to the clinic to have the effectiveness of her regimen assessed. She still has chronic pain in her hip, but now, her right knee also hurts. Which one of the following is best to recommend for M.Z.?

A. Stop the regimen and initiate an intra-articular corticosteroid.
B. Add intra-articular hyaluronic acid injections to the regimen.
C. Stop the regimen and initiate oxycodone immediate release.
D. Stop sertraline and initiate duloxetine at a low daily dose.

35. Ten years later, M.Z. visits the family medicine clinic. Now 81 years of age, she has a 4-year history of severe OA in her knees and hips. She currently walks with the aid of a cane because of the risk of falls. M.Z. is currently receiving intra-articular triamcinolone hexacetonide with adjunctive acetaminophen 1000 mg every 8 hours. Acetaminophen has been given for 6 months. Before today’s visit, she has received three intra-articular injections in the knees during the past 12 months. The patient has inadequate pain control with this regimen and thinks the regimen has not improved her function or quality of life. Which one of the following is best to recommend for M.Z.?

A. Oxycodone controlled-release tablets.
B. Glucosamine in divided doses.
C. Duloxetine titrated to maximal dose.
D. Surgical consultation.

Questions 36 and 37 pertain to the following case.

L.K. is an 83-year-old woman with OA of the hands. She was a full-time secretary for 50 years, but recently, she went to part-time status. She presents to the family medicine clinic with an aching pain in more than 10 joints of her hands. She does not have a significant medical history and does not currently take any medications. L.K. has not been seen by her family physician for 5 years and has had no recent laboratory tests.

36. Which one of the following is best to recommend for L.K.?

A. Celecoxib 200 mg once daily.
B. Duloxetine 60 mg once daily.
C. Acetaminophen 1000 mg every 6 hours.
D. Oxycodone 10 mg twice daily.

37. Topical diclofenac gel 1% was initiated for L.K., but after 3 months it has proved ineffective. Which one of the following would be best to recommend for L.K.’s OA of the hands?

A. Tramadol 50 mg every 6 hours.
B. Diclofenac patch applied twice daily.
C. Naproxen 220 mg every 12 hours.
D. Glucosamine 500 mg three times daily.

Questions 38–40 pertain to the following case.

S.R. is a 67-year-old man who has spent most of his life working on a loading dock. Recently, he had to take a desk job because “the lifting and unloading became too hard for me.” He presents to the family practice clinic with concerns that include knee pain after prolonged standing or walking. On physical examination S.R. has minor limitations in range of motion, with bony tenderness, but no joint effusion or crepitus is noted. He currently takes acetaminophen 1000 mg every 6 hours, which he has taken continuously for 6 months. He also tried glucosamine in the past, but it caused him too much GI distress. He has been experiencing morning stiffness for about 30 minutes. Other than OA, his medical history is unremarkable, and he is taking no other medications.

38. Which one of the following is best to recommend for S.R.?

A. Celecoxib 200 mg once daily.
B. Naproxen 250 mg twice daily.
C. Tramadol 100 mg three times daily.
D. Oxycodone 10 mg every 12 hours.

39. Six months later, S.R. is taking warfarin for an idiopathic episode of deep venous thrombosis. He has another 3 months of warfarin therapy before possible discontinuation. Overall, his current therapy is moderately effective but he would like additional symptom control. Which one of the following is best to recommend for S.R.?

A. Add topical diclofenac gel with multiple daily dosing.
B. Replace the previous agent with indomethacin.
C. Replace the previous agent with intra-articular corticosteroid.
D. Discontinue all previous agents and initiate intra-articular hyaluronic acid.

40. S.R.’s physician would like to use an assessment scale for pain of OA at future follow-up visits. Which one of the following assessment scales is the best tool to use at S.R.’s next visit?

A. WOMAC.
B. BPI.
C. McGill Pain Questionnaire.
D. Arthritis Impact Measurement Scale.
Learning Objectives

1. Classify overweight and obesity and develop patient-specific weight loss goals.
2. Assess the role of endocrine, neurohormonal, and environmental factors on the development of obesity.
3. Analyze a patient profile to identify potential drug induced weight gain and suggest alternatives that are weight neutral or associated with weight loss.
4. Devise a patient-specific treatment plan, including evidence-based comprehensive lifestyle recommendations, for a patient who is overweight or obese.
5. Evaluate the safety and efficacy of drug therapy for the treatment of obesity.
6. Distinguish between the types, expected benefits, and risks of bariatric surgery.
7. Devise a nutritional plan for a patient after bariatric surgery and evaluate the need for changes in the individual’s drug regimen.

Introduction

Classification of overweight and obesity

Overweight and obesity are defined according to body mass index (BMI) (Table 3-1). Body mass index is calculated using weight in kilograms divided by height in meters squared. Online calculators are also available. Overweight and obesity in children and adolescents 2–19 years of age are based on the Centers for Disease Control and Prevention growth charts, which define overweight as a BMI in the 85th–95th percentile and obesity as a BMI in the 95th percentile or greater. The use of BMI to classify overweight and obesity has been criticized because body composition is not considered; therefore, overweight and obesity may be overestimated in patients with more muscle mass and underestimated in patients with decreased muscle mass.

Epidemiology

The combined prevalence of overweight and obesity among U.S. adults is 68.8%, with 35.7% considered...
Overweight and obesity are chronic health conditions that are associated with type 2 diabetes mellitus (T2DM), hypertension, dyslipidemia, stroke, coronary heart disease, obstructive sleep apnea, reproductive complications, gallbladder disease, liver disease, depression, osteoarthritis, incontinence, increased risk of surgical complications, dermatologic complications, and certain types of cancer. Excess visceral (abdominal) fat, as evaluated by waist circumference, is an independent risk factor for comorbidities; elevated waist circumference is currently defined as greater than 102 cm (40 inches) in men and greater than 88 cm (35 inches) in women. The direct medical cost of overweight and obesity combined is estimated to be about 5% to 10% of U.S. health care spending. Compared with healthy weight individuals, the annual per-person direct medical cost of overweight, obesity, and extreme obesity is $266, $1723, and $3012 higher, respectively (Tsai 2011).

A meta-analysis of 97 trials found an increased risk of all-cause mortality for obesity class II and III relative to obesity class I, which was not associated with an increased mortality risk (hazard ratio [HR] 0.95; 95% CI, 0.88–1.01). Overweight was associated with significantly lower all-cause mortality (HR 0.94; 95% CI, 0.91–0.96) (Flegal 2013).

### Pathophysiology

#### Energy Balance

Maintaining a stable weight requires that energy expenditure equals caloric intake. For weight loss to occur, energy expenditure must exceed caloric intake. Although this concept seems straightforward, certain factors challenge both dieters and researchers.

Many people struggle with their weight, despite eating conservatively and being physically active, whereas others seem to be able to eat anything they desire, are no more active, and are able to maintain a healthy weight. Several potential explanations exist for these observations. Although age, sex, height, and weight explain much of the variation in basal energy expenditure, in some individuals it may vary considerably from what is predicted from these values. The “fidget factor” (thermogenesis caused by nonexercise activity) may be a variable for some individuals. This effect can be seen when comparing the energy expenditure of a person who sits quietly most of the day with that of someone who maintains constant movement of the leg while sitting. Standing for longer periods each day as opposed to sitting also expends more calories. However, the magnitude of this factor is hard to predict because of the wide variation among patients. Some patients are able to dissipate large amounts of excess energy intake as heat, whereas others are unable to activate this nonexercise activity thermogenesis and thus store more excess calories as fat. These differences may have an underlying genetic basis.

Controversy exists regarding whether calories from fat and carbohydrates are equal in their ability to promote excess body weight. Some researchers believe the effect of diet composition on weight gain plays only a minor role. Conversely, others believe that low-fat diets are likely to

<table>
<thead>
<tr>
<th>Classification</th>
<th>BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt; 18.5</td>
</tr>
<tr>
<td>Healthy weight</td>
<td>18.5 to &lt; 25</td>
</tr>
<tr>
<td>Overweight</td>
<td>25 to &lt; 30</td>
</tr>
<tr>
<td>Obese class I</td>
<td>30 to &lt; 35</td>
</tr>
<tr>
<td>Obese class II</td>
<td>35 to &lt; 40</td>
</tr>
<tr>
<td>Extreme obesity (Obese class III)</td>
<td>≥ 40</td>
</tr>
</tbody>
</table>

### Abbreviations in This Chapter

- **AGB**: Adjustable gastric banding
- **BPD**: Biliopancreatic diversion
- **BPD-DS**: Biliopancreatic diversion with duodenal switch
- **GLP-1**: Glucagon-like-peptide-1
- **NHANES**: National Health and Nutrition Examination Survey
- **POMC**: Pro-opiomelanocortin
- **RYGB**: Roux-en-Y gastric bypass
- **SG**: Sleeve gastrectomy
- **T2DM**: Type 2 diabetes mellitus

---

Obese (Flegal 2012). Data from 2009–2010 suggest that the rising trends in obesity are slowing, because the overall increase between 2003 and 2008 was not significant. However, when compared with data from 1999 to 2008, there was a significant increase in obesity among men and non-Hispanic African American and Mexican American women.

The prevalence of obesity among U.S. children and adolescents is 16.9%, unchanged since 2007–2008 (Ogden 2012). However, during the past 12 years, a significant increase occurred in obese males aged 2–19 years, and the prevalence of obesity is higher among non-Hispanic African American and Hispanic children and adolescents.
result in weight gain because fat is more satiating than carbohydrate, which could result in overeating by the patient on a low-fat diet. A third contention is that during ketosis, as seen in patients on very low-carbohydrate diets, energy from food is used less efficiently, thereby affecting the degree of weight loss.

Overall, the increasing problem of overweight and obesity is fueled by excessive caloric intake coupled with decreasing physical activity. Data from the National Health and Nutrition Examination Survey (NHANES) indicate that between 1971 and 2010, the average daily energy intake of men increased from 2450 kcal to 2502 kcal and for women from 1542 kcal to 1778 kcal. The highest values, 2615 kcal/day for men and 1828 kcal/day for women, were recorded in 2006. A consistent decrease in percentages of kcal from fat and increase in the percentages of kcal from carbohydrate also occurred during this period (NCHS 2013).

**Appetite Regulation**

Adipose tissue serves several functions including providing thermoregulation, fatty acid storage, and secretion of adipokines. Obesity leads to the dysregulation of these adipokines, including decreased secretion of adiponectin (a protein hormone involved in glucose regulation) and increased secretion of leptin (acts as satiety signal in the brain), resistin (promotes insulin resistance and endothelial dysfunction), retinol-binding protein 4 (contributes to insulin resistance), and inflammatory cytokines from macrophages. These changes are partly responsible for the increased risk of insulin resistance, T2DM, metabolic syndrome, and cardiovascular disease associated with obesity.

<table>
<thead>
<tr>
<th>Table 3-2. Drugs Associated with Weight Gain and Alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drugs Associated with Weight Gain</strong></td>
</tr>
<tr>
<td><strong>Psychiatric Drugs</strong></td>
</tr>
<tr>
<td>Antidepressants: SSRIs, TCAs, MAOIs</td>
</tr>
<tr>
<td>Antipsychotics (particularly clozapine, olanzapine, and risperidone)</td>
</tr>
<tr>
<td><strong>Neurologic Drugs</strong></td>
</tr>
<tr>
<td>Anticonvulsants (valproic acid, gabapentin, carbamazepine)</td>
</tr>
<tr>
<td>Lithium</td>
</tr>
<tr>
<td><strong>Diabetes Drugs</strong></td>
</tr>
<tr>
<td>Insulin, sulfonylureas (particularly glyburide and glipizide), meglitinides, thiazolidinediones</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Antihypertensive drugs</strong></td>
</tr>
<tr>
<td>Non-selective β-blocker (particularly propranolol), α-adrenergic blockers (prazosin, terazosin)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Other drugs</strong></td>
</tr>
<tr>
<td>Hormonal contraception (particularly medroxyprogesterone depot injection)</td>
</tr>
<tr>
<td>Antihistamines</td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; MAOI = monoamine oxidase inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.
Endocrine regulation of weight is accomplished through circulating concentrations of leptin, amylin, glucagon like peptide-1 (GLP-1), cholecystokinin, peptide YY, and ghrelin. Leptin is secreted in response to adipocytes and decreases appetite; however, its effect is decreased in obese patients (termed leptin resistance). Amylin, a pancreatic hormone secreted in response to food intake, results in decreased appetite; however, its effect is decreased in obese patients. Glucagon-like peptide-1 (GLP-1), cholecystokinin, peptide YY, and ghrelin. Leptin is secreted from adipocytes and decreases circulating concentrations of leptin, amylin, glucagon like peptide-1, cholecystokinin, and peptide YY, all secreted from the gastrointestinal tract in response to food intake, to increase satiety. Glucagon-like peptide-1 also delays gastric emptying. Ghrelin is released from the stomach and duodenum before meals and results in increased appetite.

Neurohormonal appetite regulators include serotonin, norepinephrine, and dopamine. These catecholamines stimulate pro-opiomelanocortin (POMC) neurons in the hypothalamus, which release α-melanocortin—stimulating hormone (α-MSH) and β-endorphin. The α-MSH acts on the melanocortin-4 receptors, inducing anorectic properties, and β-endorphin sends feedback inhibition to POMC neurons, decreasing this effect. Mutations in the melanocortin-4 receptor gene have been linked with obesity. Neuropeptide Y, anti-agouti-related protein, and melanocyte-concentrating hormone all increase appetite. The complex physiology underlying weight regulation presents several possible future targets for antiobesity pharmacotherapy.

Caloric restriction and weight loss result in endocrine and neurohormonal changes that favor increased appetite and weight regain to maintain homeostasis. Weight loss can result in significant reductions in leptin, cholecystokinin, amylin, and peptide YY and in increased concentrations of ghrelin. These changes can persist for up to 1 year after initial weight loss, illustrating that the high relapse rate after weight loss likely has a physiologic basis.

Environmental Factors

The rapid increase in the prevalence of obesity in the developing world suggests this epidemic is caused more by environment than by heredity. The two main behaviors affecting body weight (i.e., increased caloric intake and decreased physical activity) have led to increased rates of obesity. Although the percentage of caloric intake supplied as fat in the American diet has decreased during the past several decades, the number of absolute fat grams consumed has likely increased as total calories have increased. Although a trend toward more fruit and vegetable intake has been documented since 1970, french fries and potato chips were counted as vegetable servings. During 2007–2010, American adults consumed, on average, 11.3% of their daily calories in the form of fast food. The highest percentage of consumption occurred in those 20–39 years of age, non-Hispanic African Americans, and those who were already obese (Fryar 2013). Consumption of sugar-sweetened beverages, large restaurant portions, and food advertising have been identified as contributing factors.

The 2011 NHANES data showed that only 21% of those surveyed met both the national recommendations for aerobic activity and muscle strengthening, whereas 47.6% reported meeting neither guideline (NCHS 2013). Television viewing and increased time spent on computers have been linked to overall inactivity. The many hours that children devote to these passive activities is of concern. Many schools have cut physical education programs because of financial constraints or concerns regarding academic quality. These trends in reduced activity levels and food consumption are public health challenges.

Drug-Induced Weight Gain

Drug-induced weight gain may represent a modifiable risk factor for some patients who are overweight or obese. Both the first- and second-generation antipsychotics have been associated with weight gain (Table 3-2). The mechanism by which these agents increase weight may involve dopamine D₁, serotonin-2A, and serotonin-2C and histamine-1 receptors. Although the amount of weight gain varies by agent, clozapine and olanzapine are associated with the largest increases. Changes in weight caused by clozapine vary widely, with reports of weight loss of up to 17.5 kg and weight gain up to 12.9 kg; however, the average change is weight gain of 2.4 kg. Olanzapine is associated with weight gain of up to 9.2 kg. Aripiprazole and ziprasidone are associated with the least amount of weight gain and may be weight neutral for some patients (Malone 2005).

Several antidepressants are also associated with weight gain through their effect on serotonin, histamine-1 receptors, dopamine, and nitric oxide. Tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs), and selective serotonin reuptake inhibitors (SSRIs) have been associated with varying degrees of weight gain, whereas bupropion has been associated with weight loss. Citalopram and paroxetine have been associated with the most weight gain. Extreme weight gain (defined as 7% or more from baseline) occurred in 25.5% of patients taking paroxetine for 26–32 weeks. Citalopram has been associated with weight gain of up to 14.3% from baseline (Malone 2005).

Anticonvulsants can also affect weight. Weight gain has been associated with the use of valproic acid, gabapentin, carbamazepine, and lithium; drugs associated with weight loss include lamotrigine, topiramate, and zonisamide. Valproate is associated with an average 3.7-kg weight gain. The weight gain associated with gabapentin is dose related, with gains of up to 15% with dosages greater than 2000 mg. Weight gain with carbamazepine is variable, with 2%–25% of patients experiencing gain. Long-term lithium use is associated with weight gain of up to 10 kg (Malone 2005).

Antihyperglycemic agents such as insulin therapy, sulfonylureas, meglitinides, and thiazolidinediones are...
also associated with weight gain. Insulin is associated with an average 4-kg weight gain. Among the sulfonylureas, glyburide is associated with the most weight gain (2.6 kg), whereas glimepiride may be weight neutral. Repaglinide and nateglinide are associated with weight gains of 1.8 kg and 0.7 kg, respectively. Exenatide, liraglutide, and pramlintide are associated with weight loss, and the dipeptidyl peptidase type 4 inhibitors (e.g., sitagliptin) are weight neutral.

Agents for hypertension associated with weight gain include nonselective β-blockers and α-blockers. The weight gain associated with β-blockers may be caused

<table>
<thead>
<tr>
<th>Table 3-3. Pharmacotherapy for Obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug</strong></td>
</tr>
<tr>
<td>Orlistat</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Lorcaserin</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Phentermine/topiramate</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
| | | | SBp
by decreased sympathetic nervous system activity and reduced physical activity from fatigue and shortness of breath caused by β-blockers. Propranolol is associated with a 1-kg placebo-subtracted weight gain. Other agents associated with weight gain include first-generation antihistamines; hormonal contraceptives (particularly depot medroxyprogesterone acetate which is associated with weight gain of up 5 kg); and corticosteroids.

**TREATMENT**

**Goals**

Modest, sustained weight loss of 3%–5% has been associated with better health outcomes, including reductions in blood glucose, cholesterol, and blood pressure (Jensen 2013). In patients with T2DM who are overweight or obese, weight loss of 2%–5% lowers A1C by 0.2%–0.3%. Weight loss of 3 kg lowers TG by 15 mg/dL; a 5- to 8-kg loss is associated with reductions in LDL-C of about 5 mg/dL and increases in HDL-C of 2–3 mg/dL. Weight loss of 5% is associated with a reduction in systolic (3 mm Hg) and diastolic (2 mm Hg) blood pressure.

Setting achievable weight-loss goals is essential to sustained weight loss. An appropriate weight-loss goal is 5%–10% from baseline within a 6-month period. Patients should be reevaluated every 6 months to determine whether additional weight loss is appropriate. Prevention of regain is often difficult; as a result, obesity should be treated as a chronic condition.

**Guidelines**

Weight loss is recommended for patients with a BMI of 30 kg/m² or greater and for patients with a BMI of 25–29.9 kg/m² who have cardiovascular risk factors (e.g., T2DM, hypertension, dyslipidemia, elevated waist circumference) or other obesity-related comorbidities (Figure 3-1) (Jensen 2013). Patients who meet these criteria should initiate therapy with comprehensive lifestyle interventions, preferably in consultation with a trained interventionist or nutrition professional.

Patients who do not achieve a 5% weight loss in 6 months who are unable to sustain weight loss with lifestyle interventions alone may be candidates for drug therapy. Pharmacotherapy may be considered as an adjunct to lifestyle modifications for patients who are obese regardless of comorbidities and for individuals with a BMI of 27 kg/m² or greater and with obesity-related comorbidities. Patients who are extremely obese and patients with a BMI of 35 kg/m² or greater and with obesity-related comorbidities are candidates for pharmacotherapy or surgical intervention, if weight loss cannot be achieved with comprehensive lifestyle interventions.

**Comprehensive Lifestyle Interventions**

The patient who is overweight or obese and trying to lose weight should participate in a comprehensive lifestyle program for at least 6 months. This program should assist patients in adhering to lower-calorie diets and increasing physical activity by using behavioral strategies. Programs consisting of all three components (i.e., diet, exercise, behavior therapy) produce average losses of up to 8 kg in 6 months (Jensen 2013).

**Diet**

Successful dietary modification is the most important factor for weight loss. Caloric intake should be reduced by 500–750 kcal/day from the current level to produce a 30% energy deficit. Patients should be provided instructions on how to modify their diets to achieve this goal. Moderate caloric reduction is the goal for most patients, although diets with greater caloric deficits may be used during active weight loss. In general, diets containing 1200–1500 kcal/day are recommended for most women, and diets containing 1500–1800 kcal/day are recommended for most men. Diets containing less than 800 kcal/day should only be used in limited circumstances and only when provided by trained professionals in controlled, supervised settings. Although dietary fat is a rich source of calories, reducing dietary fat without reducing calories will not produce weight loss. Long-term changes in food choices are more likely to be successful when the patient’s preferences are considered and when the patient is educated about food composition, labeling, preparation, and portion size.

Many studies have compared diets that modify the intake of certain macronutrients (e.g., low fat, high fat, low carbohydrate, high protein). Some commercial plans include diets low in carbohydrates/high in protein (Atkins, Zone, South Beach) or very high in carbohydrates/low in fat (Ornish). The Mediterranean diet is a moderate-fat, restricted-calorie diet that is rich in vegetables and low in red meat, with the main source of added fat coming from olive oil or nuts; this diet has been included in several studies.

One trial evaluated low-fat versus high-fat and average-protein versus high-protein diets with varying carbohydrate contents, and another trial compared low-carbohydrate diets with low-fat diets; no difference in weight loss was found (Foster 2010; Sacks 2009). A study comparing the Atkins, Zone, and Ornish diets in premenopausal women found that the Atkins diet resulted in the greater weight loss than the Zone diet after 12 months (4.7 kg vs. 1.6 kg; p<0.05) (Gardner 2007). Another trial found that weight loss after 2 years with the Mediterranean diet (4.4 kg) and a low-carbohydrate diet (4.7 kg) was superior to a low-fat diet (2.9 kg) (p<0.0001) (Shai 2008). A meta-analysis of 20 trials of greater than 6 months compared diets in patients with T2DM. The Mediterranean diet resulted in significantly greater weight loss than the comparator diets (1.84 kg). Low-carbohydrate, low-glycemic index, Mediterranean, and high-protein diets all resulted in significant A1C reductions, with the
Figure 3-1. Treatment algorithm for overweight and obesity.

Once stratified by BMI and comorbidities, selection of therapeutic option (pharmacologic, AGB, or bariatric surgery) depends on patient-specific parameters including other disease states, concomitant drug use, amount of weight loss desired, adverse effects, patient preference, and cost.

Insufficient data to recommend pharmacotherapy to patients with preexisting cardiovascular disease and patients older than 65 years.

AGB = adjustable gastric banding; BID = twice daily; PHEN/TPM = phentermine/topiramate; TID = three times daily; WC = waist circumference.
Mediterranean diet resulting in the greatest reduction (0.47%) (Ajala 2013).

The overall difference in weight loss associated with the previously discussed diets has been small and results have been inconsistent. A consistent finding among the trials is that adherence with dietary programs and physical activity was most associated with weight loss and improvement in disease-related outcomes. Macronutrient content may influence dietary adherence because of differences in the satiating properties of protein, carbohydrate, and fat.

Food preferences, cultural or religious traditions, food availability, and food intolerances should be considered when selecting a diet plan for a specific patient because these factors may affect adherence. Poor adherence leads to weight regain, again emphasizing the chronic nature of overweight and obesity. The best approach is to counsel patients to choose a dietary plan that they find easiest for long-term adherence.

Exercise

Physical activity plays a less important role in initial weight loss than caloric restriction; however, it is useful for preventing weight regain and reduces the risk of heart disease more than weight loss alone. In addition, body fat may be reduced and muscle mass may be maintained by physical activity during weight loss.

All adults should set a long-term goal to achieve at least 150 minutes per week (30 minutes/day) of aerobic physical activity such as brisk walking. This provides an additional 100–200 kcal/day deficit to the calorie restriction. Physical activity should be increased slowly to avoid injury. An exercise regimen that includes resistance training is typically recommended to further improve lean body mass and reduce fat mass and waist circumference. However, the addition of resistance training to aerobic training in a clinical trial did not result in significant changes in these values and required double the time commitment (Willis 2012). Resistance training may be more feasible than aerobic exercise for patients with physical limitations such as cardiovascular disease, arthritis, or other mobility issues. Higher levels of physical activity (e.g., 200–300 minutes/week) are recommended to maintain weight loss or minimize weight regain long term (greater than 1 year). Regardless of its effect on weight, physical activity can improve overall health, increase resting metabolic rate, and result in a negative energy balance and should be encouraged for all patients as appropriate.

Behavior Therapy

Structured behavior change programs that include regular self-monitoring of food intake, physical activity, and weight should be part of all comprehensive lifestyle interventions. Patients should participate in frequent (weekly) group or individual face-to-face counseling sessions with a trained interventionist (registered dietitian, psychologist, exercise specialist, health counselor, or other trained professional) for 6 months. Programs consisting of 14 or more sessions in 6 months are associated with the greatest weight loss (Jensen 2013). Continued counseling for an additional 6 months produces weight losses up to 8 kg at 1 year. Continued bimonthly intervention visits after the first year are associated with slower average weight regain of 1–2 kg/year. Alternatively, comprehensive weight loss interventions including frequent self-monitoring of weight, food intake, physically activity, and personalized feedback from a trained interventionist delivered electronically, can produce weight loss of up to 5 kg at 6–12 months.

Pharmacologic

Short-term therapy

Given that obesity is a chronic condition, short-term therapies are unlikely to be successful in maintaining meaningful weight loss. Agents for short-term use include benzphetamine, phendimetrazine, phentermine, and diethylpropion. The weight loss associated with these agents is not typically sustained, and patients are susceptible to weight regain upon discontinuation. These agents are associated with increased blood pressure and heart rate. Although these agents carry FDA-approved labeling for short-term use (defined as less than 12 weeks), these drugs should not be recommended.

Long-term Therapy

Orlistat

Orlistat 120 mg received a labeled indication for overweight and obesity in 1999, and the over-the-counter 60-mg dose was approved in 2007. Both strengths are dosed three times daily with fat-containing meals. Orlistat reduces the absorption of dietary fat by 30% (120 mg) or 25% (60 mg) by reversibly inhibiting gastric, pancreatic, and carboxyl ester lipase. Orlistat is indicated for long-term use in patients who are overweight or obese when used in conjunction with lifestyle modifications (Table 3-3).

In a meta-analysis that included 16 randomized, placebo-controlled trials (n=10,631) lasting 1–4 years, treatment with orlistat 120 mg reduced body weight by 2.9% more than placebo (95% CI, 2.5%–3.4%); this equaled a 2.9-kg loss (95% CI, 2.5–3.2 kg) (Rucker 2007). Orlistat was associated with significant reductions in waist circumference (2.1 cm), systolic blood pressure (1.5 mm Hg), TC (12 mg/dL), and LDL-C (10 mg/dL) compared with placebo. Patients with T2DM lost 2.6% more weight than placebo (95% CI, 2.1%–3.2%) or 2.3 kg (95% CI, 1.6–3 kg). Significant reductions in A1C (0.4%) and fasting glucose (18 mg/dL) were observed in patients with T2DM. In a 4-year trial, orlistat reduced the incidence of T2DM in high-risk patients from 9% to 6.2% (HR 0.63; 95% CI, 0.46–0.86) (Torgerson 2004).

Gastrointestinal adverse effects are common with orlistat use. Unabsorbed fat, triglycerides, and cholesterol are
excreted in the feces, resulting in loose stool, fecal urgency, oily fecal leakage, flatus with discharge, or fecal incontinence. These adverse effects diminish over time and can be reduced by limiting excessive consumption of dietary fat. Psyllium (12 g mixed with water) has been shown to reduce GI adverse effects (Cavaliere 2001). Orlistat may decrease the absorption of fat-soluble vitamins, requiring patients to take a daily multivitamin. Administration of vitamins should be separated by at least 2 hours from the orlistat dose. Decreased absorption of vitamin K may lead to interactions with warfarin. Orlistat may affect the absorption of lipophilic drugs such as cyclosporine, amiodarone, lamotrigine, and valproic acid. If possible, these combinations should be avoided. If avoidance is not feasible, separating the administration reduces the interaction.

Orlistat is contraindicated in patients with chronic malabsorption syndromes, cholestasis, and pregnancy. Rare cases of oxalate-induced acute kidney injury have been reported with orlistat; this may be secondary to reduced enteric calcium from unabsorbed fat and resultant increased oxalate (Weir 2011). Although reports of hepatic injury, pancreatitis, and GI bleeding have been reported with orlistat use, no causality has been established (Morris 2012).

Lorcaserin

Lorcaserin received a labeled indication in 2012 as an adjunct to lifestyle modifications for chronic weight management. A selective serotonin 2C receptor agonist, the drug promotes satiety through activation of the anorexigenic POMC neurons in the hypothalamus. Lorcaserin is dosed at 10 mg twice daily (see Table 3-3).

Three randomized placebo-controlled phase III trials established the weight-loss effects of lorcaserin. The Behavioral Modification and Lorcaserin for Overweight and Obesity Management (BLOOM) trial included 3182 patients (mean BMI 36.2 kg/m²) and had a duration of 2 years (Smith 2010). The Behavioral Modification and Lorcaserin Second Study for Obesity Management (BLOSSOM) trial included 4008 patients who were overweight and obese and had a duration of 1 year (Fidler 2011). The Behavioral Modification and Lorcaserin for Obesity and Overweight Management in T2DM (BLOSSOM-DM) trial included 604 patients (mean BMI 36 kg/m²) with T2DM (mean A1C 8.1%) treated with metformin, a sulfonylurea, or both and had a duration of 1 year (O’Neil 2012). Key exclusion criteria from these trials included T2DM (except BLOSSOM-DM); age older than 65 years; BMI greater than 45 kg/m²; recent cardiovascular events; history of valvulopathy; major psychiatric disease; and use of SSRIs, serotonin–norepinephrine reuptake inhibitors (SNRIs), insulin, exenatide, or pramlintide.

Patients in the BLOOM trial were randomized 1:1 to receive lorcaserin 10 mg twice daily or placebo for the first year. Half of the patients (n=1553) elected to continue to the second year, during which patients in the placebo group continued with placebo but patients in the lorcaserin group were randomly reassigned to placebo or to continue lorcaserin. After 1 year, patients in the lorcaserin group lost an average (+SE) of 5.81% plus 0.16% of their baseline body weight as compared with 2.16% plus 0.14% in the placebo group. Significantly more patients (47.5%) taking lorcaserin lost at least 5% of their baseline weight versus 20.3% in the placebo group (p<0.001). At least 10% weight loss was achieved by 22.6% of patients in the lorcaserin group versus 7.7% in the placebo group (p<0.001). Patients who continued in the lorcaserin group for both years lost a mean total of 5.56 kg (5.5% of their initial body weight) versus 2.43 kg (2.4%) for patients who continued on placebo. During the second year, all groups gained back some of the weight lost during year 1; patients who remained on placebo for the full 2 years gained back 1 kg compared with patients who remained on lorcaserin, who gained back 2.5 kg. Patients who switched from lorcaserin to placebo gained back 4.8 kg. Reductions were reported in fasting glucose, TC, LD-C, and TG during year 1 in all trials; however, these reductions were not significant by the end of the BLOSSOM trial.

Common adverse effects of lorcaserin include headache, nausea, fatigue, dizziness, dry mouth, and constipation. The risk of cardiac valvulopathy was not significantly increased by lorcaserin (relative risk [RR] 1.1; 95% CI, 0.69–1.85) (Smith 2010). In patients with T2DM treated with metformin or a sulfonylurea, hypoglycemia occurred more often in patients taking lorcaserin than placebo; the risk was higher in patients taking a sulfonylurea. Depression and suicidal thoughts were noted as a potential concerns but did not occur at a higher rate in patients taking lorcaserin in the BLOOM, BLOSSOM, or BLOOM-DM trial. Other reported rare adverse effects include priapism, hyperprolactinemia, cognitive impairment, hallucinations, and dissociation. Lorcaserin is contraindicated in pregnancy.

As a serotonin-2C agonist, lorcaserin has the potential to increase the risk of serotonin syndrome when co-administered with other serotonergic drugs (e.g., SSRIs, SNRIs, MAOIs, triptans, dextromethorphan, bupropion). Lorcaserin is a cytochrome P450 (CYP) 2D6 inhibitor; dextromethorphan is a substrate of CYP2D6 and has an increased potential for a significant drug interaction.

Phentermine/Topiramate

The combination of immediate-release phentermine with extended-release topiramate was approved in 2012 as an adjunct to lifestyle modifications for chronic weight management. The combination product reduces body weight through several pharmacologic effects. Phentermine is a centrally acting sympathomimetic amine that works as an anorectic by stimulating the release of norepinephrine and, to a lesser extent, dopamine. The exact mechanism by which topiramate suppresses appetite and enhances...
satiety is unknown. The drug enhances γ-aminobutyrate (GABA) activity at GABA$_A$ receptors, modulates voltage-gated ion channels, and inhibits glutamate receptors and carbonic anhydrase (see Table 3-3).

Phentermine/topiramate should be administered once daily in the morning to avoid insomnia. The starting dose is 3.75/23 mg; this is titrated to 7.5/46 mg after 14 days. Patients should be reevaluated after 12 weeks. If a patient does not lose at least 3% of baseline weight, phentermine/topiramate may be discontinued or the dose can be titrated to 11.25/69 mg for 14 days and then increased to 15/92 mg. To discontinue the drug from the 15/92 mg dose, it should be tapered by taking a dose every other day for 1 week to avoid the risk of precipitating a seizure. Patients with moderate or severe kidney disease (CrCl less than 50 mL/minute) or moderate hepatic impairment (Child-Pugh class B) should not exceed 7.5/46 mg.

Three randomized placebo-controlled phase III trials established the safety and efficacy of phentermine/topiramate. The controlled-release phentermine/topiramate in severely obese adults trial (EQUIP) included 1267 patients (BMI of 35 kg/m$^2$ or greater; mean BMI 42 kg/m$^2$) and had a duration of 56 weeks (Allison 2011). The effects of low-dose, controlled-release phentermine plus topiramate on weight and associated comorbidities in overweight and obese adults trial (CONQUER) included 2487 patients (BMI 27–45 kg/m$^2$; mean 36.6 kg/m$^2$) with two or more comorbidities (hypertension, dyslipidemia, prediabetes, T2DM [in patients with T2DM there was no minimum BMI and use of metformin was allowed], and abdominal obesity) and had a duration of 56 weeks (Gadde 2011). The 2-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults trial (SEQUEL) included 676 patients and had a duration of 108 weeks; this was the extension of the CONQUER trial (Garvey 2012). Key exclusion criteria from the trials were history of depression or history of suicidal behavior or ideation with intention to act, nephrolithiasis, heart failure, unstable angina, valvular heart disease, glaucoma, stroke, myocardial infarction, and coronary revascularization.

Patients in the CONQUER trial were randomized 2:1:2 to receive placebo, phentermine/topiramate 7.5/46 mg, or phentermine/topiramate 15/92 mg. After 56 weeks, patients lost 1.4 kg (1.2%), 8.1 kg (7.8%), and 10.2 kg (9.8%), respectively, from their baseline weight. More patients lost 5% of their baseline body weight in the active treatment groups versus placebo (62% in the 7.5/46 mg group, 70% in the 15/92 mg group, and 21% in the placebo group). More patients in the active treatment groups also lost 10% of their baseline body weight (37% in the 7.5/46 mg group, 48% in the 15/92 mg group, and 7% in the placebo group). Over 75% of the eligible population continued into the extension (SEQUEL) trial. After an additional 52 weeks (108 weeks total), weight loss was maintained; patients lost 1.8% of baseline weight in the placebo group, 9.3% in the 7.5/46 mg group, and 10.5% in the 15/92 mg group. Patients in the EQUIP trial lost 9.3% of their baseline weight in the phentermine/topiramate 15/96 mg group; this higher weight loss is expected given that patient baseline BMIs were higher.

The SEQUEL trial demonstrated improvement in glycemic control. Patients without T2DM experienced reductions in both fasting glucose and insulin concentrations. The annualized incidence rates for progression to T2DM were 3.7% in the placebo group, 1.7% in the 7.5/46 mg group, and 0.9% in the 15/92 mg group, suggesting reduction in the progression to T2DM. In the subgroup with T2DM at baseline, patients in the 7.5/46 mg and 15/92 mg groups had reductions in A1C of 0.4% and 0.2%, respectively. This finding was not demonstrated in the placebo group.

Common dose-related adverse effects include dry mouth, dizziness, constipation, insomnia, dysgeusia, headache, and paresthesia. Topiramate has been associated with cognitive impairment including disturbances in attention and concentration. Symptoms of depression, including suicidal ideation, were assessed in the three studies. Depression-related, emergent adverse events occurred less often in the active treatment group. The risk of suicide was not increased; however, those at greatest risk of suicide were excluded from the trial. Topiramate may cause hypokalemia and low serum bicarbonate; nephrolithiasis may also occur. Increased serum creatinine has also been reported. High-dose phentermine/topiramate was associated with an increase in heart rate versus placebo (i.e., an increase of 1.4 beats/minute [p=0.08] in EQUIP and 1.8 beats/minute [p<0.0001] in CONQUER). Phentermine/topiramate is contraindicated in pregnancy, glaucoma, hyperthyroidism, and within 14 days of taking a MAOI. An FDA Risk Evaluation and Mitigation Strategy is in place because of the teratogenicity of topiramate, which may increase the risk of oral cleft.

Phentermine and topiramate are both associated with drug interactions. Phentermine may cause additive effects with other drugs that have stimulatory effects; topiramate may have additive effects with other drugs that have cognitive effects. Topiramate may induce CYP3A4 and is a weak inhibitor of CYP2C19. Coadministration of phentermine/topiramate with oral contraceptives results in reductions in the area under the curve of ethinyl estradiol and increases the area under the curve of norethindrone. Increased risk of pregnancy is unlikely because of the teratogenicity of topiramate, which may increase the risk of oral cleft.

Investigational Drugs

Bupropion has been associated with weight loss because its stimulatory effect on POMC neurons results in appetite suppression. Two combination products with bupropion have demonstrated weight loss in clinical trials. The combination of bupropion SR and zonisamide...
**Patient Care Scenario**

A 39-year-old woman (height 68 inches) with a medical history of obesity, migraine headaches, hypertension, irritable bowel syndrome (IBS), and gastroesophageal reflux disease (GERD) presents for weight management. On receiving a diagnosis of hypertension 6 months ago, she decided to lose weight and began a reduced-calorie diet and exercise routine. She was disappointed by a modest 1.8-kg loss over 5 months and initiated the Atkins diet 1 month ago after which she quickly lost an additional 2.4 kg. She is now finding it more difficult to adhere to this strict no-carbohydrate diet and would like advice for increasing her weight loss. She asks about the new agents for weight loss.

Her current home drugs include amitriptyline 25 mg at bedtime, sumatriptan 50 mg as needed for migraine, hydrochlorothiazide 25 mg daily, citalopram 20 mg daily, and lansoprazole 30 mg daily. Her current laboratory values (fasting) are TC 238 mg/dL, HDL-C 38 mg/dL, LDL-C 164 mg/dL, TG 180 mg/dL, A1C 5.8%, and serum glucose 110 mg/dL.

Her vital signs:

<table>
<thead>
<tr>
<th>Today:</th>
<th>BP: 140/82 mm Hg</th>
<th>Weight: 111.8 kg</th>
<th>BMI: 37.4 kg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months ago:</td>
<td>BP: 152/90 mm Hg</td>
<td>Weight: 116 kg</td>
<td>BMI: 38.8 kg/m²</td>
</tr>
</tbody>
</table>

What is best to recommend for this patient?

**Answer**

This patient is at increased risk of cardiovascular disease, given her history of obesity, hypertension, and dyslipidemia. Her current A1C and fasting glucose suggest prediabetes. She should continue to be monitored for T2DM and potential lipid-lowering therapy. The patient has achieved a 3.6% weight loss through lifestyle modification; this is below the 6-month goal of 5%–10%. Because the patient is motivated to continue losing weight, she is a candidate for weight-loss therapy. Both drug therapy and surgical options are appropriate given her comorbid conditions; however, the patient is seeking advice on oral agents only. Before initiating drug therapy, the patient’s diet should be addressed because lifestyle modifications must continue along with drug therapy.

The Atkins diet should be discontinued because her concerns about adherence may lead to weight regain. The best approach is to counsel the patient to choose a dietary plan that she finds easiest to adhere to in the long term.

Drug therapy options for weight loss includes orlistat, lorcaserin, and phentermine/topiramate. Orlistat is associated with loose stools and may be problematic in patients with IBS. Also, orlistat is associated with the least amount of weight loss (2.9%). Lorcaserin is a serotonin-2C agonist and may increase the risk of serotonin syndrome with sumatriptan, citalopram, and amitriptyline. In addition, lorcaserin is associated with a placebo-subtracted weight reduction of 3.1%, which is less than that with phentermine/topiramate, which is associated with a placebo-subtracted weight reduction of up to 8.7%. In addition to weight loss, phentermine/topiramate has been associated with improved glycemic control and waist circumference. Phentermine/topiramate should be initiated at 3.75/23 mg daily for 2 weeks and then increased to 7.5/46 mg daily. The patient should be reevaluated after 12 weeks; if weight loss is less than 3%, consider stopping or titrating to 11.25/69 mg for 14 days; then increase to 15/92 mg and reevaluate weight loss after an additional 12 weeks. If weight loss is less than 5%, discontinue by tapering to every other day for at least 1 week to avoid precipitating seizures. Patient tolerance and satisfaction, together with a basic metabolic panel, should be evaluated yearly.

The FDA requires a Risk Evaluation and Mitigation Strategy (REMS) based on the risk of teratogenicity with phentermine/topiramate. Because this patient is of reproductive potential, she must undergo pregnancy testing before initiating phentermine/topiramate and monthly thereafter. She must also receive additional counseling regarding the risk of teratogenicity. This patient must commit to taking contraceptive measures while taking phentermine/topiramate.

This patient’s drug regimen should also be assessed because both amitriptyline and citalopram are associated with weight gain. A potential alternative for amitriptyline, if used for IBS, is an antispasmodic such as dicyclomine. Topiramate may be helpful if amitriptyline is used for migraine prophylaxis. A potential alternative to citalopram is bupropion, which is associated with weight loss.

SR may work by enhancing serotonergic and dopaminergic receptors. In a phase IIb trial lasting 24 weeks, zonisamide/bupropion 360/360 mg demonstrated weight loss averaging 14% in 56 patients; phase III trials are under way. Naltrexone SR may induce weight loss by blocking b-endorphin from providing feedback inhibition to POMC neurons. The combination of bupropion SR and naltrexone SR demonstrated weight loss in four randomized, placebo-controlled, 1-year, phase III trials (COR-I, COR-II, COR-behavioral modification [COR-BMOD], and COR-T2DM [COR-DM]) (FDA 2010). Weight loss with naltrexone/bupropion 16/180 mg twice daily was 3.3%–5.2% from baseline. Treatment with bupropion and naltrexone also demonstrated reductions in waist circumference (2.1–4.6 cm), triglycerides (8.1%–10.4%) and hemoglobin A1C (0.49%), and HDL cholesterol concentrations increased 3.2–4.6 mg/dL. Initial treatment with bupropion/naltrexone resulted in negligible increases in blood pressure (1 mm Hg); however, mean blood pressure decreased by week 12 and remained below baseline values (up to 2 mm Hg) throughout the 56 weeks. Heart rate increased by 1 to 3 beats/minute in patients treated with bupropion/naltrexone, whereas the placebo group fluctuated by 1 beat/minute. A New Drug Application (NDA) was resubmitted in 2013 after the FDA requested that the manufacturer further evaluate cardiovascular safety.

Several antihyperglycemic agents have demonstrated weight loss and are being investigated for their potential role in the treatment of obesity. The use of GLP-1 receptor agonists has resulted in weight loss. A meta-analysis of 25 randomized, placebo-controlled trials in patients with and without T2DM (n=6411) demonstrated that patients treated with GLP-1 receptor agonists achieved a mean weight loss of 2.9 kg (95% CI, 3.6–2.2) (Vilsbøll 2012). The results were similar between exenatide twice daily, exenatide once weekly, and lixisenatide once daily. Pramlintide is a synthetic analog of human amylin that may slow gastric emptying and increase satiety. In a 52-week double-blind, placebo-controlled, dose-ranging study of patients without T2DM, pramlintide was associated with placebo-subtracted weight loss of up to 7.2 kg (Smith 2008).

Dietary Supplements for Obesity

Multiple dietary supplements are promoted for weight reduction, although clinical data are modest at best (Table 3-4). Trial results are conflicting and often limited by poor trial design, short duration, and small sample sizes. Additional concerns about weight-loss supplements are based on the lack of standardization and regulation. Dosages may not be standardized, and some supplements have been adulterated with undeclared drugs such as sibutramine. Safety data are lacking for most supplements. For these reasons, dietary supplements should not be recommended.

Bariatric Surgery

Surgical Options

Bariatric surgery can help some patients with obesity achieve significant and sustainable weight loss. Candidates for surgery include motivated patients with a BMI greater than 40 kg/m² regardless of comorbidities, or greater than 35 kg/m² with one or more comorbid conditions. These conditions include T2DM, obstructive sleep apnea, obesity hypoventilation syndrome, coronary artery disease, hypertension, dyslipidemia, gastroesophageal reflux disease (GERD), nonalcoholic steatohepatitis, asthma, urinary incontinence, debilitating arthritis, or substantially impaired quality of life when nonsurgical attempts at weight loss have failed. One procedure, laparoscopic adjustable gastric banding (AGB), has FDA-approved labeling for use in patients with a BMI as low as 30 kg/m² and at least one comorbidity. Patients with a history of or current substance abuse, severe or uncontrolled psychiatric illness, or perceived poor ability to maintain the lifestyle changes necessary after the procedure are generally considered poor candidates for surgery. Patients with unstable coronary artery disease and advanced liver disease with portal hypertension are also high-risk candidates.

Bariatric surgical procedures reduce caloric intake by modifying the anatomy of the GI tract. Procedures are either classified as restrictive or malabsorptive. Restrictive procedures limit intake by creating a small gastric reservoir with a narrow outlet to delay emptying, and include sleeve gastrectomy (SG), AGB, or a combination of these two procedures. Malabsorptive procedures bypass varying portions of the small intestine where nutrient absorption occurs. Malabsorptive procedures include biliopancreatic diversion (BPD), most commonly performed by means of a duodenal switch (BPD-DS). Roux-en-Y gastric bypass (RYGB) is often referred to as a combined restrictive-malabsorptive procedure. Procedures with malabsorptive components may be more appropriate for patients with a BMI greater than 40 kg/m², whereas restrictive procedures are generally preferred in patients with a BMI less than 40 kg/m².

In AGB, a synthetic inflatable band is wrapped around the stomach just below the gastroesophageal junction to create a small pouch with a narrow outlet. A subcutaneous access port is inserted to allow for adjustment of gastric restriction by the injection or withdrawal of saline (Figure 3-2). The band can be removed in an outpatient setting with anesthesia. Vertical SG involves resection of most of the gastric body, leaving a narrow tube of stomach (100–200 mL) as an alimentary conduit. In RYGB, the stomach is stapled to create an upper gastric pouch, 15–30 mL in volume, and a lower gastric remnant. The small intestine is divided at the jejunum, and the distal portion (known as the alimentary, or Roux limb) is anastomosed to the gastric pouch. The distal portion of the stomach and proximal small intestine (the biliopancreatic limb) are...
<table>
<thead>
<tr>
<th>Supplement</th>
<th>Proposed Mechanism</th>
<th>Clinical Data</th>
<th>Adverse Effects and Safety Concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chitosan</td>
<td>A cellulose-type polysaccharide reported to bind dietary fat and prevent absorption</td>
<td>Meta-analysis (14 trials) demonstrated average placebo-subtracted weight loss of 1.7 kg; average weight loss of 0.8 kg in trials &gt;4 weeks</td>
<td>GI effects common (constipation, diarrhea, flatulence, bloating, nausea, heartburn) Avoid in patients with a shellfish allergy</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Increased thermogenesis by inhibiting the breakdown of cAMP</td>
<td>Several clinical trials demonstrate short-term weight loss when used in combination with ephedra (no longer available)</td>
<td>Common adverse effects: insomnia, irritability, tachycardia, anxiety</td>
</tr>
<tr>
<td>Green tea</td>
<td>Polyphenols and caffeine act synergistically to decrease fat absorption, reduce lipogenesis, and cause thermogenesis</td>
<td>Several clinical trials demonstrate potential weight loss of up to 2 kg</td>
<td>See caffeine Reports of hepatotoxicity</td>
</tr>
<tr>
<td>Guarana (Brazilian cocoa, <em>Paullinia cupana</em>)</td>
<td>See caffeine (seed contains 2.5%–7% caffeine)</td>
<td>See caffeine</td>
<td>See caffeine</td>
</tr>
<tr>
<td>Yerba mate (<em>Ilex paraguariensis</em>)</td>
<td>See caffeine</td>
<td>See caffeine</td>
<td>See caffeine Hot drinks may increase risk of esophageal cancer</td>
</tr>
<tr>
<td><em>Citrus aurantium</em> (bitter orange, Seville orange, sour orange)</td>
<td>Contains synephrine (structurally similar to epinephrine)</td>
<td>No evidence of efficacy when used alone; limited data suggest minimal weight loss when used in combination with caffeine and St. John’s wort (&lt; 1-kg weight loss)</td>
<td>Cardiovascular effects (increase heart rate, blood pressure) Reports of angina, increased QT interval, seizures, and ischemic colitis Potential drug interactions because inhibits intestinal CYP3A4</td>
</tr>
<tr>
<td>Hydroxycitric acid (<em>Garcinia, garcinia cambogia</em>)</td>
<td>Theorized to inhibit production of lipids</td>
<td>No evidence of weight loss</td>
<td>Reports of hepatotoxicity, rhabdomyolysis (avoid use with statins) May inhibit platelet aggregation</td>
</tr>
<tr>
<td>Glucomannan (konjac)</td>
<td>Fibrous polysaccharide; may work similar to fiber (promote/prolong satiety)</td>
<td>Limited data suggest minimal weight loss (1–2 kg)</td>
<td>GI adverse effects (nausea, bloating, flatulence)</td>
</tr>
<tr>
<td>Hoodia</td>
<td>Unknown; reported to be an appetite suppressant</td>
<td>No clinical trials to support use</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

cAMP = cyclic adenosine monophosphate
anastomosed farther down the jejunum. Food comes in contact with pancreatic enzymes and bile only below this anastomosis, in the segment of the small intestine known as the common channel. The shorter the common channel (and the longer the Roux limb), the less absorption of nutrients and the greater the weight loss. This is currently the most common type of bariatric surgery performed in the United States and Canada.

In the BPD-DS procedure, a vertical gastrectomy is performed, followed by the creation of the alimentary limb that delivers stomach contents to the small intestine, and a biliopancreatic limb that transports bile from the liver. Both pathways end in the distal small intestine. This procedure is less common because of higher risk of complications and higher mortality rates, and it is reserved for patients requiring greater weight loss.

All procedures can be performed laparoscopically with a lower rate of complications than open procedures. The AGB is considered nonmetabolic, whereas SG, RYGB, and BPD-DS are considered metabolic procedures because they are associated with improvements in blood glucose, lipids, and blood pressure that are independent of weight loss. These benefits are partly caused by alterations in GI hormones including GLP-1, peptide YY, and ghrelin.

Selection of a procedure should be based on individualized therapeutic goals, the surgical expertise available, patient preference, and assessment of risk. Assessment of a candidate is a complex process involving psychological, surgical, dietetic, and medical review. The individual must be physically and psychologically fit to proceed to surgery and also must be able to adhere to requirements after surgery. The decision to proceed with surgery considers the benefits the candidate is likely to gain and the level of risk peri- and postoperatively.

**Nutrient and Pharmacotherapy Considerations**

Nutrient and pharmacotherapy adjustments should be considered preoperatively with the goal of preventing complications. Patients should discontinue oral contraceptives and hormone therapy 3–4 weeks before surgery to reduce the risk of thromboembolism (Mechanick 2013). In patients with a history of gout, prophylactic agents should be considered to prevent a gouty attack after surgery. To prevent gouty attacks, oral colchicine is recommended in patients who will undergo RYGB; oral ursodiol should be considered for patients who have not had a cholecystectomy.

Patients who have undergone bariatric surgery are at increased risk of nutritional deficiencies because of increased gastric pH and malabsorption. Malabsorptive procedures are more often associated with deficiencies than purely restrictive procedures. Protein malnutrition accounts for the most common macronutrient deficiency and is associated with BPD and BPD-DS (Bal 2012). Patients should be evaluated for signs and symptoms of protein malnutrition, including hair loss and hypoalbuminemia. Patients should be instructed to consume 60–120 g of protein daily, and enteral feeding with liquid protein supplements may be necessary.

Deficiencies in micronutrients, trace elements, essential minerals, and vitamins are also common. Empiric supplementation with daily multivitamins plus minerals, calcium, and vitamin D is universally recommended (Mechanick 2013). Recommendations for the content of multivitamins vary, but a reasonable goal is 65 mg of elemental iron, 400–800 mcg of folate, 100–200 mg of thiamine, and 2–4 mg of copper. Calcium citrate 1200–1500 mg is preferred to calcium carbonate because reduced gastric acid can lead to reduced absorption of calcium carbonate. Daily supplementation with 3000 international units of vitamin D3, or D should be provided. Patients who have undergone RYGB or SG should take 2 chewable multivitamins daily for the first 3–6 months, whereas patients who have undergone AGB require just 1 oral multivitamin daily. Iron and vitamin B12 status should be monitored at baseline and then annually or as needed. Additional iron supplementation with or without vitamin C to increase absorption may be required and is routinely recommended in menstruating women. Oral vitamin B12 supplementation of 1000 mcg by mouth daily or 500 mcg intranasally weekly should be initiated in patients who are deficient.

Bariatric surgery also affects drug selection. Drug absorption is altered by all bariatric surgeries and is particularly affected by malabsorptive procedures. Pharmacokinetic changes in drug absorption occur because of decreased gastric surface area for absorption, increased gastric pH as a result of fewer proton pumps, decreased intestinal transit time, and altered first-pass metabolism. Based on these changes, many drug interactions potentially may occur. Drugs with a narrow therapeutic window should be routinely monitored for efficacy and toxicity. Weakly acidic drugs may have decreased absorption and weakly basic drugs may have increased absorption. Extended-release and entericoated products are poorly absorbed and should be avoided. During the first 8 weeks after surgery, all drugs should be immediate acting and in a crushed or liquid formulation. Drugs that require enterohepatic recycling may have decreased absorption; therefore, low-dose oral contraceptives should be avoided. Highly lipophilic drugs and drugs that undergo first-pass metabolism may have decreased bioavailability. Limited data from small clinical studies have identified specific agents with alterations in bioavailability after RYGB: concentrations of sertraline, tacrolimus, sirolimus, and mycophenolate were decreased, whereas concentrations of morphine and ethanol were increased (Edwards 2012).
Additional considerations are based on adverse effects. Nonsteroidal anti-inflammatory drugs (NSAIDs) have been associated with anastomotic ulceration and perforations and should be completely avoided after bariatric surgery. Salicylates and corticosteroids may increase the risk of gastrointestinal irritation and ulceration and should be avoided. Bisphosphonates increase the risk of anastomotic ulceration; if indicated, injectable bisphosphonates such as zoledronic acid or ibandronate should be recommended. In patients with T2DM, insulin dosages should be adjusted, and insulin secretagogues such as sulfonylureas and meglitinides may require discontinuation because of increased risk of hypoglycemia from reduced caloric intake. Agents that improve insulin sensitivity such as metformin and incretin-based therapies should be considered for patients not achieving their glycemic goals.

Given the potential impact of bariatric surgery on the bioavailability of selected drug therapies, careful consideration of the pharmacokinetic properties of all agents administered, together with increased monitoring, is warranted.

**Evaluation of Outcomes**

The primary goal of bariatric surgery is to promote excess weight loss, referred to as the difference between the actual and ideal body weight (weight lost/[actual body weight – ideal body weight] x 100%). Excess weight loss of 50% or more is considered a surgical success. Peak weight loss occurs 1–2 years after surgery, followed by
slow weight regain, and subsequent weight stabilization. Sustained weight loss has been maintained for up to 10 years for BPD-DS, up to 15 years with AGB, and up to 25 years with RYGB (O’Brien 2013).

A meta-analysis of trials evaluating the efficacy of bariatric surgery at 1 year demonstrated a mean percentage of excess weight loss of 61.2% overall; with 47.5% for AGB, 61.6% for RYGB, 57.7% for SG, and 70.1% for BPD-DS (Vest 2013). The duration of long-term follow-up data vary for each procedure, ranging from 2.5 to 25 years. Mean long-term excess weight loss results include 42.8% for AGB at 12–15 years, 66% for SG at 3 years, 62% for RYGB at 5 years, and 84% for BPD-DS at 3 years (O’Brien 2013; Vest 2013).

As bariatric surgery has become a mainstream treatment strategy for obesity, the focus has shifted from weight loss to the impact on obesity-related comorbidities (Table 3-5) (Vest 2013). In addition to its effect on comorbidities, bariatric surgery showed a 53% lower occurrence of cardiovascular death compared with patients in the control group. The number of first-time fatal or nonfatal cardiovascular events was 33% lower in the surgery group (Sjöström 2012).

Complications
Mortality rates 30 days after surgery are 0.1% with AGB, 0.5% with RYGB, and 1.1% with BPD-DS (Vest 2013). Mortality rates are highest in patients who are men, aged 45 years or older, with a BMI greater than 50 kg/m², with hypertension or thromboembolic risk factors, or requiring open surgery. Venous thromboembolism is the leading cause of mortality with bariatric surgery, with an incidence of 0.34% (Vest 2013). Risk should be minimized with perioperative mechanical and pharmacologic prophylactic measures. Gastrointestinal leak is the most feared technical complication, with rates ranging from 1% with AGB to 2% with RYGB and SG. Most leaks occur at staple lines or anastomotic sites (Vest 2013).

Dumping syndrome, a complex of neurohormonally mediated symptoms, occurs in up to 70% of patients after RYGB and is characterized by facial flushing, light-headedness, palpitations, abdominal pain, fatigue, nausea, and diarrhea (Vest 2013). These symptoms typically occur after consumption of concentrated sweets; as a result, patients who have had RYGB are discouraged from consuming food high in glucose. Other dietary modification, including reducing carbohydrates and avoiding liquids for 30 minutes after a meal, may decrease the incidence of dumping syndrome.

Other complications include wound infections, bleeding, incidental splenectomy, incisional and internal hernias, and early small bowel obstruction. Postoperative nausea and vomiting occurs in more than 50% of patients undergoing restrictive bariatric procedures. Gastric banding is subject to band slippage, leakage, and erosion, resulting in reintervention at rates as high as 20% (Vest 2013).

Several studies have shown higher suicide rates in patients who have had bariatric surgery. A recent systematic review of 28 studies estimated a suicide rate of 4.1 per 10,000 person-years (95% CI, 3.2–5.1) in patients who underwent bariatric surgery, which is higher than the World Health Organization estimated rate of 1 per 10,000 person-years in the general population. Seven of the included studies provided information regarding the time after surgery at which suicide occurred. This time ranged from 18 months to 5 years after surgery (Peterhansel 2013). This is particularly alarming given that other data have suggested that people with obesity tend to have a lower suicide rates than people with healthy weight. The reason for this increased suicide risk is unclear, but further research is warranted. Careful patient assessment for underlying psychiatric conditions before surgery and continuous follow-up programs to evaluate for suicide risk, even years after surgery, are needed.

Economic Considerations
Despite successful weight loss, resolution of comorbidities, and fewer cardiovascular events, bariatric surgery has not been associated with overall health care cost savings. Total costs are greater during the second and third years after bariatric surgery: patients have lower prescription and office visit costs but higher inpatient costs. In one study, laparoscopic surgery was associated with lower costs in the first few years, but these differences did not persist, and no one type of surgery is likely to reduce long-term health care costs over another (Weiner 2013).

Conclusion
Overweight and obesity constitute a health care crisis in the United States. Weight loss therapy starts with comprehensive lifestyle modifications with the most effective approach being one that the individual finds easiest to adhere to because obesity is a chronic condition. Pharmacotherapy may be considered for patients with a BMI of 27–29.9 kg/m² with obesity-related comorbidities or BMI greater than 30 kg/m². Selection of the most appropriate agent should be based on comorbidities, concomitant drug therapy, weight loss desired, adverse effects, patient preference, and cost. Lifestyle modifications must continue together with pharmacotherapy. Patients with a BMI of 35–39.9 kg/m² with comorbidities or BMI greater than 40 kg/m² may be candidates for bariatric surgery. Although effective, bariatric surgery is associated with complications and may lead to absorption-related nutritional deficits. Given the potential impact of bariatric surgery on drug therapy, the pharmacokinetic properties of all agents administered, together with increased monitoring, should receive careful consideration.
Overweight and obesity should be viewed as chronic disease states that need lifelong attention to maintain and sustain weight loss. Comprehensive lifestyle interventions are first line for all patients who are overweight or obese trying to lose weight. The most effective dietary plan is one that the individual patient finds easiest for adherence. Physical activity should be encouraged but is more useful in preventing weight regain than assisting in initial weight loss. Behavior therapy including group or individual counseling should be implemented for at least 6 months to enhance diet and exercise changes. Patients with BMI greater than 27 to less than 30 kg/m² with 1 or more indicators of CV risk or BMI greater than 30 kg/m² are candidates for pharmacotherapy as an adjunct to comprehensive lifestyle interventions. Selection of the most appropriate agent should be based on comorbidities, concomitant drugs, amount of weight loss desired, adverse effects, patient preference, and cost. In clinical trials lasting more than 2 years, phentermine/topiramate, lorcaserin, and orlistat resulted in weight loss of up to 8.7%, 3.1%, and 2.9% over placebo; these agents have not been compared in head-to-head trials. Patients who do not achieve at least 5% weight loss in 12 weeks should discontinue pharmacotherapy. Patients with BMI greater than 35 to less than 40 kg/m² with comorbidities or BMI greater than 40 kg/m² are candidates for bariatric surgery. Bariatric surgery results in significant weight loss and metabolic benefits. Given the potential impact of bariatric surgery on the bioavailability of medication, careful consideration of the pharmacokinetic properties of all agents administered together with increased monitoring is warranted.

Table 3-5. Effect of Bariatric Surgery on Obesity-Related Comorbidities

<table>
<thead>
<tr>
<th>Disease/Symptom</th>
<th>Improvement or Remission at &lt; 2 years (%)</th>
<th>Improvement or Remission at &lt; 5-7 years (%)</th>
<th>Improvement or Remission at 10 years (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>72</td>
<td>54</td>
<td>36</td>
</tr>
<tr>
<td>Hypertension</td>
<td>24</td>
<td>66</td>
<td>41</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>63</td>
<td>82</td>
<td>46</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>22</td>
<td>56</td>
<td>21</td>
</tr>
<tr>
<td>Sleep apnea</td>
<td>94 clinical improvement, resolved at 1 year</td>
<td>66 clinically resolved, 92 resolved or improved</td>
<td></td>
</tr>
<tr>
<td>Nonalcoholic fatty liver disease</td>
<td>84 steatosis resolution, 75 fibrosis resolution</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudotumor cerebri</td>
<td>84 at 1 year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>50 improvement in Beck Depression Inventory at 1 year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polycystic ovary syndrome</td>
<td>50 resolution in hirsutism, 100 restoration of normal menstruation at 1 year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stress urinary incontinence</td>
<td>64 resolved, 92 resolved/ improved at 1 year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Migraine</td>
<td>50 reduction in number of headache days at 6 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Degenerative joint disease</td>
<td>50 improvement in pain scores and osteoarthritis severity at 6 months</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

References


Tsai AG, Williamson DR, Glick HA. *Direct medical cost of overweight and obesity in the USA: a quantitative systematic review.* Obes Rev 2011;12:50-61.


Questions 41 and 42 pertain to the following case.
M.K. is a 42-year-old woman (height 67 inches, baseline weight 82 kg) with a medical history of obstructive sleep apnea, glaucoma, dyslipidemia, and partial seizures. Her drug regimen includes timolol ophthalmic solution, atorvastatin, and lamotrigine.

41. Which one of the following 6-month weight-loss goals is the best for M.K.?
   A. A loss of 2.2 kg is likely to improve comorbidities.
   B. A loss of at least 5 kg is necessary to improve comorbidities.
   C. A loss of 4.1 kg is appropriate, but her BMI would still be classified as overweight.
   D. A loss of 8.2 kg is appropriate goal, but her BMI would be classified as a healthy weight.

42. M.K. states that she has tried a dietitian-prescribed diet and exercise plan for 6 months but has not attained her weight-loss goal. In addition to comprehensive lifestyle interventions, which one of the following is best to recommend for weight loss for M.K.?
   A. No additional interventions are warranted at this time.
   B. Lorcaserin.
   C. Orlistat.
   D. Phentermine/topiramate.

Questions 43 and 44 pertain to the following case.
E.T. is a 37-year-old woman (height 64 inches, weight 69 kg) seeking weight loss advice. Two months ago she began the Mediterranean diet plan and has lost 4 kg. Although she plans to continue the diet, she would like a recommendation to increase her weight loss. E.T. has a medical history of depression and type 2 diabetes mellitus (T2DM). Her drug regimen includes paroxetine 20 mg daily and metformin 500 mg orally twice daily.

43. Which one of the following changes would have the greatest impact on E.T.’s weight?
   A. Discontinue metformin; initiate insulin glargine.
   B. Discontinue metformin; initiate glimepiride.
   C. Discontinue paroxetine; initiate bupropion.
   D. Discontinue paroxetine; initiate citalopram.

44. Which one of the following is best to recommend for weight loss for E.T.?
   A. No additional interventions are warranted.
   B. Lorcaserin.

45. A 32-year-old woman (height 69 inches, baseline weight 104.5 kg) has a medical history of generalized anxiety disorder treated with duloxetine. She states that she has tried many lifestyle interventions during the past several years. With each attempt, she is able to lose 5%-10% of her baseline weight but has been unsuccessful in sustaining the weight loss. In addition to an intensive comprehensive lifestyle intervention, which one of the following is best to recommend for weight loss in this patient?
   A. Lorcaserin.
   B. Phentermine/topiramate.
   C. Adjustable gastric banding (AGB).
   D. Roux-en-Y gastric bypass (RYGB).

46. A 44-year-old man (height 70 inches, weight 100 kg) has a medical history of dyslipidemia, hypertension, and T2DM. His current regimen includes lisinopril, rosvastatin, and metformin. He has tried lifestyle interventions on and off for several years with variable weight loss results ranging from 5% to 20%; however, he has been unable to achieve sustained weight loss. His prescriber is inquiring about the appropriateness of medication for weight loss. Which one of the following is best to recommend for this patient?
   A. Lifestyle interventions should be continued because he is not a candidate for pharmacotherapy for obesity.
   B. Orlistat would be expected to result in a greater improvement in his LDL-C than lorcaserin and phentermine/topiramate.
   C. Phentermine/topiramate is most appropriate for this patient because of drug interactions between his current drugs and both lorcaserin and orlistat.
   D. Lorcaserin would be expected to cause greater improvement in his blood pressure than orlistat and phentermine/topiramate.

47. A 32-year-old woman (height 63 inches, baseline body weight 80 kg) initiated pharmacotherapy after several failed attempts at lifestyle interventions. Three months after initiation, she reports that she has taken phentermine/topiramate 7.5/46 mg as prescribed and is tolerating it well. However, she is disappointed with the weight loss. Her weight is now 73 kg. Which one of the following is the best recommendation for this patient’s phentermine/topiramate therapy?
A. Continue at the current dose and explain that this amount of weight loss is typical.
B. Discontinue pharmacotherapy because it is not effective for this patient.
C. Discontinue phentermine/topiramate and initiate orlistat.
D. Increase the dose to 15/92 mg daily by titration.

**Question 48 and 49 pertain to the following case.**
F.K. is a 43-year-old man (height 69 inches, weight 107.8 kg) with a history of T2DM. Three days ago he underwent laparoscopic RYGB. The surgery was a success, and he has not experienced any complications.

48. Which one of the following best describes F.K.’s risk of postsurgical complications?
A. He is at high risk of dumping syndrome because of the type of surgery he underwent.
B. His risk of 30-day mortality is high because of his age and presurgical BMI.
C. His risk of suicide is higher within the first 3 months after surgery.
D. He is at risk of band slippage, leakage, and erosion.

49. Which one of the following is best to recommend for F.K.’s postsurgical pain management?
A. Oral acetaminophen with codeine.
B. Oral aspirin.
C. Intramuscular ketorolac.
D. Oral sustained-release oxycodone.

50. A 45-year old woman (height 63 inches, weight 102 kg) has a history of T2DM, hyperlipidemia, and osteoarthritis. Her regimen includes metformin 1000 mg twice daily, insulin glargine 60 units daily, insulin lispro 10 units with meals, and atorvastatin 20 mg daily. Her recent A1C was 9.9%. She has implemented lifestyle modification with little weight loss. She is open to all treatment options. Which one of the following would best target weight loss and related comorbidities in this patient?
A. Phentermine/topiramate 15/92 mg daily.
B. Exenatide extended release 2 mg subcutaneously once weekly.
C. Biliopancreatic diversion with duodenal switch (BPD-DS).
D. RYGB.

51. A 40-year-old man (height 67 inches, weight 107 kg) is motivated to lose weight. His history is significant for T2DM, osteoarthritis, obstructive sleep apnea, and depression. His regimen includes metformin, hydrochlorothiazide, acetaminophen, and venlafaxine extended release. He inquires about surgical options for weight loss and the effect it may have on his current regimen. Which one of the following is the most appropriate counseling point to discuss with this patient?
A. He will require a daily vitamin supplement containing vitamin B6 and vitamin D.
B. He will require a daily mineral supplement containing calcium carbonate and iron.
C. He will need to switch to the immediate-release formulation of venlafaxine.
D. He will need to switch to ibuprofen to manage his osteoarthritis.

52. A 41-year-old woman (height 66 inches, weight 80.5 kg) has a history of obstructive sleep apnea. She has a family history of hypertension, T2DM, and cardiovascular disease. She is motivated to lose weight to lower her risk of developing obesity-related comorbidities and to improve her life expectancy. Which one of the following is the most appropriate education point for this patient?
A. Her current BMI is associated with increased all-cause mortality.
B. Long-term use of orlistat may delay progression to T2DM in patients at increased risk.
C. Achieving 10% weight loss that is sustained for greater than 2 years through use of lorcaserin has been associated with increased life expectancy.
D. Achieving 10% weight loss that is sustained for greater than 2 years through use of phentermine/topiramate has been associated with reduced mortality.

53. Which one of the following interventions is likely to produce the highest percentage of weight loss?
A. Orlistat 120 mg three times daily.
B. Lorcaserin 10 mg twice daily.
C. Moderate-intensity exercise for 30 minutes on most days of the week.
D. Phentermine/topiramate 7.5/46 mg once daily.

54. A 47-year-old man (height 73 inches, weight 111.4 kg) has a history of T2DM. He initiated lifestyle modifications and metformin 1 year ago and lost more than 5 kg. However, his current regimen of metformin 1000 mg twice daily has been unsuccessful in achieving an A1C goal of less than 7%. He is concerned about the weight gain that is associated with many agents for T2DM and his provider would like assistance in selecting an agent. Which one of the following agents is most likely to result in additional weight loss for this patient?
A. Insulin glargine 10 units subcutaneously at bedtime.
B. Exenatide extended release 2 mg subcutaneously once weekly.
C. Glimepiride 4 mg orally once daily.
D. Sitagliptin 100 mg orally once daily.

55. A 52-year-old woman (height 62 inches, weight 79.5 kg) has a medical history of T2DM. Her home drugs include metformin 1000 mg twice daily, glyburide 5 mg twice daily, and sitagliptin 100 mg daily. Despite these interventions, she has been unable to achieve her A1C goal of less than 7%. She has been incorporating appropriate lifestyle interventions and has successfully lost 3.2 kg. She asks if she is a candidate for bariatric surgery. Which one of the following surgical methods would be best to consider for this patient?
A. RYGB.
B. AGB.
C. BPD-DS.
D. Sleeve gastrectomy (SG).

56. A 62-year-old man (height 69 inches, weight 98.6 kg) has a history of hypertension and obstructive sleep apnea. He is interested in lifestyle modifications to reduce his weight. Which one of the following is best to recommend to encourage initial weight loss in this patient?
A. Restricting dietary intake of fat.
B. Participating in aerobic exercise for at least 150 minutes per week.
C. Participating in resistance training at least twice per week.
D. Restricting calories with the Mediterranean diet.

57. A 47-year-old woman (height 65 inches, weight 71.4 kg) with hypertension and T2DM is interested in methods to help get both her weight and T2DM under better control. Recent laboratory values include A1C 7.4% and LDL-C 102 mg/dL. Her home drugs include metformin 1000 mg twice daily, glipizide extended release 10 mg once daily, lisinopril 20 mg once daily, and atorvastatin 20 mg once daily. Which one of the following would be best to recommend to help this patient achieve her goals?
A. Lorcanarin 10 mg twice daily.
B. Phentermine/topiramate 7.5/46 mg once daily.
C. Mediterranean diet.
D. Zone diet.

58. Endocrine regulation of weight is accomplished through circulating levels of several neurohormonal substances. Many investigational agents target these neurohormonal substances. Which one of the following represents a mechanism of action that would be most likely to cause weight loss?
A. Leptin agonist.
B. Ghrelin antagonist.
C. Cholecystokinin antagonist.
D. Peptide YY antagonist.

59. A 42-year-old man (height 70 inches, baseline weight 110 kg) who does not have comorbidities initiates pharmacotherapy and intense comprehensive lifestyle changes for weight loss. Twelve weeks after initiating lorcanarin 10 mg twice daily, he is disappointed with his weight loss. His current weight is 107 kg. Which one of the following is best to recommend for this patient?
A. Continue lorcanarin and explain that this amount of weight loss is typical.
B. Continue lorcanarin for another 12 weeks; it requires 6 months for maximal weight loss.
C. Discontinue lorcanarin and schedule AGB.
D. Discontinue lorcanarin and initiate phentermine/topiramate.

60. A 50-year-old woman (height 62 inches, baseline weight 86 kg) has a history of depression, insomnia, and T2DM. She began intense lifestyle modifications and pharmacotherapy for weight loss 6 months ago and lost 9 kg. Her current drug regimen is escitalopram 10 mg daily, insulin glargine 10 units at bedtime, and orlistat 120 mg three times daily. Which one of the following is best to recommend for this patient?
A. Continue current regimen.
B. Discontinue orlistat because she has attained an appropriate weight-loss goal.
C. Discontinue orlistat and initiate lorcanarin, which is associated with more weight loss.
D. Discontinue orlistat and initiate phentermine/topiramate, which is associated with more weight loss.
Learning Objectives

1. Distinguish the types of care transitions and relevant challenges patients may experience in the health care system.
2. Assess patients for risk factors associated with adverse events during transitions of care (TOC).
3. Design a plan to improve the transitions of care process using established TOC models and the primary literature.
4. Apply existing quality metrics endorsed by health care quality-sponsoring organizations to improve TOC.
5. Develop an individualized patient plan to improve the TOC process.

Introduction

The National Transitions of Care Coalition (NTOCC) defines transitions of care (TOC) as the movement of patients between health care locations, providers, or different levels of care within the same location as their conditions and care needs change. Transitions may occur within health care settings (e.g., from the intensive care unit [ICU] to the general medicine ward), between health care settings (e.g., from hospital to ambulatory clinic), across health states (e.g., personal residence to assisted living), or between providers (e.g., generalist to specialist practitioner).

Inadequate TOC can result in patient and caregiver confusion about the care plan, medication errors, lapses in care from lack of communication and follow-up, and increased resource use. Around 20% of Medicare beneficiaries have a hospital readmission within 30 days of discharge; of these, about 50% did not see their physician between discharge and rehospitalization (Jencks 2009). Within 3 weeks of hospital discharge, 19% of patients experienced an adverse event, of which adverse drug events (ADEs) were the most common (Forster 2003).

Pharmacists can provide continuity and optimize pharmacotherapeutic outcomes during TOC. Pharmacists are members of interdisciplinary teams in every care delivery setting, including hospitals, emergency departments (EDs), long-term care facilities (LTCFs), skilled nursing facilities (SNFs), infusion centers, ambulatory clinics, community pharmacies, and home health.

This chapter reviews key elements of TOC, including challenges and risk factors, established TOC models and national initiatives, and reimbursement for TOC services.

Baseline Knowledge Statements

Readers of this chapter are presumed to be familiar with the following:
- The various care settings in the health system
- Regulatory and quality improvement organizations

Additional Readings

The following free resources are available for readers wishing additional background information on this topic.
- Patient Safety Primer: Adverse Events After Hospital Discharge.
- Community Care Transitions Toolkit
- Transitions of Care: The Need for a More Effective Approach to Continuing Patient Care
- Transitions of Care: The Need for Collaboration Across Entire Care Continuum
Defining TOC

Home to Hospital

The transition from the outpatient to the inpatient setting has been less studied than the inpatient to outpatient transition. According to the Centers for Disease Control and Prevention (CDC), the ED serves as the point for admission for most patients. In 2010, there were about 129 million ED visits in the United States, around 13 million of which resulted in a hospital admission (CDC 2010). The paucity of data on this type of transition should not undermine its importance to patient care. Lack of communication between outpatient and inpatient providers and incomplete patient information may adversely affect care. In addition, incomplete knowledge of outpatient drugs may result in inaccurate medication reconciliation. Errors in the preadmission medication history may cause unintentional and potentially harmful drug discrepancies (Pippins 2008).

Hospital to Home or Ambulatory Care

Factors that may contribute to inadequate hospital to home TOC include primary care providers (PCPs) not informed of patient hospitalization or discharge, patients not scheduling an appointment after discharge, and the unavailability of appointments in the office practice. Deficiencies in communication among health care providers and appropriate medical follow-up are associated with adverse events after discharge. One study found that communication between hospital physicians and PCPs occurred infrequently (3%–20%); availability of the discharge summary at the first and 4-week postdischarge visits was low (12%–34% and 51%–77%, respectively); and discharge summaries often lacked important information such as treatment or hospital course (7%–22%), discharge drugs (2%–40%), and follow-up plans (2%–43%) (Kripalani 2007). Another study found that hospital physicians had recommended outpatient workups (e.g., diagnostic procedures, subspecialty referrals, laboratory tests) for only about 40% of their discharged patients (Moore 2007).

Hospital Transfers

When a patient remains within the same inpatient facility, but there is a change in the team primarily responsible for care (e.g., medical ward to ICU), it is important to consider this transition. However, published data on this type of transfer are limited.

Hospital to/from LTCF

Long-term care facilities (LTCFs) (e.g., nursing homes, SNFs) provide health care to people unable to manage independently in the community. This care may represent custodial care (i.e., non-skilled, personal care such as help with activities of daily living), chronic care management, or short-term rehabilitative services. These types of care differ from long-term hospital care (LTHC), which refers to acute care inpatient stays that are, on average, greater than 25 days (CMS Glossary).

Transitions of care are common for older patients with acute and chronic illnesses and may adversely affect health and functioning. Medication changes that occur with transfers from and to LTCFs are common and may result in ADEs. A study that evaluated 122 admissions of 87 patients from four nursing homes found an average of 3.1 medication changes made during transfer from nursing home to hospital and 1.4 medication changes during transfer from hospital to nursing home. Of the 71 bidirectional transfers reviewed, ADEs occurred in 20% of transfers. Most of the ADEs occurred in the nursing home after nursing home readmission (Boockvar 2004). Proper attention to TOC with respect to medication reconciliation after readmission to an LTCF is important to decrease the risk of ADEs and medication errors.

LTCF to Home

Patients transitioning from an LTCF to home are at a higher risk of medication errors because they are assuming responsibility for their own care. Primary care providers may not be fully informed about the care provided to, and the discharge care plans for, patients discharged from LTCFs. A quasi-experimental study evaluated a postdischarge medication reconciliation program in 521 Kaiser Permanente Colorado patients transitioning from

Doorway to Home

The transition from home to hospital has been even less studied than the inpatient to outpatient transition. In 2010, there were about 21.8 million discharges from home to hospital (Kaiser Family Foundation 2010). The paucity of data on this type of transition should not undermine its importance to patient care. Lack of communication between home and hospital providers and incomplete patient information may adversely affect care. In addition, incomplete knowledge of outpatient drugs may result in inaccurate medication reconciliation. Errors in the preadmission medication history may cause unintentional and potentially harmful drug discrepancies (Pippins 2008).

Abbreviations in This Chapter

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADE</td>
<td>Adverse drug event</td>
</tr>
<tr>
<td>CTI</td>
<td>Care Transitions Intervention (program)</td>
</tr>
<tr>
<td>EHR</td>
<td>Electronic health record</td>
</tr>
<tr>
<td>GC</td>
<td>Guided Care (model)</td>
</tr>
<tr>
<td>H2H</td>
<td>Hospital to Home (initiative)</td>
</tr>
<tr>
<td>HCAHPS</td>
<td>Hospital Consumer Assessment of Healthcare Providers and Systems</td>
</tr>
<tr>
<td>HEDIS</td>
<td>Healthcare Effectiveness Data and Information Set</td>
</tr>
<tr>
<td>LTCF</td>
<td>Long-term care facility</td>
</tr>
<tr>
<td>LTHC</td>
<td>Long-term hospital care</td>
</tr>
<tr>
<td>NTOCC</td>
<td>National Transitions of Care Coalition</td>
</tr>
<tr>
<td>PCP</td>
<td>Primary care provider</td>
</tr>
<tr>
<td>PCPI</td>
<td>Physician Consortium for Performance Improvement</td>
</tr>
<tr>
<td>RED</td>
<td>(Project) Re-engineered Discharge</td>
</tr>
<tr>
<td>SNF</td>
<td>Skilled nursing facility</td>
</tr>
<tr>
<td>STAAR</td>
<td>State Action on Avoidable Rehospitalizations (initiative)</td>
</tr>
<tr>
<td>TCM</td>
<td>Transitional care model</td>
</tr>
<tr>
<td>TOC</td>
<td>Transitions of care</td>
</tr>
</tbody>
</table>

PSAP 2014 • Chronic Illnesses

80

Transitions of Care
an SNF to home. Data showed more than 90% of all discharge summaries in the intervention group contained at least one potential drug-related problem, including duplicate drugs, omitted therapy, and drug contraindications. Patients in the medication reconciliation intervention group had a statistically significant 78% reduction in the risk of death from any cause (Delate 2008).

When patients who received post-hospitalization SNF care (mean SNF stay, around 30 days) received a post-discharge clinic visit by an advanced nurse practitioner, readmission rates and inpatient days within 30 days after the intervention were reduced (Park 2013). Pharmacist-provided medication reconciliation and coordination of information between health care providers and patients during transitions between LTCFs and home may increase the safety and quality of this TOC.

Challenges Related to TOC

Barriers to implementing successful TOC programs include financial limitations, staffing shortages, inconsistent transition processes, inadequate communication between providers, and incomplete or nonexistent electronic sharing of information. In addition to the system challenges associated with TOC, patient factors such as health literacy must be considered when developing a program.

Financial and Staffing Challenges

Often, institutions pilot new TOC services without expanding staffing and without enough financial resources to support the new systems. Most pilot programs draw staff from existing services that must continue. When a program is piloted this way, gaps in care may occur because the transition services are not available every day and during all hours. It is usually only after improved quality and safety outcomes have been demonstrated that the pilot can be justified financially.

Lack of Standardized Processes

Organizations continue to experiment to identify the best TOC model for their environment and culture. Because there is a lack of standardized processes among health care organizations, care providers who are receiving patients cannot have a consistent expectation of the information to be shared. However, standardized formats on discharge summaries have improved the receiving providers’ perceptions on the quality of the shared document (Kripalani 2007). Nevertheless, patients cannot expect to receive the same care processes and document formats from one health care organization to another.

Health Information Technology Interoperability

Interoperability of health information technology systems is the ability of electronic health records (EHRs) to share information with other EHR software and systems. Interoperability can facilitate reliable and quick transmission of TOC information, such as discharge summaries and plans.

Meaningful Use of EHRs

The Health Information Technology for Economic and Clinical Health (HITECH) Act of 2009 provides financial incentives (additional payments) to providers and hospitals for the meaningful use of EHRs. "Meaningful

<table>
<thead>
<tr>
<th>Medical Condition</th>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>HF</td>
<td>DM, CAD, aortic stenosis, COPD, prior stroke, prior PCI, BUN &gt; 40 or SCr &gt; 2.5 mg/dL, male sex, single, using Medicaid, increased number of address changes, lacking self-management skills</td>
</tr>
<tr>
<td>AMI</td>
<td>DM, prior MI, prior PCI, prior stroke, COPD, HF on presentation, HTN, history of PUD, renal failure</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>DM, HF, CAD, chronic lung disease, history of renal disease, dementia, immunosuppressant use, cancer</td>
</tr>
</tbody>
</table>

AMI = acute myocardial infarction; CAD = coronary artery disease; DM = diabetes mellitus; HF = heart failure; HTN = hypertension; MI = myocardial infarction; PCI = percutaneous coronary intervention; PUD = peptic ulcer disease.

use” denotes the use of certified health information technology to (1) improve the quality, safety, and efficiency of health care; (2) reduce health disparities; (3) engage patients and families; (4) improve care coordination; (5) improve population and public health; and (6) ensure adequate privacy and security protection for personal health information. Interoperability and information exchange are requirements for incentives.

Exchange outside health networks and between different vendors has been limited. At least two measures for stage 2 meaningful use affect care coordination. To receive incentives for stage 2 meaningful use from the Centers for Medicare & Medicaid Services (CMS), providers must electronically share a care summary record that includes diagnostic test results as well as a problem list, drug list, and list of allergies for more than 50% of referrals and TOC. The deadline for achieving stage 2 meaningful use was extended to allow hospitals and providers additional time to meet criteria. To stimulate information exchange between health care providers using different EHR vendors and outside organization networks, CMS is requiring providers to carry out at least one instance of exchange with a provider using a different EHR vendor or test vendor.

Before the HITECH Act specified meaningful-use criteria, care standards for communication between providers of care during transitions had not been clearly defined. Even now, with performance measures endorsed by quality organizations and adopted by payers, discharge summaries are not always communicated reliably and quickly between organizations. The receiving care provider may be unable to provide appropriate care to a patient if the discharge plan and summary have not been relayed in a timely manner.

Moreover, despite recommendations by the American Geriatrics Society to improve TOC by developing electronic communication systems that facilitate the sharing of important clinical data among providers using diverse EHR systems, challenges still exist (Coleman 2003). Some outpatient clinics and hospitals in affiliated health systems share similar EHR functionality, making communication between providers more streamlined. However, many outpatient providers use EHRs that are not interoperable with EHRs from another vendor; hence, patient information is not effectively transferred between settings.

Source of Prescription Drug Information

A Canadian prospective cohort study compared medication histories recorded in the ED with prescription records from community pharmacies. Results showed that pharmacy records identified 41.5% more prescribed drugs than ED-obtained medication histories (Tamblyn 2013). Patients who filled prescriptions at more than one pharmacy or who took greater than 12 drugs were more likely to have drugs omitted from the ED medication list. When secure messaging within a patient Web portal was used to assist with medication reconciliation after an inpatient-to-outpatient TOC, drug discrepancies and potential ADEs were identified (Heyworth 2013). Developing health information exchanges that include data about prescriptions dispensed from community pharmacies and that use patient-interface health information technology tools could improve the process of obtaining an accurate medication history throughout TOC.

Health Literacy and Educational Needs

Evaluating Health Literacy

Health literacy is defined as “the degree to which individuals can obtain, process, and understand the basic health information and services they need to make appropriate health decisions” (Ratzan 2000). Health literacy, as well as the amount of information shared during TOC, must be considered when communicating with patients. Tests used to identify low health literacy include the Rapid Estimate of Adult Literacy in Medicine (REALM) and the Test of Functional Health Literacy in Adults (TOFHLA). Health care providers should apply these measurement tools in clinical practice only if they are willing to adapt their findings to communications with patients who have low health literacy (Davis 1998). Other indicators of patient low health literacy include claiming to forget reading glasses, consistently bringing someone along to office visits, or incompletely or inaccurately filling out forms (Williams 2002).

Health Literacy of Hospitalized Patients

In a 1995 study of patients in two public hospitals (n=2659), 62% of Spanish-speaking patients and 35% of English-speaking patients had inadequate or marginal functional health literacy using their native language, as measured by TOFHLA. In this study, 42% of patients did not understand directions for taking a drug on an empty stomach, 26% did not understand when the next appointment was scheduled, and 60% did not understand a standard informed consent form. Inadequate or marginal functional health literacy was more common among elderly patients (Williams 1995). Inadequate or marginal health literacy has been noted in 60% of adults hospitalized for medical diagnoses such as cardiovascular disease, congestive heart failure, pneumonia, cardiac arrhythmias, chronic obstructive pulmonary disease (COPD), and skin and subcutaneous infections. Health literacy was measured using the short form of the TOFHLA (s-TOFHLA). Patients in the inadequate literacy category were older, less well educated, had lower income, and were more likely to be non-white (Morris 2011). Similar rates of health literacy were found in patients hospitalized for cardiovascular diseases. Health literacy, as measured using the s-TOFHLA, was inadequate (42%) or marginal (19%) in hospitalized patients with a diagnosis of heart failure (Dennison 2011). In a study of hospitalized patients...
with acute coronary syndromes, 44% had inadequate health literacy as measured by the REALM (Kripalani 2010). Health literacy as measured by the s-TOFHLA was higher in adults hospitalized for acute coronary syndromes or acute decompensated heart failure (inadequate 11%, marginal 9%) (Marvanova 2011).

A study of elderly patients investigated the association between health literacy and medication discrepancies after hospital discharge. In more than half of participants, a discrepancy was seen between the discharge drug list and the patient’s actual home drug use within 48 hours of discharge (Lindquist 2012). Patients with inadequate and marginal health literacy were more likely to be unintentionally nonadherent to drugs than were patients with adequate health literacy. To address patient needs, the Joint Commission has set standards for hospital performance to ensure effective patient-centered communication and cultural competence. Other standards address the need to educate patients about follow-up care and services during TOC.

Communication Considerations

The teach-back method can be used by health care providers to clearly explain information to patients and families. Teach-back should always be used to ensure that patients understand what they have just been taught. Teach-back involves asking patients in a caring way to show or explain in their own words what they need to know or do. Misunderstanding is better detected by open-ended questions rather than yes-no questions; the health care provider should avoid asking patients whether they understand.

The teach-back method provides an opportunity to re-explain in a different way if a misunderstanding is discovered. One approach is for health care providers to explain that they want to make sure they have explained instructions clearly. Asking patients to demonstrate how they will explain the information to family or friends after they get home is part of the teach-back method. A health literacy educational resource for pharmacy personnel who share health information with patients, as well as an assessment tool to evaluate how prepared pharmacies are to care for patients with limited health literacy, are available on the Agency for Healthcare Research and Quality (AHRQ) Pharmacy Health Literacy Center Web site.

Diversity factors to consider when interacting with patients, family members, and caregivers include educational level, primary language, and race/ethnicity. English proficiency should be evaluated, and translator services should be offered and available when needed.

At-Risk Patient Populations

Health-related and social factors can contribute to an increased risk of hospital readmission. Most studies in this area evaluated 30-day rates of hospital readmission, ADEs, and medication discrepancies. Medical Conditions

Medical conditions associated with increased readmission rates include heart failure, myocardial infarction, pneumonia, COPD, previous stroke, heart disease, and diabetes (Dharmarajan 2013; Coleman 2004a; Smith 2000). With the CMS Readmissions Reduction Program now targeting heart failure, acute myocardial infarction (AMI), and pneumonia, hospitals must focus on reducing hospital readmissions for these medical conditions. Table 4-1 shows the specific risk factors associated with readmission rates for these three medical conditions.

One study found 30-day readmission rates for Medicare patients with heart failure and pneumonia to be around 27% and 20%, respectively (Jencks 2009). Incorporating electronic risk calculators into hospital EHRs may help clinicians determine which patients will benefit from TOC interventions (Sutariya 2013).

Previous Hospitalizations

The number of previous hospitalizations has also been associated with an increased risk of readmission. More than one hospital admission in the past year has been associated with an increased risk of readmission in addition to the number of hospitalizations and ED visits within the past 6 months (Hasan 2009; Smith 2000).

Drug-Related Factors

The number of prescribed daily drugs also increases ADEs. One study found that the mean number of ADEs per patient increased by 10% for each additional drug (Gandhi 2003).

Medication discrepancies are common in elderly patients with chronic medical problems who transition from hospital to home (Coleman 2005). The Medication Discrepancy Tool was used to record differences between prehospital drug records, hospital discharge summary drug lists, and posthospital drug containers in the home. The Tool captures information about the discrepancy, including patient- and system-level causes and contributing factors and actions taken to resolve the problem. Patient-level causes include adverse drug reactions, intolerance, and the inability to afford prescriptions. System-level causes include factors like unclear discharge instructions, duplicate therapy, and unrecognized cognitive impairment.

Medication discrepancies represent a potential for a drug error because of a lack of consistency; this is not necessarily an actual drug error. In one study, about 14% of patients experienced at least one medication discrepancy. The drug classes that caused more than half of the medication discrepancies included anticoagulants, diuretics, angiotensin-converting enzyme inhibitors, lipid-lowering agents, and proton pump inhibitors. Because more patients who experienced a medication discrepancy were readmitted to the hospital within 30 days than patients who did...
not experience a discrepancy (14.3% vs. 6.1%, p=0.04), medication discrepancies should be reduced in an effort to improve readmission rates.

**Social Factors**

Social factors such as low income and low self-rated health also serve as predictors of readmissions (Hasan 2009; Coleman 2004a; Philbin 2001). Combinations of risk factors are also predictors of hospital readmissions. Such combinations include functional impairment and comorbidities, stroke and low self-rated health, heart disease and visual impairment, and diabetes and other comorbidities (Coleman 2004a). See Table 4-1 for social risk factors related to heart failure.

**TOC Interventions and Outcomes in Primary Literature**

The main goal of most TOC interventions is to reduce hospital readmissions. Of 17 randomized controlled trials of TOC interventions enrolling 100 or more subjects and investigating ED visits, readmission, length of stay, or mortality outcomes, only six studies included interventions made by pharmacists (Table 4-2) (Marusic 2013; Gillespie 2009; Jack 2009; Crotty 2004; Nazareth 2001; Stewart 1998). All but one of the 17 studies investigated interventions involving patients who were discharged from hospital to home. The exception is a study of patients being discharged from the hospital to an LTCF (Crotty 2004).

The results of trials investigating pharmacist interventions were mixed. Two trials showed no reduction in ED visits (Marusic 2013) or hospital readmissions (Marusic 2013; Nazareth 2001). Three studies confirmed the benefit of pharmacist interactions in reducing ED visits (Gillespie 2009; Crotty 2004), readmissions (Gillespie 2009; Crotty 2004), and a composite of readmissions and out-of-hospital deaths (Stewart 1998). One study showed reduced ED visits and hospitalizations when a clinical pharmacist provided postdischarge telephone calls and a nurse discharge advocate supported additional TOC interventions, which included setting follow-up appointments and completing medication reconciliation (Jack 2009). Interventions not involving pharmacists that have reduced ED visits, readmissions, and mortality typically offer more comprehensive interventions than telephone calls, including postdischarge home visits.

**Established TOC Models**

**Project RED**

Project Re-engineered Discharge (RED) is a research group at Boston University Medical Center whose work is supported by grants from several organizations, including the AHRQ and the National Heart, Lung, and Blood Institute. Project RED includes many important aspects of the TOC process, including providing discharge medication reconciliation, making appointments for follow-up medical appointments and laboratory tests or studies, expediting transmission of the discharge summary to the clinicians accepting care of the patient, and providing postdischarge telephone calls (see Table 4-2). Although the estimated costs of implementation were not provided, they did include 0.5 full-time equivalents for a nurse and 0.15 full-time equivalents for a clinical pharmacist (Jack 2009). Project RED has also been adapted for use in the SNF setting (Berkowitz 2013). An intervention study with a historical control showed reduced 30-day hospital readmissions (from 18.9% to 10.2%; p<0.05) for patients being discharged to an SNF.

**Care Transitions Intervention**

The core principle of the Care Transitions Intervention (CTI) program is self-management; a transitions “coach” facilitates patient behaviors and communication skills to improve confidence in responding to problems encountered during TOC. The intervention includes a home visit and three telephone interactions with patients after discharge from the hospital to home. The CTI provides medication self-management, a personal health record, appropriate follow-up with primary and/or specialty care, and support for patient recognition of symptoms necessitating follow-up action. The program has been tested in several settings and widely adopted. The Medication Discrepancy Tool, a key component of the CTI, can be used to document medication discrepancies discovered during TOC. The CTI Program is based in the Division of Healthcare Policy and Research at the University of Colorado Denver School of Medicine and has the exclusive authority to provide training on the CTI program. The annual cost of implementing the CTI program is estimated at $74,000 (Coleman 2006). Items included in the estimate are salary and benefits for the transitions coach, cellphone and pager, mileage reimbursement, and photocopying and supply costs. The transitions coach manages 24–28 patients at a time.

In one study, elderly patients discharged to home from the hospital who received CTI for 30 days experienced sustained reductions in readmissions at 30, 90, and 180 days compared with controls (Coleman 2004b). In a randomized controlled trial of CTI conducted in elderly hospitalized patients in an integrated health delivery system, 30- and 90-day readmission rates were lower for patients receiving CTI compared with the control group (Coleman 2006) (see Table 4-2). Mean hospital costs at 180 days were lower for intervention patients than for control patients. A quasi-experimental prospective cohort study that enrolled fee-for-service Medicare patients and compared CTI with usual care found that the 30-day readmission rate was lower for patients who received CTI (Voss 2011).

**Transitional Care Model**

The transitional care model (TCM) was developed by a multidisciplinary team at the University of Pennsylvania.
<table>
<thead>
<tr>
<th>Trial</th>
<th>Population (n)</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coleman 2006</td>
<td>≥ 65 years, living in community, admitted to general hospital medicine service (750)</td>
<td>TOC intervention: APN transitions coach provided personal health record and home and telephone visits; coordinated follow-up with PCP after hospital discharge</td>
<td>30-day readmission rates: 8.3 vs. 11.9%, p=0.048. 90-day readmission rates: (16.7 vs. 22.5%, p=0.04). 180-day readmission rates: 25.6 vs. 30.7%, N.S.</td>
</tr>
<tr>
<td>Crotty 2004</td>
<td>Hospital discharge to first-time LTCF (110)</td>
<td>Pharmacist transition coordinator provided medication management</td>
<td>↓ Hospital usage (ED visits or rehospitalization) for patients alive at follow-up in the intervention vs. control group: RRR 0.38 (95% CI, 0.15–0.99). No effect on hospital usage for any patients at follow-up, intervention vs. control: RRR 0.58 (95% CI, 0.28–1.21)</td>
</tr>
<tr>
<td>Finn 2011</td>
<td>Hospitalized general medicine patients (872)</td>
<td>APN completed discharge paperwork, coordinated outpatient hospital follow-up, and educated patients</td>
<td>No significant difference between groups in 30-day ED visits or rehospitalization</td>
</tr>
<tr>
<td>Gillespie 2009</td>
<td>Hospitalized patients &gt; 80 years (400 randomized, 368 analyzed)</td>
<td>Hospital-based pharmacist provided medication management, patient education, follow-up with PCP, and 2-month telephone call to patients</td>
<td>↓ 16% in all hospital visits in the intervention group (quotient 1.88 vs. 2.24; estimate 0.84; 95% CI, 0.72–0.99). ↓ 47% in ED visits in the intervention group (quotient 0.35 vs. 0.66; estimate 0.53; 95% CI, 0.37–0.75). ↓ 80% in drug-related readmissions in the intervention group (quotient 0.06 vs. 0.32; estimate 0.20; 95% CI, 0.10–0.41)</td>
</tr>
<tr>
<td>Jack 2009</td>
<td>General hospital medicine patients &gt; 18 years (749)</td>
<td>Project Re-engineered Discharge: Nurse discharge advocate set up follow-up appointments, provided patient education, and completed medication reconciliation; clinical pharmacist conducted telephone follow-up 2–4 days postdischarge</td>
<td>↓ ED visits and hospitalizations within 30 days of discharge in the intervention group: RRR 0.695 (95% CI, 0.15–0.99)</td>
</tr>
<tr>
<td>Kasper 2002</td>
<td>Hospitalized patients with primary diagnosis of HF, NYHA functional class III/IV HF and judged to be at high risk of HF readmission (200)</td>
<td>Team consisting of cardiologist, HF nurse, telephone nurse coordinator, and patient’s PCP</td>
<td>↓ Combination of deaths and total number of HF admissions at 6 months in the intervention group compared with usual care (49% vs. 73%; p=0.09)</td>
</tr>
<tr>
<td>Kimmelstiel 2004</td>
<td>Hospitalized with primary diagnosis of HF (200)</td>
<td>Disease management for 90 days by nurse, including home visit, education, scheduled telephone calls, and communication with HF physician specialist and PCP</td>
<td>↓ HF hospitalizations at 90 days (RR 0.48, p=0.027), ↓ hospital days for HF (RR 0.54, p&lt;0.001), ↓ CV hospitalizations (RR 0.57, p=0.043), and ↓ hospital days from CV causes (RR 0.64, p&lt;0.001) in the intervention vs. control group</td>
</tr>
<tr>
<td>Koelling 2005</td>
<td>Hospitalized patients with systolic HF (223)</td>
<td>1-hour one-on-one teaching session with a nurse educator added to standard discharge process</td>
<td>↓ Rehospitalization or death at 6 months in the intervention group vs. control: RR 0.65 (95% CI, 0.45–0.93; p=0.018) ↓ HF rehospitalization at 6 months in the intervention group vs. control: RR 0.49 (95% CI, 0.27–0.88; p=0.015)</td>
</tr>
<tr>
<td>Trial</td>
<td>Population (n)</td>
<td>Intervention</td>
<td>Outcomes</td>
</tr>
<tr>
<td>------------</td>
<td>----------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Legrain 2011</td>
<td>Consecutive inpatients ≥ 70 years (665)</td>
<td>Geriatricians provided comprehensive medication review, education on self-management of disease, and detailed TOC communication with outpatient health professionals</td>
<td>↓ 3-month readmission and ED visit rates in the intervention vs. control group (23% vs. 30.5%; p=0.03). 3-month event-free survival higher in the intervention group (HR 0.72; 95% CI, 0.53–0.97; p=0.03). No difference in readmissions/ED visits or event-free survival at 6 months</td>
</tr>
<tr>
<td>Lim 2003</td>
<td>Inpatients &gt; 65 years who were discharged to home requiring community services (598)</td>
<td>Case management and discharge planning provided by post–acute care coordinator</td>
<td>No difference in mortality, unplanned readmissions, and ED visits. Intervention patients used ↓ hospital bed days in the 6 months postdischarge (mean 3.0 vs. 5.2 days; p=0.01)</td>
</tr>
<tr>
<td>Marusic 2013</td>
<td>Hospitalized elderly patients prescribed ≥ 2 medications for treatment of chronic diseases (160)</td>
<td>Predischarge counseling about medications by clinical pharmacist</td>
<td>No difference in readmission and ED visit rates in the intervention vs. control group (p=0.224). More patients in the intervention group were readmitted or visited the ED for ADRs (p=0.022)</td>
</tr>
<tr>
<td>Naylor 1999a</td>
<td>Hospitalized patients ≥ 65 years admitted for medical or surgical reasons (363)</td>
<td>Transitional care model: APNs provided discharge planning and home follow-up for 4 weeks postdischarge</td>
<td>24 weeks after hospital discharge, control group had higher single readmission rates (37.1% vs. 20.3%; p&lt;0.001) and multiple readmission rates (14.5% vs. 6.2%; p=0.01) than intervention group</td>
</tr>
<tr>
<td>Naylor 2004</td>
<td>Hospitalized patients with HF ≥ 65 years (239)</td>
<td>TOC model: APNs provided discharge planning and home follow-up for 3 months postdischarge</td>
<td>↓ Readmissions at 52 weeks (364 days) in the intervention vs. control group (104 vs. 162; p&lt;0.047)</td>
</tr>
<tr>
<td>Nazareth 2001</td>
<td>Hospitalized patients ≥ 75 years and taking ≥ 4 medications at discharge (362)</td>
<td>Hospital pharmacist developed discharge plan and community pharmacist follow-up</td>
<td>No difference in rate of patients readmitted between intervention and control group at baseline, 3 months, and 6 months postdischarge</td>
</tr>
<tr>
<td>Nikolaus 1999</td>
<td>Elderly patients with acute illnesses admitted from home to geriatric hospital (545)</td>
<td>Comprehensive geriatric assessment and postdischarge home intervention (intervention), comprehensive geriatric assessment alone (assessment) or usual care</td>
<td>Intervention group showed significant ↓ in hospital LOS (33.49 days vs. 40.7 days in assessment group and 42.7 days in control group; p=0.05) and rate of immediate nursing home placement (4.4% vs. 7.3% and 8.1%; p&lt;0.05). No difference in survival, hospital readmissions, or new admissions to nursing home. Intervention group had shorter hospital readmissions (22.2 days vs. 34.2 days and 35.7 days; p&lt;0.05) and nursing home placements (114.7 days vs. 161.6 days and 170.0 days; p&lt;0.05)</td>
</tr>
<tr>
<td>Rich 1995</td>
<td>≥ 70 years hospitalized with HF (282)</td>
<td>Nurse-directed, multidisciplinary intervention involving education, prescribed diet, planning for early discharge, review of medications, and intensive follow-up</td>
<td>Higher readmission rate in the control vs. intervention group (RR 0.56; p=0.02). HF readmissions ↓ 56.2% in the intervention group (p=0.04). Several readmissions ↓ in the intervention vs. control group: 16.4% vs. 6.3% (RR 0.39; p=0.01)</td>
</tr>
</tbody>
</table>
In the TCM, a transitional care nurse coordinates care for older adults transitioning from acute care to another setting. The primary goal of the program is to support the patient and caregivers in preventing rehospitalization from clinical decline by sharing resources, skills, knowledge, and a self-management plan. Ten essential elements of TCM have been identified through clinical trials and implementation of the intervention (Box 4-1). These elements support the transitional care nurse in creating a patient-centric, multidisciplinary, collaborative, comprehensive plan of care, together with home care and post–acute care clinic follow-up visit support.

The TCM reduces costs while improving health outcomes. Several studies have shown that a TCM provided to elderly hospitalized patients results in lower readmission rates (Naylor 2004, 1999a, 1999b, 1994), lower multiple readmission rates (Naylor 1999a, 1999b), more days between discharge and readmission (Naylor 1999a), shorter lengths of stay during readmission (Naylor 1999b, 1994), and fewer hospital days (Naylor 1999a). Time to first readmission or death was longer for patients who received TCM intervention (Naylor 2004). Cost of care was reduced by TCM (Naylor 2004, 1999a, 1994). Short-term improvements in quality of life and patient satisfaction metrics have been reported for patients receiving TCM intervention (Naylor 2004).

Patients who received a 3-month TCM intervention after hospital discharge had fewer readmissions at 52 weeks postdischarge. Direct costs for the intervention (n=118) were about $50,000 higher than for the control group (n=121). Costs were attributed to advanced practice nurse home visits, higher salaries, and the involvement of multidisciplinary heart failure experts. Direct costs were offset by savings from reductions in hospitalizations,
Box 4-1. Transition of Care Model Essential Elements

1. Use of advanced knowledge and skills by a TCN to serve as primary care coordinator to deliver and coordinate care of high-risk older adults within and across all health care settings
2. Comprehensive, holistic assessment of each older adult’s priority needs, goals, and preferences
3. Collaboration with older adults, family caregivers, and team members in implementation of a streamlined, evidence-based plan of care designed to promote positive health and cost outcomes
4. Regular home visits by the TCN with available, ongoing telephone support (7 days/week) for an average of 2 months
5. Continuity of health care between hospital, post–acute care, and primary care clinicians facilitated by the TCN accompanying patients to visits to prevent or follow up on an acute illness care management
6. Active engagement of patients and family caregivers with a focus on meeting their goals
7. Emphasis on patients’ early identification and response to health care risks and symptoms to achieve longer-term positive outcomes and avoid adverse and untoward events that lead to acute care service use (e.g., ED visits, rehospitalizations)
8. Multidisciplinary approach that includes the patient, family caregivers, and health care providers as members of a team
9. Strong collaboration and communication between older adults, family caregivers, and health care team members across episodes of acute care and in planning for future transitions (e.g., palliative care)
10. Ongoing investment in optimizing transitional care through performance monitoring and improvement

TCN = transitional care nurse.
Information from: Transitional Care Model, Essential Elements.

acute care visits to the ED and physicians, and home visits by other health care professionals (Naylor 2004).

Guided Care Model

In the Guided Care (GC) model, a trained registered nurse collaborates with patients, physicians, and other health care providers in the primary care setting to coordinate patient-centered care. The target population is patients with several chronic conditions, not only those experiencing TOC, although care coordination is provided when patients transition through care settings. The services provided to patients in collaboration with PCPs include comprehensive assessment, evidence-based care planning, proactive monitoring, care coordination, transitional care, coaching for self-management, caregiver support, and access to community-based services.

Patients using the GC model employed home health services at a 29% lower rate (Boult 2013) and assessed the quality of care higher compared with patients receiving usual care (Boult 2013; Boyd 2010). In a study investigating the impact of the GC model on health services use, the only effect in the entire patient sample was a reduction in home health care use (Boult 2011). When only analyzing patients receiving care from an integrated health delivery system, results showed fewer SNF days and admissions compared with usual care. Physician practices wanting to implement the GC model must obtain a license from Johns Hopkins University; this license includes access to important forms and protocols.

The GC model may be associated with less use of high-cost health services (i.e., hospital, SNF, and home care services) compared with usual care according to insurance claims. The annual net savings in health care costs has been estimated at $1364 per patient. The factors included in the cost of using the GC model were the nurse’s salary, fringe benefits, Internet and cellphone communications, computer and cellphone equipment, and travel. Physician time was not included in the cost estimate because physicians reported their time investment as insignificant. The GC nurse role managed an average of 55 patients at a time (Leff 2009).

Patient-Centered Primary Care Collaborative: Patient-Centered Medical Home

The patient-centered medical home strives to provide structured and coordinated care centered on the specific needs of the patient. The Patient-Centered Primary Care Collaborative joint principles include a personal relationship with the physician or licensed practitioner, a team approach, a comprehensive/whole-person approach, coordination and integration of care across all domains of the health care system, quality and safety, expanded access to care, and recognition of added value. Comprehensive medication management is an integral component of the patient-centered medical home and ensures that each patient’s drug is appropriate for that individual, effective for the medical condition, safe given the patient’s comorbidities and concomitant drugs, and able to be taken by the patient (PCPCC 2012).

To provide comprehensive medication management in the medical home, the following steps must be taken to produce positive patient outcomes and add value to patient care: assessment of the patient’s medication-related needs, identification of the patient’s medication-related problems, development of a care plan with individualized therapy goals and personalized interventions, and follow-up evaluation to determine actual patient outcomes. Pharmacists can use the time-based Current Procedural Terminology (CPT) codes 99605, 99606, and 99607 as...
a means of receiving payment from health plans that provide a medication management benefit.

**National Initiatives and Resources**

**BOOST Program**
The Society for Hospital Medicine’s BOOST (Better Outcomes for Older Adults Through Safe Transitions) program provides health care providers with the 8Ps risk assessment tool for older adults (Box 4-2). Risk factors for adverse events after discharge include problem drugs, psychological issues, principal diagnosis, polypharmacy, poor health literacy, poor patient support, prior hospitalization in the past 6 months, and palliative care. Although not validated in the literature, the 8Ps tool allows providers to assess the risk of adverse events during TOC.

**National Transitions of Care Coalition**
The NTOCC is a multidisciplinary team of health care providers whose goal is to raise awareness about TOC among health care professionals, government leaders, patients, and caregivers to increase quality of care, reduce drug errors, and enhance clinical outcomes. Specific goals outlined in the NTOCC policy paper include improving communication during transitions between providers, patients, and caregivers; implementing electronic medical records that include standardized medication reconciliation elements; increasing the use of case management; expanding the pharmacist’s role in TOC; implementing payment systems that align with incentives; and developing performance measures to encourage better TOC (NTOCC 2008a).

The NTOCC has online resources to help health care providers implement TOC initiatives. For example, the “Improving on Transitions of Care: How to Implement and Evaluate a Plan” guidebook contains implementation and evaluation outlines specific to hospital/home transitions (NTOCC 2008b). Steps in the outline include selecting what plan to study (e.g., target the area for change), assessing the current process, determining the current performance level (e.g., whether information is being communicated by the hospital to the patient and to the patient’s PCP within the appropriate time interval), and determining the intervention strategy.

The NTOCC Measures Work Group document provides a framework for measuring TOC according to the key elements of optimal TOC (NTOCC 2008c). These elements include structure (e.g., an accountable provider at all point-of-care transitions), care team processes (e.g., medication reconciliation, test tracking, follow-up appointment tracking, admission and discharge tracking), information transfer/communication between providers and care settings, and patient and family education and engagement. The Measures Work Group document also has assessment outcomes, including patient/caregiver satisfaction, provider satisfaction with quality of collaboration among providers, health care use and costs (e.g., readmissions), and other health outcomes (e.g., medical errors, continuity of care).

**Box 4-2. Risk Categories in the Project BOOST 8P Screening Tool**

**Problem medications**
- Anticoagulants
- Insulin
- Oral hypoglycemic agents
- Aspirin and clopidogrel dual therapy
- Digoxin
- Narcotics

**Psychological**
- Depression screen positive
- History of depression diagnosis

**Principal diagnosis**
- Cancer
- Stroke
- DM
- COPD
- HF

**Polypharmacy**
- ≥ 5 routine medications

**Poor health literacy**
- Inability to use the teach-back method

**Patient support**
- Absence of caregiver to assist with discharge and home care

**Prior hospitalization**
- Nonelective hospitalization in the past 6 months

**Palliative care**
- Would you be surprised if this patient died in the next year?
- Does this patient have an advanced or progressive serious illness?


**H2H Initiative Project**
The Hospital to Home (H2H) initiative is a national quality improvement initiative led by the American College of Cardiology and the Institute for Healthcare Improvement (IHI); it is designed to improve TOC and reduce unnecessary readmissions for patients with heart failure or AMI. The H2H initiative serves as a clearinghouse for information, tools, and practical strategies for providers to improve TOC, with the goal of a 20% relative reduction in the national CMS 30-day all-cause
readmission rate. Interested participants (e.g., hospitals, private practices, home health agencies, nurses, hospitalists, pharmacists) can enroll online for free to participate in the H2H initiative. The program asks that registered participants take action in obtaining administrative support, assembling an improvement team, developing an improvement plan, and reporting on progress through periodic responses to brief surveys.

IHI STAAR Initiative

The IHI launched the State Action on Avoidable Rehospitalizations (STAAR) initiative in May 2009 to reduce rehospitalizations by working across organizational boundaries and engaging payers; stakeholders at the state, regional, and national levels; and patients, families, and caregivers. The STAAR initiative is currently working with providers in Massachusetts, Michigan, and Washington.

In its How-to Guide on improving transitions from the hospital to the clinical office practice, the STAAR initiative outlines recommended changes to mitigate the typical failures (Schall 2013). These recommendations include providing timely access to care after a hospitalization, preparing the patient and clinical team before the visit (e.g., reviewing the discharge summary, a reminder call to help prepare patients/caregivers for the visit), assessing patients and initiating a new care plan, and communicating the continuing care plan at the end of the visit (e.g., providing a reconciled drug list, ensuring the next appointment is made).

The STAAR initiative provides three categories for the patient’s risk of rehospitalization. (1) Low-risk patients have had no other hospital admissions in the past year, and the patient/family caregiver has a high degree of confidence in using the teach-back method to carry out self-care at home. (2) Moderate-risk patients have been admitted one additional time in the past year, and the patient/family caregiver has a moderate degree of confidence in carrying out self-care at home. (3) High-risk patients have been admitted two or more additional times in the past year, are unable to use the teach-back method, and have a caregiver with a low degree of confidence in carrying out self-care at home. Patients deemed at high risk should be seen by home health care or a PCP within 48 hours after discharge, and those deemed at moderate risk should be given a follow-up telephone call within 48 hours and be seen by a provider within 5 days. The clinician assesses the patient’s ability to perform self-care practices, including use of drugs, diet, nutrition, symptom awareness and management, and reasons to call the physician.

The How-to Guide provides several resources on patient self-management and use of health literacy principles and the teach-back method. Additional STAAR guides cover transitions from the hospital to SNFs, home health care, and community settings to reduce avoidable rehospitalizations.

MATCH Tool

The Medications at Transitions and Clinical Handoffs (MATCH) toolkit was developed by a multidisciplinary team as a systematic resource to improve medication reconciliation, regardless of the type of health care setting. The goal of this initiative was to decrease medication discrepancies and reduce potential and actual patient harm. The appendix of the toolkit can be used as a work plan to implement or improve medication reconciliation. A study using the MATCH principles identified risk factors and potential harm related to drug errors during hospital admission. Pharmacist-obtained drug histories were compared with hospital physician-obtained drug histories and admission orders for 651 patients admitted to the adult medicine inpatient service at an academic hospital. Medication discrepancies that required an order change were considered errors. Study patients experienced a drug error 35.9% of the time. Of patients with discovered errors, 85% (n=309) had order errors related to inaccurate admission medication histories. Almost 50% of errors were omissions, whereas different doses and frequencies accounted for 30.4% and 11% of errors, respectively. Almost 12% of errors were categorized as potentially harmful based on pharmacist and physician analysis. Patients who presented a drug list on hospital admission were less likely to experience a drug order error rated as potentially requiring monitoring or an intervention or as potentially causing harm (odds ratio [OR] 0.35; 95% confidence interval [CI], 0.19–0.63). Risk factors associated with the same error ratings included age 65 years or older (OR 2.17; 95% CI, 1.09–4.30) and number of preadmission prescription drugs (OR 1.21; 95% CI, 1.14–1.29). The results emphasize the importance of obtaining an accurate admission medication history, especially in older patients taking several drugs (Gleason 2010).

Medication Reconciliation: MARQUIS Trial

The Multicenter Medication Reconciliation Quality Improvement Study (MARQUIS) is an AHRQ-funded study led by the Society of Hospital Medicine. The first two study aims, already completed and published, are as follows. (1) Develop a toolkit of recommendations for medication reconciliation. (2) Conduct a multicenter quality improvement project in which hospitals adopt and implement the toolkit. Future goals of the study are to evaluate the toolkit’s effectiveness in improving patient safety by reducing unintentional medication discrepancies and to assess which elements of a medication reconciliation program are most likely to improve safety. The toolkit is divided into three sections addressing preparation and site assessment, the MARQUIS intervention components, and ready-to-use tools. Some tools include training on how to take the best possible medication history and how to obtain senior leadership buy-in (e.g., a return-on-investment [ROI] calculator). Of note, the toolkit has not yet been proved to improve drug safety (Mueller 2013).
Care Coordination Measures Atlas

One of the broad approaches recommended in the AHRQ’s Care Coordination Measures Atlas is medication management. The atlas was created as a guide for researchers and evaluators seeking metrics for interventions designed to improve care coordination, mainly in the ambulatory care setting. Each care coordination metric is presented in a table format structured to categorize measures by the perspectives of patients and family members, health care professionals, and the health care system, as well as by care coordination activities and broad approaches. As care coordination services are implemented, the atlas can serve as a resource to identify relevant, clearly defined, quantitative, and validated metrics by which to measure the effect of new programs. The atlas provides detailed information on 30 care coordination metrics that evaluate some aspect of medication management. Of these metrics, 18 are categorized as having a patient and family perspective, 6 are labeled as having a health care professional perspective, and 6 are classified as having a system perspective.

Fundamentals of Reducing Acute Care Hospitalizations: Best Practice Intervention Package

The Home Health Quality Improvement National Campaign promotes best practice intervention packages for home health care providers. This program aims to improve TOC by enhancing communication and understanding of causes of hospital readmission. The manual includes tools to reduce acute care hospitalizations such as the patient emergency plan and the hospitalization risk assessment. Podcasts, webinars, team and education resources, checklists, and case studies are also available.

ACCP Process Indicators of Quality Clinical Pharmacy Services in TOC

This American College of Clinical Pharmacy white paper provides guidance on process indicators of quality care during pharmacists’ involvement in TOC according to the type of setting in which the transition occurs (Kirwin 2012). For example, on admission to a hospital or facility, process indicators may include the percentage of patients who have a completed medication history within 24 hours. With the transition from hospital to home or an ambulatory setting, process indicators may include use of the TOC performance measurement set, as discussed previously. The main process indicator of pharmacist effectiveness in TOC has been the completion of medication reconciliation forms; however, several additional process indicators measure the quality of pharmacist services, as outlined in the white paper.

Performance Metrics

The Joint Commission – NPSG 03.06.01

The Joint Commission’s NPSG (National Patient Safety Goal) 03.06.01 highlights the need to “maintain and communicate accurate patient medication information.” The goal has five elements of performance, including obtaining information on current drugs when a patient is admitted to a hospital and providing written information on current drugs at discharge. The Healthcare Facilities Accreditation Program and the Det Norske Veritas Healthcare also accredit hospitals and measure the quality of TOC and medication reconciliation as required by CMS.

National Quality Forum – Preferred Practices for Care Coordination

The National Quality Forum (NQF) has endorsed the Three-Item Care Transitions Measure (CTM-3) as a voluntary consensus standard. The metric is a patient-reported outcome measure evaluating patient responses to three questions that apply to all adult discharged patients who stayed in a general acute care hospital at least 1 night (Table 4-3). Patient answers are rated as strongly disagree, disagree, agree, or strongly agree. The CMS issued a final rule for fiscal year 2013 for hospitals stating that the CTM-3 had been added to the Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) patient survey.

HCAHPS Survey

The AHRQ created the HCAHPS survey – a national, standardized, publicly reported 32-item survey of patient perspectives on the hospital experience (CMS 2013). Hospitals subject to the inpatient prospective payment system and participating in the Hospital Value-Based Purchasing (HVBP) program must submit HCAHPS data for payment calculation. Results are publicly reported on the Hospital Compare Web site. The patient survey includes questions about how adequately hospital staff members communicate with patients about new drugs and whether important information is shared with patients at hospital discharge. As mentioned earlier, the CTM-3 questions endorsed by the NQF are now included in the HCAHPS survey.

Physician Consortium for Performance Improvement Quality Measures

The American Medical Association organized the Physician Consortium for Performance Improvement (PCPI) to develop and approve evidence-based clinical performance metrics to promote performance improvement. The measures are field tested and then offered free of charge to health care organizations and payers for benchmarking and tracking performance. The PCPI has developed the NQF-endorsed care transitions performance measurement set, the first phase of which focuses on transitions in inpatient and ED settings. The PCPI plans to address other care setting transitions in future phases. Three measures of the existing set are closely related for patients discharged from an inpatient setting and are bundled (see Table 4-3). A draft measure aims to evaluate discharge planning for patients...
with heart failure. The PCPI supports patient understanding and adherence to postdischarge treatment plans by adding associated questions to the HCAHPS survey.

**CMS Quality Initiatives**

**HVBP Program**

The HVBP program was established by the Affordable Care Act (ACA) of 2010 as a method of providing value-based incentive payments to acute care hospitals, based either on how well the hospitals perform on certain quality measures or on how much a hospital’s performance improves on certain quality measures from a baseline period. The program began in fiscal year 2013 for discharges occurring on or after October 1, 2012. This program consists of two domains, clinical process of care (weighted 70%) and patient experience of care (weighted 30%). A hospital’s clinical process of care domain score is calculated as the percentage of possible points scored on applicable clinical process measures. The patient experience of care is calculated as the sum of the HCAHPS base score and the HCAHPS consistency score. A hospital’s total performance score is the sum of the weighted domain scores.

**CMS Hospital Readmissions Reduction Program**

The CMS Hospital Readmissions Reduction Program aims to decrease unnecessary hospital readmissions (defined as an admission within 30 days of a discharge) by reducing payments to hospitals with excess readmissions. This program was implemented in October 2012 (fiscal year 2013) for readmissions for AMI, heart failure, and pneumonia. The program does not discriminate between types of pneumonia. However, some have challenged CMS to consider excluding or making adjustments for the proportion of patients with health care–associated pneumonia and/or restricting penalties to readmission for community-acquired pneumonia (Sexton 2013). Beginning in fiscal year 2015, CMS plans to expand the program to include patients admitted for an acute COPD exacerbation and for elective total hip and knee arthroplasty.

The program methodology calculates the excess readmission ratio for each applicable condition, which is used, in part, to calculate the readmission payment adjustment. A hospital’s risk-adjusted excess readmission ratio for these three medical conditions is a measure of a hospital’s readmission performance compared with the national average for the hospital’s set of patients with that applicable condition. The CMS established a policy of using the risk-adjustment methodology endorsed by the NQF for the readmissions measures for AMI, heart failure, and pneumonia to calculate the excess readmission ratios, which includes an adjustment for factors that are clinically relevant (e.g., patient demographics, comorbidities, and patient frailty). The Hospital Readmissions Reduction Program is penalty driven (i.e., hospitals may lose up to 2% of their reimbursement), with the penalty increasing to 3% in 2014.

Providers and patients can view readmission rates on the Hospital Compare Web site.

Patient safety organizations (PSOs) were authorized by the Patient Safety and Quality Improvement Act of 2005 to improve the safety and quality of health care delivery in the United States. The ACA designates PSOs to support hospitals in lowering readmission rates. The AHRQ developed the Common Format-Readmissions, Version 1.0 Beta, to analyze hospital readmissions by assisting PSOs and providers in collecting and aggregating standardized data about rehospitalizations.

**National Committee for Quality Assurance HEDIS Measures**

The National Committee for Quality Assurance (NCQA) Healthcare Effectiveness Data and Information Set (HEDIS) was developed by payers, employers, and insurers in the early 1990s. The NCQA is the accrediting body for managed care organizations, and HEDIS is the quality measurement data set used by NCQA. The HEDIS metrics measure the quality of care and service provided by health plans and enable targeting for performance improvement activities (see Table 4-3). Eligible patients must have coverage through a Medicare special needs plan.

The definition of medication reconciliation for this measure is a review in which the discharge drugs are reconciled with the most recent list in the outpatient medical record. Documentation of the CPT code 1111F or a dated notation that the drugs prescribed at discharge in the outpatient medical record were reconciled with current outpatient drugs meets the specifications for

**Decision Scenario**

You are the internal medicine clinical pharmacy specialist at a hospital. The hospital’s administrative staff would like to implement a patient-centered metric that evaluates the quality of preparation for transitions of care at hospital discharge with respect to medications. Which metric would you recommend for use?

**Answer**

The Three-Item Care Transitions Measure (CTM-3) would be the most appropriate patient-centered performance metric in this situation. The CTM-3 was added to the HCAHPS patient survey in fiscal year 2013. One of the items in the CTM-3 survey pertains to how clearly patients understand the reason for taking their medications at hospital discharge (Table 4-3).

Transitions of Care

Documentation in the outpatient medical record is required. For this metric, medication reconciliation should be provided by a prescribing practitioner, clinical pharmacist, or registered nurse.

The HEDIS plan all-cause readmissions measure reports the number of acute inpatient stays followed by an acute readmission for any diagnosis within 30 days and the predicted probability of an acute readmission (see Table 4-3). The risk-adjustment weights for each index hospital stay are based on age, sex, comorbidity, discharge condition, and surgical procedures. Rates are reported in age categories by totals and sex, and they include the average adjusted probability.

**Table 4-3. Transitions of Care Performance Metrics**

<table>
<thead>
<tr>
<th>Organization</th>
<th>Metric(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NQF</td>
<td>CTM-3 Patient Questions</td>
</tr>
<tr>
<td></td>
<td>• The hospital staff considered my preferences and those of my family or</td>
</tr>
<tr>
<td></td>
<td>caregiver when deciding what my health care needs would be when I left the</td>
</tr>
<tr>
<td></td>
<td>hospital</td>
</tr>
<tr>
<td></td>
<td>• When I left the hospital, I had a good understanding of the things I</td>
</tr>
<tr>
<td></td>
<td>was responsible for in managing my health</td>
</tr>
<tr>
<td></td>
<td>• When I left the hospital, I clearly understood the purpose of taking</td>
</tr>
<tr>
<td></td>
<td>each of my medications</td>
</tr>
<tr>
<td>HCAHPS</td>
<td>Care Transitions Performance Measurement Set</td>
</tr>
<tr>
<td></td>
<td>• Percentage of patients discharged from an inpatient facility to home or</td>
</tr>
<tr>
<td></td>
<td>any other site receiving a reconciled medication list and transition</td>
</tr>
<tr>
<td></td>
<td>record</td>
</tr>
<tr>
<td></td>
<td>• Percentage of patients for whom a transition record was transmitted</td>
</tr>
<tr>
<td></td>
<td>within 24 hours of discharge to the facility/health care professional</td>
</tr>
<tr>
<td></td>
<td>responsible for follow-up care</td>
</tr>
<tr>
<td></td>
<td>• Percentage of patients discharged from the ED to ambulatory care or</td>
</tr>
<tr>
<td></td>
<td>home health care receiving a transition record at ED discharge</td>
</tr>
<tr>
<td>PCPI Care Transitions</td>
<td>Care Transitions Performance Measurement Set</td>
</tr>
<tr>
<td>Performance Measurement Set</td>
<td>• Percentage of hospital discharges during the measurement year for</td>
</tr>
<tr>
<td></td>
<td>patients ≥ 66 years for whom medications were reconciled in the outpatient</td>
</tr>
<tr>
<td></td>
<td>medical record within 30 days of discharge</td>
</tr>
<tr>
<td>CMS Readmissions Reduction Program</td>
<td>• Readmission rates for AMI, HF, and pneumonia</td>
</tr>
<tr>
<td>NCQA HEDIS Medication Reconciliation Postdischarge Measure</td>
<td>• Percentage of hospital discharges during the measurement year for patients ≥ 66 years for whom medications were reconciled in the outpatient medical record within 30 days of discharge</td>
</tr>
<tr>
<td>NCQA HEDIS Plan All-Cause</td>
<td>For members ≥ 18 years, the number of acute inpatient stays during the</td>
</tr>
<tr>
<td>Readmissions Measure</td>
<td>measurement year that were followed by an acute readmission for any</td>
</tr>
<tr>
<td></td>
<td>diagnosis within 30 days and the predicted probability of an acute</td>
</tr>
<tr>
<td></td>
<td>readmission. Reported categories include:</td>
</tr>
<tr>
<td></td>
<td>• Count of index hospital stays</td>
</tr>
<tr>
<td></td>
<td>• Count of 30-day readmissions</td>
</tr>
<tr>
<td></td>
<td>• Average adjusted probability of readmission</td>
</tr>
</tbody>
</table>

AMI = acute myocardial infarction; HF = heart failure; MRP = medication reconciliation postdischarge.


**Reimbursement**

**CMS Transitional Care Management Payment**

Effective January 1, 2013, CMS introduced two new CPT codes, 99495 and 99496, that cover transitional care management services within a 30-day period starting on the date of hospital discharge (CMS 2013). Components included in the transitional care management payment are as follows: interactive contact with the patient within 2 days postdischarge by telephone, e-mail, or face-to-face interaction; certain non–face-to-face services (e.g., reviewing discharge information, reviewing need for or follow-up on pending tests, interacting with other health
care professionals, providing education to patients); and a face-to-face visit within 7–14 days, depending on the degree of medical decision complexity. Although the rule does not include pharmacists as one of the nonphysician practitioners legally authorized to provide transitional care management, pharmacists can be part of the health care team that delivers these services to patients.

Justifying Resources

Showing ROI for pharmacist-provided TOC services can help secure resources for converting a pilot project to a full service. Data collection to measure program outcomes must start at the beginning of pilot projects to ensure the appropriate evidence is gathered to support program expansion. Metrics that can establish ROI include hospital and ED admissions and readmissions, length of stay, disease-specific metrics, patient satisfaction or HCAHPS metrics, and drug-related problems. Some drug-related problems that can be detected and resolved during medication reconciliation or management include therapeutic duplication, drug omission for disease treatment, inappropriate dosing, and drug interactions. If performance measures can be integrated into EHR systems, automated data collection can improve measurement efficiency. If outcome, process, structure, and patient-centered measures were integrated in the EHR, prospective tracking of performance could occur when care is provided to patients.

Pharmacists who contribute to providing non-face-to-face services, like evaluating and supporting drug adherence, medication management, and patient education for self-management, should also document and track efforts that support physician practices’ ability to seek reimbursement for transitional care management from CMS. Pharmacists may also bill health plans, including Medicare Part D, for face-to-face medication therapy management using CPT codes 99605, 99606, and 99607.

Conclusion

The pharmacist’s role as an integral part of the multidisciplinary team providing TOC services requires further development. Of importance, patients who will benefit most from pharmacist interventions at TOC should be prioritized to focus services appropriately and justify financial investment. Pharmacists should focus on providing TOC services to patients identified as being at a higher risk of readmissions. Health care systems should strive to standardize processes by adopting national standards and should measure success by comparing metrics with national benchmarks.

References


American College of Cardiology. Hospital to Home (H2H) National Quality Improvement Initiative.


Boston Medical Center Research Group. Components of Re-Engineered Discharge (RED).


Centers for Disease Control and Prevention (CDC). National Hospital Ambulatory Medical Care Survey: Emergency Department Summary Tables. 2010.


Centers for Medicare & Medicaid Services (CMS). Hospital Value-Based Purchasing.

Centers for Medicare & Medicaid Services (CMS). Readmissions Reduction Program.


Joint Commission National Patient Safety Goals: Hospital Accreditation Program. 2014.


National Transitions of Care Coalition (NTOCC). Improving transitions of care: the vision of the National Transitions of Care Coalition. 2008a.


Self-Assessment Questions

61. A 78-year-old man is transferred from a long-term care facility (LTCF) to the ED for mental status changes. After initial assessment in the ED, he is admitted to the medical ICU. During his stay in the ICU, he is sent for a CT scan. Three days later, he leaves the ICU and spends 3 days in the general medicine department. The patient is discharged today to the LTCF with a prescription for an additional 5-day course of antibiotics for a complicated urinary tract infection. Which one of the following best describes the number of transitions of care (TOC) this patient has undergone?
   A. Two.
   B. Three.
   C. Four.
   D. Five.

62. An 80-year-old woman presents with a medical history of hypertension, heart failure (HF), type 2 diabetes mellitus, and atrial fibrillation. Current medications include lisinopril, carvedilol, insulin glargine, and warfarin. Her last hospitalization was 1 year ago. At her most recent clinic visit, she had good recall and comprehension when the provider used the teach-back method. According to the BOOST (Better Outcomes for Older Adults Through Safe Transitions) 8P risk assessment tool for adverse events after discharge, which one of the following best describes this patient’s risk categories?
   A. Problem medications and psychological issues.
   B. Principal diagnosis and poor health literacy.
   C. Problem medications and polypharmacy.
   D. Principal diagnosis and problem medications.

63. A 60-year-old man is currently hospitalized for community-acquired pneumonia. His medical history includes hypertension, COPD, and a myocardial infarction 2 years ago. According to the CMS Readmissions Reduction Program, which one of the following best represents the patient’s current medical condition that would be subject to decreased reimbursements for excessive readmissions?
   A. Community-acquired pneumonia.
   B. Myocardial infarction.
   C. COPD.
   D. Hypertension.

64. As the internal medicine clinical pharmacist at a hospital, you work with a team of health care providers to implement Project Re-engineered Discharge (RED) interventions for improving the hospital’s discharge process. According to Project RED, which one of the following best describes the clinical pharmacist’s role in the discharge process?
   A. Arrange follow-up medical appointments.
   B. Provide postdischarge home visit.
   C. Arrange follow-up laboratory tests and studies.
   D. Perform postdischarge telephone calls.

65. A 56-year-old man admitted to the hospital with symptoms of polyuria and polydipsia receives a diagnosis of type 2 diabetes mellitus. During the hospitalization, he was initiated on daily insulin glargine and insulin aspart before meals. He is now ready for discharge. The patient has received a reconciled medication list and discharge counseling by a pharmacist. Which one of the following interventions is most important as the patient transitions from the hospital to ambulatory care?
   A. Provide a hospital discharge summary to his primary care provider (PCP) in a timely fashion.
   B. Arrange for weekly telephone calls from the patient’s community pharmacy.
   C. Provide the telephone numbers of hospital personnel for the patient to call.
   D. Place a telephone call to the patient 1 month after discharge.

66. An 82-year-old woman was hospitalized for dizziness after taking several β-blockers while living in an LTCF. She is now being discharged back to the same LTCF. Which one of the following is the most important intervention to reduce the risk of adverse drug events (ADEs) after her transition to the LTCF?
   A. Follow-up of her laboratory tests.
   B. Postdischarge medication reconciliation.
   C. Follow-up appointment with her PCP within 1 week.
   D. Transmission of discharge summary to the PCP.

Questions 67 and 68 pertain to the following case.
A.G. is a 71-year-old man on your hospital rounding service whose medical history is significant for HF with reduced ejection fraction, chronic stable angina, type 2 diabetes mellitus, hypertension, and asthma. The patient has been hospitalized twice in the past year for HF exacerbations, and his caregiver is unable to show confidence in caring for A.G. at home.

67. Your hospital has adopted the Institute for Healthcare Improvement (IHI) State Action on Avoidable Hospitalizations (STAAR) initiative. According to the
STAAR initiative, which one of the following best describes A.G.’s risk category and target postdischarge follow-up?

A. High risk, post discharge clinic appointment within 48 hours.
B. High risk, post discharge telephone call within 48 hours.
C. Moderate risk, post discharge telephone call within 48 hours.
D. Moderate risk, post discharge clinic appointment within 5 days.

68. Your hospitalist would like to enroll in the Hospital to Home (H2H) initiative in order to receive tools and strategies to improve TOC. Which one of the following medical conditions would best qualify A.G. for the H2H initiative program?

A. Chronic stable angina.
B. Diabetes.
C. HF.
D. Asthma.

69. A 68-year-old woman is admitted to your general medicine service for a COPD exacerbation. Your team consists of you (the clinical pharmacist), the attending physician, medical residents, and a licensed clinical social worker. Which one of the following would be best to add to your discharge team to serve as a transitions coach?

A. Occupational therapist.
B. Advanced practice nurse.
C. Medical assistant.
D. Registered dietitian.

70. The hospital pharmacy director has tasked you, the clinical pharmacist, with developing a plan for implementing measures to improve the H2H transition process pertaining to medications for general medicine patients. Which one of the following resources will best help you with this task?

A. National Transitions of Care Coalition (NTOCC).
B. Physician Consortium for Performance Improvement (PCPI) quality measures.
C. Patient-centered medical home.
D. Care Coordination Measures Atlas.

71. A health system has excess 30-day readmissions for patients with myocardial infarction. The quality improvement team reviews readmissions during the past 6 months and identifies medication reconciliation, medication discrepancies, and preventable ADEs as the key causes. The chief executive officer asks the management team to identify an evidence-based model of care that includes pharmacists who will implement system-wide interventions to reduce the 30-day readmission rate. Which one of the following established TOC models would be the best solution to suggest?

A. Project RED.
B. Care Transitions Intervention (CTI) program.
C. Transitional care model (TCM).
D. Guided Care (GC model).

72. A 72-year-old woman is being discharged from the hospital to home today. Her PCP uses an electronic health record (EHR) system, but it is not the same system used by the hospital. The hospital is unable to electronically transfer the patient’s discharge summary to the PCP. Which one of the following criteria will best meet stage 2 requirements for the hospital to receive CMS incentives for the meaningful use of EHRs to be used in care coordination?

A. Carry out at least one exchange with a provider using a different EHR system, like that used by this patient’s PCP.
B. Share care summaries that include a problem list, drug list, and list of allergies with the health care providers responsible for follow-up care for more than 50% of the TOC and referrals.
C. Transmit a transition record within 24 hours of discharge to the health care provider responsible for follow-up care.
D. Use a standardized format for discharge summaries in the EHRs of all patients.

73. A 76-year-old Hispanic man recently admitted to the hospital for an HF exacerbation is being discharged this afternoon. One change in his medication regimen is an increase from lisinopril 10 mg orally once daily to 20 mg orally once daily. You have the patient’s new prescription vials that were just filled by the hospital’s outpatient pharmacy, and you have explained the dosage change to him. Using the teach-back method, which is the best way to determine whether the patient understands what you told him?

A. Do you understand how to take lisinopril after you get home?
B. To make sure I did a good job explaining the instructions, using your own words, please tell me how you will take your new lisinopril dose after you get home.
C. To make sure I did a good job explaining the instructions, please tell me how you will explain to your wife your new lisinopril dose after you get home.
D. Please show me which vial contains lisinopril, and tell me how many tablets you will take every day after you get home.
74. A 68-year-old woman being discharged from the hospital today has several predictors for readmission. The hospital administrators would like to adopt a TOC program to prevent this patient from being readmitted. According to randomized controlled trial results, which one of the following transition models of care has shown the most prolonged effect on hospital readmission rates?

A. GC model.
B. Project RED.
C. CTI program.
D. TCM.

75. A 73-year-old woman is hospitalized for COPD, hypertension, and hyperlipidemia. Her home drugs, which have not changed, include lisinopril 20 mg orally once daily, hydrochlorothiazide 25 mg orally once daily, tiotropium inhaler 2 inhalations once daily, and simvastatin 40 mg orally once daily. Which one of the following interventions would most likely prevent the need for home health care after this patient’s discharge?

A. CTI program.
B. TCM.
C. Project RED.
D. GC model.

76. The hospital you work for has created an interdisciplinary team to improve medication reconciliation on one unit of the hospital. The goal of this team project is to identify process and system changes for improving how often medication reconciliation is conducted before hospital discharge using continuous improvement methods. Medication reconciliation that occurs in the outpatient setting is out-of-scope for this project. After the new process is identified, it will be used in other units of the hospital. Which one of the following nationally recognized quality measures is most likely to improve because of this project?

A. HEDIS MRP measure.
B. CMS Readmissions Reduction Program.
C. HCAHPS survey.
D. PCPI quality measures.

77. You are particularly busy because 20 high-risk patients are being discharged today, and you wish to prioritize which patients to see first in case you cannot counsel them all. You decide to prioritize the patients according to each patient’s number of risk factors for readmission. Which one of the following patients has the most risk factors for hospital readmission?

A. A 76-year-old man with COPD and hyperthyroidism taking tiotropium.
B. An 81-year-old woman with macular degeneration and a recent myocardial infarction taking warfarin.
C. A 55-year-old man with benign prostatic hypertrophy and diabetes mellitus taking terazosin.
D. A 59-year-old woman with osteoporosis and a history of gastrointestinal bleeding taking ranitidine.

78. You have been asked by your department’s director to provide data justifying the value of your discharge medication counseling service to the chief executive officer of the hospital. Which one of the following performance metrics will most directly measure outcomes from your service?

A. HEDIS MRP measure.
B. CMS Readmissions Reduction Program.
C. HCAHPS survey.
D. PCPI quality measures.

79. A 75-year-old woman is admitted for community-acquired pneumonia. She takes 10 prescription medications and 3 over-the-counter medications at home. She is initiated on an antibiotic and cough suppressant at discharge. Which one of the following actions taken during the discharge process would most likely reduce medication order errors for this patient if she were readmitted to the hospital?

A. Provide the patient with a medication list to keep with her at all times.
B. Use the teach-back method to counsel her on the newly prescribed medications.
C. Send a reconciled discharge medication list to the patient’s PCP by facsimile.
D. Electronically transmit a reconciled discharge medication list to the patient’s PCP.

80. You are the pharmacist on your health system’s TOC improvement committee. This health system wants to reduce readmission rates by improving quality of responsibility. You are also responsible for reviewing and updating pharmacy department protocols and serving on the hospital’s patient education and TOC committees.
care. Excess readmission rates for your hospital have been obtained from the Medicare Hospital Compare Web site. Which one of the following would be most likely to help improve readmission performance for all patients hospitalized in the health system?
A. PCPI quality measures.
B. CMS Readmissions Reduction Program.
C. A PSO (patient safety organization) supported by the AHRQ.
D. H2H initiative.
Chronic Illnesses II
Chronic Illnesses II

Series Editors:
John E. Murphy, Pharm.D., FCCP, FASHP
Professor of Pharmacy Practice and Science
Associate Dean for Academic and Professional Affairs
University of Arizona College of Pharmacy
Tucson, Arizona

Mary Wun-Len Lee, Pharm.D., FCCP, BCPS
Vice President and Chief Academic Officer
Pharmacy and Health Sciences Education
Midwestern University
Professor of Pharmacy Practice
Midwestern University
Chicago College of Pharmacy
Downers Grove, Illinois

Faculty Panel Chair
Susan P. Bruce, Pharm.D., BCPS
Chair and Professor
Department of Pharmacy Practice
Northeast Ohio Medical University
Rootstown, Ohio

Myelodysplastic Syndromes

Authors
Kristen B. McCullough, Pharm.D., BCPS, BCOP
Hematology/Oncology Clinical Pharmacist
Department of Pharmacy Services
Mayo Clinic
Rochester, Minnesota

Julianna Merten, Pharm.D., BCPS, BCOP
Clinical Pharmacy Specialist
Assistant Professor of Pharmacy
College of Medicine
Oncology Pharmacy Residency
Assistant Program Director
Department of Pharmacy Services
Mayo Clinic
Rochester, Minnesota

Reviewers
Judith A. Smith, Pharm.D., BCOP,
CPHQ, FCCP, FISOPP
Associate Professor
Department of Obstetrics, Gynecology and Reproductive Sciences
Division of Gynecologic Oncology
UT Health Medical School at Houston
Houston, Texas

G. Ola Adejuwon, Pharm.D., BCPS
Clinical Pharmacy Manager
Department of Pharmacy Services
North Cypress Medical Center
Cypress, Texas

Leslie A. Hamilton, Pharm.D., BCPS
Assistant Professor
Department of Clinical Pharmacy
University of Tennessee College of Pharmacy
Knoxville, Tennessee

Chronic Myeloid Leukemia

Author
Marc A. Earl, Pharm.D., BCOP
Assistant Director of Pharmacy
Department of Pharmacy
Cleveland Clinic
Cleveland, Ohio

Reviewers
David S. Bateshansky, Pharm.D., BCPS
Clinical Pharmacist
Ambulatory Pharmacy
University of Southern California
Kenneth Norris Jr. Cancer Hospital
Los Angeles, California

Ulfat Usta, Pharm.D., BCNS, BCPS
AUBMC Pharmacy Director
Beirut, Lebanon
Pharmacology of New Targeted Therapies

Author
Salvatore M. Bottiglieri, Pharm.D., BCOP
Clinical Oncology Pharmacist
Infusion Center Pharmacy and Gastrointestinal Clinic
Moffitt Cancer Center
Tampa, Florida

Reviewers
Gabriel T. Bartoo, Pharm.D., BCOP, BCPS
Ambulatory Care Pharmacist – BMT
Department of Pharmacy Services
Mayo Clinic
Rochester, Minnesota

Kathryn A. Wheeler, Pharm.D., BCPS
Clinical Infusion/Oncology Pharmacist
SSM DePaul Cancer Center – Medical Park
St. Peters, Missouri

Oral Chemotherapy

Authors
Margaret M. Charpentier, Pharm.D., BCPS
Clinical Associate Professor
Department of Pharmacy Practice
University of Rhode Island
Kingston, Rhode Island

Karen R. Smethers, Pharm.D., BCOP
National Clinical Pharmacy Integration Leader
The Resource Group
Ascension Health
St. Louis, Missouri

Reviewers
John B. Bossaer, Pharm.D., BCPS, BCOP
Assistant Professor
Department of Pharmacy Practice
Bill Gatton College of Pharmacy
East Tennessee State University
Johnson City, Tennessee

Kimberly N. Flynn, Pharm.D., BCPS
Clinical Oncology Pharmacist
St. Joseph East Pharmacy
Kentucky One Health
Lexington, Kentucky

The American College of Clinical Pharmacy and the authors thank the following individuals for their careful review of the Chronic Illnesses II chapters:

Jeffrey T. Sherer, Pharm.D., MPH, BCPS
Clinical Associate Professor
Department of Clinical Sciences and Administration
University of Houston College of Pharmacy
Houston, Texas

Emilie L. Karpiuk, Pharm.D., BCPS, BCOP
Oncology Pharmacist
Department of Pharmacy
Froedtert Hospital
Milwaukee, Wisconsin

Marisel Segarra-Newnham, Pharm.D., MPH, FCCP, BCPS
Clinical Pharmacy Specialist, Infectious Diseases
Pharmacy Service
Veterans Affairs Medical Center
West Palm Beach, Florida
Clinical Assistant Professor of Pharmacy Practice
University of Florida College of Pharmacy
Gainesville, Florida
Learner Chapter Evaluation: Myelodysplastic Syndromes.

As you take the posttest for this chapter, also evaluate the material’s quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

1. The content of the chapter met my educational needs.
2. The content of the chapter satisfied my expectations.
3. The author presented the chapter content effectively.
4. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
5. The content of the chapter was objective and balanced.
6. The content of the chapter is free of bias, promotion, or advertisement of commercial products.
7. The content of the chapter was useful to me.
8. The teaching and learning methods used in the chapter were effective.
9. The active learning methods used in the chapter were effective.
10. The learning assessment activities used in the chapter were effective.
11. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

12. Distinguish which chemotherapeutic agent most likely contributed to the development of therapy-related myelodysplastic syndromes (MDS).
13. Compute and apply International Prognostic Scoring System (IPSS) and International Prognostic Scoring System – Revised (IPSS-R) scores for patients with MDS.
14. Devise a plan for initial therapy of the patient with MDS based on IPSS and IPSS-R risk.
15. Design an appropriate regimen for MDS based on likelihood of cure, improvement in overall survival, transfusion independence, and quality of life.
16. Classify the adverse effect profiles of therapies for MDS.
17. Evaluate the benefits versus the limitations of iron chelation and stem cell transplantation in patients with MDS.
18. Please provide any specific comments relating to any perceptions of bias, promotion, or advertisement of commercial products.
19. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter:
Learner Chapter Evaluation: Chronic Myeloid Leukemia.

As you take the posttest for this chapter, also evaluate the material’s quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

1. The content of the chapter met my educational needs.
2. The content of the chapter satisfied my expectations.
3. The author presented the chapter content effectively.
4. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
5. The content of the chapter was objective and balanced.
6. The content of the chapter is free of bias, promotion, or advertisement of commercial products.
7. The content of the chapter was useful to me.
8. The teaching and learning methods used in the chapter were effective.
9. The active learning methods used in the chapter were effective.
10. The learning assessment activities used in the chapter were effective.
11. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

12. Analyze available evidence to recommend a first-line therapy for chronic myeloid leukemia (CML).
13. Assess patient response to therapy to determine whether alternative CML treatment options are necessary.
14. Distinguish common adverse events with CML and design appropriate management strategies.
16. Detect drug-drug interactions common in CML and design a management plan for affected patients.
17. Please provide any specific comments relating to any perceptions of bias, promotion, or advertisement of commercial products.
18. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter:

As you take the posttest for this chapter, also evaluate the material’s quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

1. The content of the chapter met my educational needs.
2. The content of the chapter satisfied my expectations.
3. The author presented the chapter content effectively.
4. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
5. The content of the chapter was objective and balanced.
6. The content of the chapter is free of bias, promotion, or advertisement of commercial products.
7. The content of the chapter was useful to me.
8. The teaching and learning methods used in the chapter were effective.
9. The active learning methods used in the chapter were effective.
10. The learning assessment activities used in the chapter were effective.
11. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

12. Evaluate the clinical efficacy and optimal use of targeted therapies in the hematology/oncology patient setting.
13. Assess common adverse effects and monitoring parameters associated with the treatment of newly approved targeted therapies.
14. Account for key drug interactions and appropriate medication management with newly approved targeted therapies in the hematology/oncology patient setting.
15. Develop key patient counseling points on newly approved targeted agents.
16. Evaluate the appropriate dosing of targeted therapies in the setting of impaired organ function or drug-related toxicities.
17. Please provide any specific comments relating to any perceptions of bias, promotion, or advertisement of commercial products.
18. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter:
Learner Chapter Evaluation: Oral Chemotherapy.

As you take the posttest for this chapter, also evaluate the material’s quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

1. The content of the chapter met my educational needs.
2. The content of the chapter satisfied my expectations.
3. The author presented the chapter content effectively.
4. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
5. The content of the chapter was objective and balanced.
6. The content of the chapter is free of bias, promotion, or advertisement of commercial products.
7. The content of the chapter was useful to me.
8. The teaching and learning methods used in the chapter were effective.
9. The active learning methods used in the chapter were effective.
10. The learning assessment activities used in the chapter were effective.
11. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

12. Distinguish the common adverse drug effects (ADEs) associated with oral chemotherapy agents.
13. Develop strategies to prevent and manage ADEs.
14. Compose counseling points for patients and caregivers regarding the use of oral chemotherapy.
15. Apply best practices to improve safety in the medication use process for oral chemotherapy.
16. Justify the pharmacist’s role in improving outcomes for patients receiving oral chemotherapy agents.

17. Please provide any specific comments relating to any perceptions of bias, promotion, or advertisement of commercial products.
18. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter:

Questions 19–21 apply to the entire Chronic Illnesses II learning module.

19. How long did it take you to read the instructional materials in this module?
20. How long did it take you to read and answer the assessment questions in this module?
21. Please provide any additional comments you may have regarding this module:
Myelodysplastic Syndromes

By Kristen B. McCullough, Pharm.D., BCPS, BCOP; and Julianna Merten, Pharm.D., BCPS, BCOP

Reviewed by Judith A. Smith, Pharm.D., BCOP, CPHQ, FCCP, FISOPP; G. Ola Adejuwon, Pharm.D., BCPS; and Leslie A. Hamilton, Pharm.D., BCPS

Learning Objectives

1. Distinguish which chemotherapeutic agent is most likely to have contributed to the development of therapy-related myelodysplastic syndromes (tMDS).
2. Compute and apply International Prognostic Scoring System (IPSS) and International Prognostic Scoring System – Revised (IPSS-R) scores for patients with myelodysplastic syndromes (MDS).
3. Devise a plan for initial therapy of the patient with MDS based on IPSS and IPSS-R risk.
4. Design an appropriate regimen for MDS based on likelihood of cure, improvement in overall survival, transfusion independence, and quality of life.
5. Classify adverse effect profiles of therapies for MDS.
6. Evaluate the benefits versus limitations of iron chelation and stem cell transplantation in patients with MDS.

Introduction

Myelodysplastic syndromes (MDS) encompass a group of heterogeneous clonal disorders arising from abnormal pluripotent stem cells; these syndromes are predominantly characterized by anemia, thrombocytopenia, and leukopenia, with a predisposition towards leukemic evolution. The clinical course of MDS is highly variable and may range from indolent to rapidly progressive to acute myeloid leukemia (AML). Allogeneic hematopoietic stem cell transplant (HSCT) remains the only curative therapy; however, advanced age or comorbidities at diagnosis make most patients ineligible for this treatment. Improvement in knowledge of the disease biology, risk stratification, and development of new treatment options demonstrate important advances in MDS.

Myelodysplastic syndromes primarily affect elderly adults (median age of 76 years at diagnosis). There is a male-to-female ratio of about 1.75 to 1 (Ma 2012). The

Baseline Knowledge Statements

Readers of this chapter are presumed to be familiar with the following:

- Management of infectious complications in patients with immunosuppression
- Mechanisms of action of azacitidine, decitabine, lenalidomide, erythropoiesis-stimulating agents, thrombopoiesis stimulating agents, and iron-chelating agents
- Commonly used performance status measures including the Eastern Cooperative Oncology Group performance status and Karnofsky score.
- Normal hematopoiesis
- Basic understanding of genetic involvement in hematologic malignancies

Additional Readings

The following free resources are available for readers wishing additional background information on this topic.

- The following free resource is available for readers wishing additional background information on this topic.
overall annual incidence of MDS is 3 to 12 cases per 100,000 persons. In patients older than 65 years, the annual incidence increases to 25 to 75 cases per 100,000 persons. The Surveillance, Epidemiology, and End Result Program estimates that 19,631 new cases are diagnosed in the United States each year (NCI 2013). Despite robust population-based data, recent reports suggest that the incidence of MDS has been grossly underestimated because of inaccurate reporting and misdiagnosis by primary providers. An analysis of a Medicare claims database indicates the incidence could be as high as 45,000 new cases per year (Goldberg 2010). Many experts predict that the incidence will continue to rise with the aging population and better recognition of the disease.

Modifiable risk factors for development of MDS include tobacco use, obesity, and occupational exposure to solvents and agricultural chemicals (e.g., insecticides, pesticides, herbicides, fertilizer). Patients with some genetic syndromes are more likely to develop MDS; these include Diamond-Blackfan syndrome, Shwachman-Diamond syndrome, dyskeratosis congenita, Fanconi’s anemia, and severe congenital neutropenia (Tefferi 2009). About 10% of MDS cases develop after exposure to chemotherapy or radiation (Box 1-1) and are termed *therapy-related MDS* (tMDS) (Sill 2011).

Patients who develop tMDS after exposure to alkylating agents or radiation generally do so 5 to 10 years after exposure. These cases are typically associated with monosomy of chromosomes 5 and 7, deletions of long arms of these chromosomes, or multiple cytogenetic abnormalities. Patients exposed to topoisoasemerase II inhibitors who develop tMDS generally do so 2 to 3 years after exposure and often present with t(11;q23), t(8;21), t(15;17), and inv(16). Use of granulocyte colony–stimulating factor (G-CSF) to prevent febrile neutropenia in patients receiving chemotherapy increases the absolute risk of AML or MDS by 0.41%; however, use is associated with 3.4% absolute risk reduction in

---

**Box 1-1. Agents Associated with Therapy-Related Myelodysplastic Syndrome**

**Topoisomerase II Inhibitors**
- Dactinomycin
- Daunorubicin
- Doxorubicin
- Etoposide
- Idarubicin
- Mitoxantrone
- Teniposide

**Alkylating Agents**
- Busulfan
- Carmustine
- Carboptatin
- Cyclophosphamide
- Dacarbazine
- Ifosamide
- Lomustine
- Mitomycin
- Procarbazine
- Thiotepa

**Antimitotic Agents**
- Docetaxel
- Paclitaxel
- Vinblastine
- Vinristine

**Miscellaneous**
- Azathioprine
- Cladribine
- Fludarabine
- Iodine-131 tositumomab
- Mercaptopurine
- Methotrexate
- Radiation therapy
- Yttrium-90 ibritumomab tiuxetan

all-cause mortality because of the ability to deliver greater chemotherapy dose intensity (Lyman 2010).

Between 1% and 10% of patients with tMDS present after radioimmunotherapy (yttrium 90 ibritumomab tiuxetan or iodine-131 tositumomab), and 8% to 20% of patients develop tMDS after autologous stem cell transplantation. It is difficult to determine the impact of various treatments as single agents, or their cumulative effect on the risk of tMDS, because patients often receive multiple chemotherapy agents in addition to colony stimulating factors and/or radiation. Patients with tMDS have a poor prognosis with conventional therapy; therefore, they should receive an allogeneic HSCT if healthy enough to tolerate the procedure.

**Pathophysiology**

Myelodysplastic syndromes are characterized by ineffective hematopoiesis resulting from dysfunctional pluripotent stem cells. There is no single genetic mutation by which MDS arise but rather a multistep process that results in variable clinical phenotypes. The progressive bone marrow failure that results in peripheral blood cytopenias often produces terminally differentiated cells with functional defects. Whether the molecular lesion occurs at the progenitor or the myeloid cell level may dictate a multi- or single-lineage MDS. The clonal population may develop enhanced self-renewal abilities, increased proliferative capacity, impaired differentiation, or genetic instability. The resultant dysplastic cells may gain the ability to evade apoptosis or immune regulation.

**Bone Marrow Microenvironment**

The disease phenotype is affected extrinsically by the bone marrow stroma microenvironment including elevated inflammatory cytokines, reduced response to regulatory cytokines, and increased vascular endothelial growth factor. This results in a rapidly proliferating bone marrow accompanied by pro-apoptotic signals that impair development of mature peripheral blood cells (Bejar 2011; Tefferi 2009). Current pharmacotherapy with immunomodulatory agents capitalizes on these cytokine and apoptosis activities.

Select patients with MDS display immune dysregulation causing T-cell autoimmune-mediated myelosuppression and ineffective hematopoiesis. These cases are characterized by a sole trisomy 8 mutation, younger age, refractory anemia of short duration, a hypocellular bone marrow, and expression of human leukocyte antigen (HLA) haplotype DR 15 (Bejar 2011). Patients with these features are more likely to respond to immunosuppressive therapy with antithymocyte globulin and/or cyclosporine.

**Genomic Instability**

Chromosomal abnormalities, most often genomic losses and gains, are detected in about 50% of patients.

### Table 1-1. International Prognostic Scoring System for Myelodysplastic Syndromes

<table>
<thead>
<tr>
<th>Prognostic Variable</th>
<th>Score Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow blasts (%)</td>
<td>5</td>
</tr>
<tr>
<td>Karyotypea</td>
<td>Good</td>
</tr>
<tr>
<td>Cytopeniab</td>
<td>0 or 1</td>
</tr>
</tbody>
</table>

*aSelect the karyotype feature with the most severe prognostic implication for scoring purposes

  Good: Normal, isolated 5q deletion, isolated 20q deletion, -Y

  Intermediate: Any other abnormalities

  Poor: Trisomy 7, complex or > 3 abnormalities

*bAbsolute neutrophil count <1800 cells/mm³, hemoglobin < 10 g/dL, platelet count < 100,000 cell/mm³ (0 points for 0 or 1 cytopenia; 0.5 point for 2 or 3 cytopenias)

<table>
<thead>
<tr>
<th>Total Score</th>
<th>Risk Group</th>
<th>Median Survival (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Low</td>
<td>5.7</td>
</tr>
<tr>
<td>0.5–1</td>
<td>Intermediate-1</td>
<td>3.5</td>
</tr>
<tr>
<td>1.5–2.0</td>
<td>Intermediate-2</td>
<td>1.2</td>
</tr>
<tr>
<td>≥2.5</td>
<td>High</td>
<td>0.4</td>
</tr>
</tbody>
</table>

with de novo MDS and are one of the strongest prognostic indicators (Larson 2012). Recent revisions of the International Prognostic Scoring System (IPSS) classification include several additional chromosomal abnormalities used to predict overall survival (Table 1-1, Table 1-2) (Greenberg 1997; Greenberg 2012). Deletion 5q [del(5q)] as a sole genetic abnormality occurs in up to 12% of patients and is recognized as a distinct subtype of MDS often referred to as 5q- syndrome (Vardiman 2009). This subtype confers a favorable prognosis and high likelihood of response to lenalidomide (List 2006). Complex cytogenetics involving del(5q) do not confer the same favorable prognosis or response expectations but may still respond to lenalidomide therapy.

High-resolution single nucleotide polymorphism (SNP) array, a new type of karyotypic evaluation, allows genome-wide analysis beyond metaphase cytogenetics and has demonstrated independent prognostic value (Tiu 2011). Concurrent use of SNP array found 52% of patients with normal metaphase cytogenetics had at least one genomic point mutation (Bejar 2011). Screening is not routinely recommended because of cost and availability of genotyping technology, but future use of concurrent analysis is anticipated (Malcovati 2013).

**Epigenetics**

Epigenetics refers to mechanisms that regulate the expression of DNA without affecting its sequence. For example, DNA hypermethylation can cause aberrant silencing of tumor suppressor genes and upregulation of strictly controlled cell cycle functioning. The hypomethylating agents azacitidine and decitabine remove excess DNA methylation and restore normal tumor suppressor gene expression (Esteller 2008).

Histone acetylation, is also gaining significance in MDS. Posttranslational modifications of histones by acetylation or deacetylation can alter the structure of chromatin, creating opportunities for gene suppression or expression and leading to MDS in some patients (Quintas-Cardama 2011). Histone hypoacetylation has been documented in malignant cells, and several histone deacetylase inhibitors are being evaluated as a means to promote histone acetylation and expression of previously suppressed tumor suppressor genes in the treatment of MDS (Cashen 2012; Raza 2012).

| Table 1-2. International Prognostic Scoring System – Revised (IPSS-R) for Myelodysplastic Syndromes |
|---------------------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Prognostic variable**                          | 0               | 0.5             | 1               | 1.5             | 2               | 3               | 4               |
| Karyotypea                                        | Very Good       | Good            | Intermediate    | Poor            | Very Poor       |
| Bone marrow blast (cells/mm³)                     | ≤ 2%            | >2- <5%         | 5-10%           | >10%            |
| Hemoglobin (g/dL)b                                | ≥10             | 8-10            | <8              |
| Platelets (g/dL)b                                 | ≥100,000        | 50,000-100,000  | <50,000         |
| Absolute neutrophil count (cells/mm³)b           | ≥800            | <800            |

Select the karyotype feature with the most severe prognostic implication for scoring purposes

Very Good: -Y, del(11q)

Good: normal, del(5q), del(12p), del(20q), double including del(5q)

Intermediate: del(7q), +8, +19, i(17q), any other single or double independent clones

Poor: -7, inv(3)/t(3q)/del(3q), double including -7/del(7q), complex: 3 abnormalities

Very Poor: Complex: >3 abnormalities

<table>
<thead>
<tr>
<th>Total Score</th>
<th>Risk Group</th>
<th>Median Survival (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1.5</td>
<td>Very low</td>
<td>8.8</td>
</tr>
<tr>
<td>&gt; 1.5 – 3</td>
<td>Low</td>
<td>5.3</td>
</tr>
<tr>
<td>&gt; 3 – 4.5</td>
<td>Intermediate</td>
<td>3</td>
</tr>
<tr>
<td>&gt; 4.5 – 6</td>
<td>High</td>
<td>1.6</td>
</tr>
<tr>
<td>&gt; 6</td>
<td>Very high</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Clinical Presentation and Diagnosis

Patients with MDS may be asymptomatic, with cytopenias discovered on a complete blood count; or they may have symptoms related to anemia, thrombocytopenia, or neutropenia. Patients with anemia may complain of fatigue, lethargy, or symptoms associated with hypoxia, whereas those with thrombocytopenia may complain of easy bruising or bleeding. Patients with neutropenia may present with infection.

Diagnosis of MDS is based on exclusion of nonmalignant causes of cytopenias; information should be obtained on concomitant drugs, alcohol, smoking, prior chemotherapy, radiation, radioimmunotherapy, radioiodine, and occupational or hobby exposure (Malcovati 2013). After nonmalignant causes are ruled out, patients should have peripheral blood and bone marrow morphologic examination and cytogenetic analysis. The MDS diagnosis is given if other causes of dysplasia or cytopenia are excluded and the patient has a stable cytopenia for at least 6 months (2 months if accompanied by an MDS-specific karyotype or bilineage dysplasia).

Patients must present with one of the following: dysplasia in at least 10% of cells in one or more of three major bone marrow lineages; bone marrow blast count of 5% to 19%; or a specific MDS-associated karyotype (e.g., del(5q), del(20q), trisomy 8, del(7q)) (Valent 2007). The type of MDS is characterized by the World Health Organization Classification of MDS on the basis of peripheral blood and bone marrow blasts, cytopenias, bone marrow dysplasia, and cytogenetics (Table 1-3) (Vardiman 2009).

Prognosis

Several prognostic models to predict overall survival and risk for transformation to acute myeloid leukemia have been proposed. The IPSS was published in 1997 and continues to be used in clinical trials and treatment guidelines to guide therapy as newer models are validated (see Table 1-1) (Greenberg 1997). The International Prognostic Scoring System—Revised (IPSS-R) was published in 2012; it has five prognostic categories that estimate overall survival from 10 months to more than 8 years (see Table 1-2). It defines new categories for bone marrow blasts and depth of cytopenias, and includes more cytogenetic categories. In the IPSS-R, patient age, performance status, serum ferritin, and lactate dehydrogenase concentrations were predictive of overall survival but not leukemic transformation. Both the IPSS and IPSS-R are used to estimate risk and guide patient treatment because the newer model has not been validated in patients receiving disease-modifying therapy (Greenberg 2012).

Both prognostic models were based on patients with newly diagnosed, primary MDS who received no therapy to alter the natural history of MDS. Therefore, the predicted survival and leukemic transformation may not apply to patients with tMDS and those who receive disease-modifying therapy. Both the IPSS and IPSS-R incorporate cytogenetic analysis; however, only one-half of patients with MDS have abnormal cytogenetics. Once the full spectrum of somatic gene mutations in MDS has been defined, future models will likely incorporate molecular mutations to improve predictions. Patient-related factors including age, performance status, comorbidities, nutrition status, and cognition also influence prognosis in MDS, although more so in patients with low-risk MDS (Malcovati 2013).

Treatment

The management of MDS depends on disease-specific risk factors including cytogenetics, severity of cytopenias, and risk of progression to AML. Patient factors including age, comorbid conditions, performance status, organ function, and ability to tolerate existing symptoms or potential adverse effects must also be considered. The goals of therapy are symptom palliation in low-risk disease and alteration of the natural course in high-risk disease. Symptom palliation may include transfusion support, colony stimulating factor, immunosuppression, or DNA hypomethylating agents. High-risk disease may require intensive chemotherapy with the only curative option being allogeneic HSCT. A subset of patients with life expectancy less than or equal to what might be expected without MDS may benefit from best supportive care (BSC) alone. The same option may be extended to patients whose comorbid conditions make treatment-related risks exceed therapeutic benefit (Malco’esti 2013; Stauder 2012).

Aggressive therapy should be balanced with quality of life (QOL). Generalized tools that have been used in MDS trials to assess QOL include the Functional Assessment of Chronic Illness Therapy and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30). An MDS-specific QOL assessment tool, Quality of Life in Myelodysplasia Scale version 1 (QUALMS-1), is currently undergoing international validation. A preliminary report suggests QOL is routinely and reliably compromised in MDS patients, particularly in the domain of fatigue (Abel 2014).

Treatment Stratification and Response Evaluation

In addition to the aforementioned considerations, treatment choice is stratified based on IPSS/IPSS-R (Figure 1-1). Patients with very low– or low-risk disease (as defined by IPSS-R), or low- and intermediate-1 risk (per IPSS), benefit from supportive therapies including erythropoiesis-stimulating agents (ESAs), G-CSFs, DNA hypomethylating agents, and immunomodulating therapies (Table 1-4). Patients with intermediate-2, high, and very high risk disease are more likely to progress to AML and may benefit from DNA hypomethylating therapy or intensive chemotherapy and allogeneic HSCT if they are...
eligible. Patients defined as intermediate risk based on IPSS-R may fall into either treatment strategy depending upon additional factors such as age, performance status, transfusion needs, and serum lactate dehydrogenase levels. Patients at IPSS-R intermediate risk who are not responsive to low-risk therapies may be candidates for higher-risk therapies (Greenberg 2012). As new risk categories are defined and drugs are evaluated in combination regimens, the lines between high- and low-risk therapies have begun to blur.

Practitioners should recognize MDS is not static; as the disease progresses, symptoms may become more pronounced. This should be considered in deciding whether to treat the patient and/or when to change therapies.

Evaluation of patient response to treatment was standardized by the International Working Group (IWG) in 2000 and later refined in 2006 (Table 1-5) (Cheson 2006; Cheson 2000). It should be noted that some trials cited in this chapter were conducted before IWG 2006, Table 1-3. World Health Organization Classification of Myelodysplastic Syndromes

<table>
<thead>
<tr>
<th>Classification</th>
<th>Blood</th>
<th>Bone Marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory cytopenia with unilineage dysplasia (RCUD): (refractory anemia [RA]; refractory neutropenia [RN]; refractory thrombocytopenia [RT])</td>
<td>Unicytopenia or bicytopenia No or rare blasts (&lt;1%)</td>
<td>Unilineage dysplasia: ≥10% of the cells in one myeloid lineage &lt;5% blasts &lt;15% ringed sideroblasts</td>
</tr>
<tr>
<td>Refractory anemia with ringed sideroblasts (RARS)</td>
<td>Anemia No blasts</td>
<td>≥15% ringed sideroblasts Erythroid dysplasia only &lt;5% blasts</td>
</tr>
<tr>
<td>Refractory cytopenia with multilineage dysplasia</td>
<td>Cytopenia(s) No or rare blasts (&lt;1%) No Auer rods Monocytes &lt;1000 cells/mm³</td>
<td>Dysplasia in ≥10% of cells in ≥2 myeloid cell lines &lt;5% blasts ± 15% ringed sideroblasts No Auer rods</td>
</tr>
<tr>
<td>Refractory anemia with excess blasts-1</td>
<td>Cytopenia(s) &lt;5% blasts No Auer rods Monocytes &lt;1000 cells/mm³</td>
<td>Unilineage or multilineage dysplasia 5%-9% blasts No Auer rods</td>
</tr>
<tr>
<td>Refractory anemia with excess blasts-2</td>
<td>Cytopenia(s) 5%-19% blasts ±Auer rods Monocytes &lt;1000 cells/mm³</td>
<td>Unilineage or multilineage dysplasia ± Auer rods</td>
</tr>
<tr>
<td>Myelodysplastic syndrome, unclassified (MDS-U)</td>
<td>Cytopenias &lt;1% blastssw</td>
<td>Unequivocal dysplasia in &lt;10% of cells in one or more myeloid lineage when accompanied by a cytogenetic abnormality considered as presumptive evidence for a diagnosis of MDS &lt;5% blasts</td>
</tr>
<tr>
<td>Myelodysplastic syndrome associated with isolated deletion of 5q</td>
<td>Anemia Usually normal or increased platelet count No or rare blasts (&lt;1%)</td>
<td>Normal to increased megakaryocytes with hypolobated nuclei &lt;5% blasts No Auer rods Isolated del(5q) cytogenetic abnormality</td>
</tr>
<tr>
<td>Childhood myelodysplastic syndrome: (Provisional entity: refractory cytopenia of childhood [RCC])</td>
<td>Cytopenia(s) &lt;2% blasts</td>
<td>&lt;5% blasts Dysplasia in ≥10% of cells in ≥2 myeloid cell lines</td>
</tr>
</tbody>
</table>

and provider thresholds for transfusion of RBCs are highly variable. The IWG recognizes that improvement in overall functioning and QOL carry as much significance as laboratory values.

**Supportive Care**

All patients with MDS should receive supportive care including transfusions for symptomatic anemia, platelet transfusions (in the presence of bleeding), clinical monitoring, psychosocial support, and QOL evaluations (see Figure 1-1) (NCCN 2014). Management of infectious complications should follow applicable guideline recommendations. Patients with neutropenic fever should receive broad-spectrum intravenous antibiotics and undergo an appropriate evaluation. Routine antimicrobial prophylaxis is not generally recommended in the absence of repeated infections or profound and prolonged neutropenia (Fenaux 2013; NCCN 2014).

**Growth Factors**

**Epoetin, Darbepoetin**

Current guidelines recommend the use of ESAs for management of anemia in patients with MDS (Malcovati 2013; NCCN 2014). In contrast to recent reports in some solid tumors, no detrimental effects on overall survival or progression to leukemia have been noted in patients with MDS managed with ESAs. Meta-analyses of studies in patients with solid tumors have identified increased risk of thromboembolism and stroke in patients receiving ESAs; this type of study has not been done in MDS to determine if there is increased risk (Rizzo 2008). Patients with IPSS low- and intermediate-1 risk MDS who have a serum erythropoietin concentration less than 500 mU/mL and a history of receiving fewer than two units of RBC transfusions per month are more likely to respond (see Figure 1-1; see Table 1-5).

Two meta-analyses evaluated the efficacy of ESA monotherapy in MDS and reported hemoglobin response rates of about 30% and 58%. The first analysis included 1936 patients from 59 studies reported between 1980 and 2005 and classified response according to how it was defined in the original publication (Ross 2007). A subsequent meta-analysis of 1314 patients from 30 studies included studies from 1990 to 2006 that reported results by IWG criteria to define erythroid response (an increase in hemoglobin of 2 g/dL or transfusion independence) (Moyo 2008). The higher response rate in the second meta-analysis likely reflects inclusion of a higher proportion of patients most likely to respond to ESAs. It also suggested epoetin and darbepoetin can be used interchangeably for the management of MDS based on similar response rates.

**Combination Therapy**

Combination therapy with filgrastim (G-CSF) and epoetin may result in higher response rates than epoetin alone; however, study results are inconsistent. A large phase III, randomized controlled trial of ESAs in 110 patients with MDS compared epoetin with or without G-CSF to best supportive care (Greenberg 2009). An erythroid response was seen in 34% of patients receiving epoetin versus 5.8% of patients receiving placebo; the response rate increased to 47% after epoetin doses were escalated or G-CSF was added. No difference in overall survival or leukemic evolution was observed between patients receiving epoetin compared with best supportive care after a median follow-up period of 5.8 years.

A meta-analysis of 15 trials reported an overall erythroid response of 49%, 50.6%, and 64.5% for patients who received standard epoetin (30,000 to 40,000 units/week), standard epoetin plus G-CSF or granulocyte-macrophage colony stimulating factor (GM-CSF), or high-dose epoetin (60,000 to 80,000 units/week), respectively (Mundle 2009). The authors concluded that higher doses of single-agent epoetin are more effective than standard doses alone or in combination with G-CSF or GM-CSF. However, a significantly higher proportion of transfusion-dependent patients were enrolled in the trials using ESA combined with G-CSF or GM-CSF therapy compared with ESA monotherapy that could have negatively impacted the outcomes.

Patients with refractory anemia with ringed sideroblasts with greater than 15% ringed sideroblasts are more likely to respond to the addition of G-CSF, and combination therapy may be considered for initial therapy in those patients (NCCN 2014). Addition of G-CSF may be considered in patients who do not respond to monotherapy with epoetin after 8 weeks. Filgrastim, pegfilgrastim and sargramostim should not be used routinely as chronic monotherapy because they do not reliably prevent infection and have no effect on survival (Stone 2009). Note the data suggesting G-CSF increases the likelihood of development of t-MDS in patients receiving chemotherapy was published after studies were done using G-CSF as a treatment in MDS. Like ESAs, there is no information to suggest that there is a detrimental effect from G-CSF on survival when used to manage anemia in MDS patients.

**Eltrombopag, Romiplostim**

Romiplostim and eltrombopag are thrombopoiesis-stimulating agents with U.S. Food and Drug Administration (FDA)-approved labeling for use in patients with immune thrombocytopenia purpura; these agents have also been investigated in MDS patients (see Table 1-4). Two open-label, phase II trials evaluating romiplostim in patients with low- and intermediate-1-risk MDS with platelets less than 50,000/mm³ resulted in durable platelet responses in 30% and 46% of patients (Kantarjian 2010; Sekeres 2011). An unexpectedly high proportion of patients developed progression to AML in both studies (5% and 7%), and an additional 9% of patients...
Table 1-4. Agents in the Management of Myelodysplastic Syndrome

<table>
<thead>
<tr>
<th>Drug and Regimen</th>
<th>Adjustment in Organ Dysfunction</th>
<th>Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azacitidine 75 mg/m²/day subcutaneously or intravenously for 7 days</td>
<td>Consider dose adjustment in CrCl &lt; 30 mL/min</td>
<td>Neutropenia, thrombocytopenia, febrile neutropenia, nausea, vomiting, diarrhea, injection site erythema</td>
</tr>
<tr>
<td>Decitabine 15 mg/m² intravenously every 8 hours for 3 days (6 wks) OR 20 mg/m²/day IV for 5 days (4 wks)</td>
<td>Consider dose adjustment in CrCl &lt; 30 mL/min</td>
<td>Neutropenia, thrombocytopenia, febrile neutropenia, nausea, vomiting, diarrhea, peripheral edema, hyperbilirubinemia</td>
</tr>
<tr>
<td>Lenalidomide 10 mg orally daily</td>
<td>CrCl &gt; 30 and &lt; 50 mL/min: 5 mg orally daily CrCl &lt; 30 mL/min: 2.5–5 mg orally daily Hemodialysis: 2.5–5 mg on dialysis days, after dialysis</td>
<td>Boxed warning: Embryo-fetal toxicity, hematologic toxicity (neutropenia and thrombocytopenia), venous thromboembolism Febrile neutropenia, pruritus, rash, diarrhea</td>
</tr>
<tr>
<td>Epoetin alfa 40,000–60,000 units subcutaneously 2 or 3 times per week</td>
<td>Not applicable</td>
<td>Hypersensitivity reaction, hypertension, fever, rash, nausea, arthralgia</td>
</tr>
<tr>
<td>Darbepoetin alfa 100–300 units subcutaneously weekly or every other week</td>
<td>Not applicable</td>
<td>Hypersensitivity reaction, hypertension, rash, abdominal pain</td>
</tr>
<tr>
<td>Filgrastim 1–2 mcg/kg subcutaneously 2–3 times weekly in combination with epoetin</td>
<td>Not applicable</td>
<td>Fever, injection site pain, alkaline phosphatase elevations, bone pain, splenomegaly, headache</td>
</tr>
<tr>
<td>Deferasirox 20 mg/kg orally once daily; dose escalation up to 40 mg/kg/day permitted</td>
<td>Child-Pugh A hepatic impairment or CrCl &gt; 60 mL/min: no adjustment Child-Pugh B hepatic impairment or CrCl 40-60 mL/min: reduce by 50% Child-Pugh C hepatic impairment or CrCl &lt; 40 mL/min or SCR &gt; 2 times the age appropriate upper limit of normal: contraindicated</td>
<td>Boxed warning: renal and hepatic failure, agranulocytosis, and gastrointestinal hemorrhage Contraindicated in high-risk MDS Abdominal pain, fever, rash, headache, nausea, vomiting, diarrhea</td>
</tr>
<tr>
<td>Deferoxamine 1000-2000 mg/day or 20–40 mg/kg/day subcutaneous infusion over 8–24 hours</td>
<td>Has not been studied in hepatic impairment CrCl &gt; 50 mL/min: no adjustment CrCl 10-50 mL/min: reduce by 50%-75% CrCl &lt; 10 mL/min, dialysis: contraindicated</td>
<td>Injection site reactions, arthralgia, ocular toxicities, ototoxicity, nephrotoxicity, neuropathy, hematologic toxicity, abdominal pain, nausea, vomiting, diarrhea, rash, chromaturia</td>
</tr>
<tr>
<td>Deferiprone 25 mg/kg orally three times daily</td>
<td>Has not been studied in patients with renal or hepatic dysfunction; 75-90% is excreted in the urine.</td>
<td>Boxed warning: agranulocytosis Nausea/vomiting, abdominal pain, arthralgia, chromaturia, zinc deficiency, infection</td>
</tr>
</tbody>
</table>
in the first study had a transient increase in blasts that improved with drug discontinuation. Subsequently, a randomized, placebo-controlled trial evaluating romiplostim to manage thrombocytopenia enrolled 250 patients with low or intermediate-1 risk MDS; the study was terminated prematurely in 2011 by the data safety monitoring committee after recognition that 15% of romiplostim patients developed greater than 10% blasts compared with 3.6% of placebo patients (Giagounidis 2011). Clinical trials with eltrombopag in MDS continue to enroll patients; preliminary results from one study suggest potential efficacy (durable platelet response of 24%) and safety (no evidence of increased blast percentage) (Mittelman 2012). The available literature does not support use of thrombopoiesis-stimulating agents in MDS patients outside of a clinical trial.

Thrombopoiesis-stimulating agents generally take at least 1–2 weeks to increase platelet counts; therefore, they should not be used when a rapid platelet increase is desired because of bleeding. In general, platelet transfusions are recommended for transient thrombocytopenia when platelets are less than 10,000/mm³, or when platelets fall below 20,000/mm³ in patients with bleeding or risk factors for bleeding (e.g., fever, infection, rapid platelet decrease, invasive procedure) (Malcovati 2013).

**Pharmacy Practice**

The dosing of ESA in patients with MDS is notably higher than in treating renal causes of anemia (see Table 1-4). Expert consensus suggests doses should be titrated up or down to achieve a hemoglobin of 10–12 g/dL. Response to ESAs may be delayed in patients with MDS, so they should receive at least 8 weeks of therapy before doses are adjusted or before nonresponse is considered. The median response duration to ESAs in MDS is 1 to 2 years (see Table 1-5); ESA therapy should be discontinued if there is no benefit or the response wanes (Stone 2009).

Some, but not all studies have shown that patients who respond to ESAs have improvements in QOL (Kelaidi 2013; Nilsson-Ehle 2011; Oliva 2010; Greenberg 2009). Combination therapy is generally reserved for patients with refractory anemia with ringed sideroblasts or when there is no response to monotherapy with ESAs. The FDA’s Risk Evaluation and Mitigation Strategy (REMS) program for thrombopoiesis-stimulating agents was discontinued in 2011; however, concern remains with off-label use in patients with MDS. The use of romiplostim and eltrombopag in patients with MDS should be limited to clinical trials.

**Iron Chelation**

Patients receiving regular RBC transfusions develop secondary iron overload after 20–25 transfusions. Iron overload leads to organ dysfunction in patients with long-standing transfusion requirements (e.g., thalassemia). Patients with MDS who receive RBC transfusions develop infections and cardiac, hepatic, and endocrine dysfunction more often than nontransfused patients with MDS or the general population. Higher transfusion requirements and an elevated serum ferritin concentration are associated with a worse prognosis in MDS patients. It is unclear whether this reflects disease biology or toxicity related to the anemia or the transfusion.
Treatment with deferasirox, deferiprone, or deferoxamine effectively reduces ferritin and/or labile plasma iron in patients with MDS; however, none have demonstrated an impact on organ function (Nolte 2013; Gattermann 2012; List 2012; Gattermann 2010). Retrospective studies have indicated that iron chelation may be associated with erythroid, platelet, and neutrophil responses in up to 20% of patients (Mavroudi 2011).

There are no prospective, randomized studies evaluating the effect of iron chelation on overall survival in MDS patients. Three observational studies indicate there may be a survival benefit associated with iron chelation. A retrospective study of 18 patients with low- or intermediate-1-risk MDS reported the median overall survival had not yet been observed after 226 months in the deferoxamine group versus 40 months in the control group (Leitch 2008). A prospective cohort of 97 low- or intermediate-1-risk MDS patients reported a median overall survival time of 124 months in chelated patients versus 53 months in nonchelated patients (Rose 2010). Lastly, a retrospective, matched-pair analysis of 188 patients reported a median survival time in the iron chelation group of 74 months versus 49 months in the supportive care alone group (Neukirchen 2012). Based on the study design, it is unclear if the survival benefit is directly related to iron chelation or to confounding factors.

![Figure 1-1. General approach to the treatment of myelodysplastic syndrome.](image)

*aAll patients should be offered best supportive care and can be considered for enrollment in a clinical trial at anytime

*bIPSS-R Intermediate patients may be managed as very low/low risk or high/very high depending upon additional prognostic indicators such as age, performance status, serum ferritin, and lactate dehydrogenase.

Both deferasirox and deferiprone carry boxed warnings because they may cause significant toxicities including renal and hepatic dysfunction, agranulocytosis, and gastrointestinal hemorrhage (see Table 1-4). Nine clinical practice guidelines have been published on iron chelation in MDS with diverse recommendations about if and when to initiate iron chelation. It is also unclear what the most appropriate drug, dose, and duration of use should be.

In general, iron chelation may be considered in patients with low- and intermediate-risk disease after 20 to 30 RBC transfusions, or in patients with a serum ferritin greater than 1000–2500 ng/mL. Iron chelation is most appropriate for patients with an anticipated survival greater than 1 year and those planning to proceed to allogeneic HSCT because patients with MDS and an elevated ferritin pre-transplant have a lower survival rate (Malcovati 2013; Steensma 2011).

### DNA Hypomethylating Agents

#### Azacitidine

Reduction in excess DNA methylation by hypomethylating agents (e.g., azacitidine, decitabine) leads to expression of previously silenced tumor suppressor genes. Recommendations for the use of azacitidine in MDS stems from two core clinical trials. The first was a phase III trial of azacitidine 75 mg/m²/day for 7 days in a 28-day cycle for all risk categories of MDS. Patients were randomly assigned to supportive care alone or azacitidine. The overall response rate (including complete response [CR], partial response [PR], and improvement in hematologic parameters) in the azacitidine group was 60% (CR 7%, PR 16%) versus 5% in the supportive care group. Response was independent of baseline risk category. After 4 months of supportive care, a total of 49 patients crossed over to azacitidine with an overall response rate of 47% (CR 10%)

### Table 1-5. International Working Group Response Criteria

<table>
<thead>
<tr>
<th>Response</th>
<th>Criteria (Duration ≥ 4 weeks)</th>
</tr>
</thead>
</table>
| Complete remission (CR) | Bone marrow: ≤ 5% myeloblasts with normal maturation of all cell lines  
Peripheral blood: Hemoglobin ≥ 11 g/dL, platelets ≥ 100,000/mm³, neutrophils > 1000 cells/mm³, blasts 0% |
| Partial remission (PR) | All CR criteria if abnormal before treatment except bone marrow blasts decrease by ≥ 50% over pretreatment but still > 5% |
| Stable disease | Failure to achieve at least PR, but no evidence of progression for > 8 weeks |
| Relapse after CR or PR | At least 1 of the following:  
Return to pre-treatment bone marrow blast percentage  
Decrease of ≥ 50% from maximum remission/response levels in granulocytes or platelets  
Reduction in hemoglobin concentration by 1.5 g/dL or transfusion dependence |
| Cytogenetic response | Complete: Disappearance of the chromosomal abnormality without new abnormalities  
Partial: At least 50% reduction of the chromosomal abnormality |
| Disease progression | If 30% blasts or less: ≥ 50% increase in blasts  
Any one of the following: ≥ 50% decrease from maximum remission/response in granulocytes or platelets, reduction in hemoglobin by ≥ 2 g/dL, transfusion dependence |

<table>
<thead>
<tr>
<th>Response</th>
<th>Hematologic Improvement Criteria (Duration ≥ 8 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red cell (pre-treatment hemoglobin &lt; 11g/dL)</td>
<td>Hemoglobin increase by ≥ 1.5 g/dL; Reduction in the units of RBC transfusions by at least 4 RBC transfusion/8 weeks compared with pre-treatment; Only RBC transfusion for hemoglobin ≤ 9.0 g/dL pre-treatment will count in the RBC transfusion response evaluation</td>
</tr>
</tbody>
</table>
| Platelet | Absolute increase of ≥ 30,000 cells/mm³ for patients starting with > 20,000 cells/mm³  
Increase from < 20,000 cells/mm³ to > 20,000 cells/mm³ and by at least 500% |
| Neutrophil | At least 100% increase and absolute increase of at least 500 cells/mm³ |
| Progression or relapse | At least 1 of the following: ≥ 50% decrease from maximum response levels in granulocytes or platelets; reduction in hemoglobin by ≥ 1.5 g/dL, transfusion dependence |

were comparable in age to the landmark azacitidine trial (Silverman 2002). Routine cytogenetic evaluation was in its infancy at the time and may, in part, have contributed to the response variability. A QOL analysis identified a significant advantage for azacitidine therapy compared with supportive care alone, including improvements in physical functioning, fatigue, dyspnea, psychosocial distress, and affect (Kornblith 2002).

The second phase III clinical trial included 340 patients with high-risk MDS (IPSS of intermediate-2 or higher) and compared azacitidine with a conventional care regimen (CCR) of low-dose cytarabine, intensive chemotherapy similar to AML induction, or BSC. At 2 years, the overall survival was 51% for azacitidine and 26% for CCR. This landmark trial remains the only one to demonstrate a survival advantage in MDS (Fenaux 2009).

In an attempt to define the most suitable patients for azacitidine, a compassionate use evaluation of azacitidine was performed in 282 patients for a median of six cycles. Four factors were identified as predictors for overall survival and assigned a point value: performance status of 2 or greater (1 point), intermediate- and poor-risk cytogenetics (1 point and 2 points, respectively), presence of circulating blasts (1 point), and RBC transfusion dependency of at least 4 units within 8 weeks (1 point). Median overall survival was not reached in low-risk patients (0 points), was 15 months in intermediate-risk patients (1 to 3 points), and was 6.1 months in high-risk patients (4 to 5 points) (Itzykson 2011). The prognostic score was validated in an independent cohort of patients from the landmark azacitidine trial (Fenaux 2009) and was able to predict an improvement in overall survival for patients who demonstrated hematologic improvement despite the absence of complete or partial remission.

Decitabine

Decitabine, a hypomethylating agent, was evaluated in a multicenter randomized phase III trial of 170 patients with MDS (IPSS risk of intermediate-1 or higher). Patients received either decitabine 15 mg/m² intravenously over 3 hours every 8 hours for 3 consecutive days on a 6-week cycle, or BSC. The overall response rate (CR and PR) was 17% in the decitabine group and 0% with BSC. In contrast with azacitidine, there was no significant difference in progression to AML or overall survival between groups (Kantarjian 2006).

A similar low-dose decitabine (15 mg/m²/day over 4 hours three times daily for 3 consecutive days in 6-week cycles) was recently evaluated in a phase III randomized trial versus BSC for patients older than 60 years. The overall response rate was 19% for decitabine versus 0% with BSC. The incidence of febrile neutropenia was similar to standard-dose decitabine in younger populations, and the infection rate was no higher than BSC. However, overall survival was not statistically different (10.1 months for decitabine vs. 8.5 months for BSC). Although patients were comparable in age to the landmark azacitidine trial (Fenaux 2009), the time since diagnosis was shorter (3 months vs. 12 months). This may have allowed for the azacitidine trial to select for patients with less rapidly progressive disease. Decitabine demonstrated improvement in QOL measures for fatigue and physical functioning (Lubbert 2011).

Successive use of decitabine (median of two courses of therapy) after failure of azacitidine in 22 patients with MDS or AML resulted in disease progression in all patients, indicating therapeutic intervention with an alternative mechanism of action is most likely required (Bhatnagar 2012).

Pharmacy Practice

The time to response for hypomethylating agents is generally 3–4 months (Stone 2009). The optimal duration of ongoing therapy once response is achieved remains ill-defined. One study re-evaluated the 91 patients who achieved any level of response to azacitidine (CR, PR, or hematologic improvement) in the landmark trial. The median time to response of any type was two cycles, and 91% of responding patients achieved their first response within six cycles. The first response was the best response in 52% of patients, but the remaining 48% did not achieve their best response until a median of three additional cycles beyond their first response (Silverman 2011). Expert consensus is to continue therapy until evidence of disease progression or unacceptable toxicity, even in cases of stable disease (NCCN 2014; Garcia-Manero 2011). Clinical trials with hypomethylating agents indicate one-half of patients develop worsening cytopenias necessitating transfusion support and risk of febrile neutropenia, particularly during the first few treatment cycles.

Although hypomethylating therapy has been clinically successful, the practicality of administration every 8 hours or for 7-day stretches makes outpatient administration nearly impossible for most community practices. The only FDA-approved regimen for azacitidine is the 7-day subcutaneous route, but evaluation of a shortened schedule of 5 days in lower-risk patients demonstrated comparable rates of hematologic improvement and transfusion independence. Subcutaneous azacitidine doses greater than 4 mL should be split into two syringes and administered in separate sites, although institutional policies on maximal subcutaneous volume may vary. Intravenous administration is also available. Dose adjustment should be considered for patients receiving hypomethylating therapy who have comorbid renal dysfunction (see Table 1-4).

Lenalidomide

Lenalidomide is an immunomodulatory agent that possesses anti-inflammatory and anti-angiogenesis properties while stimulating apoptosis by modulating T-cell activity and inhibiting tumor necrosis factor-alpha. Lenalidomide is indicated for patients with clonal deletion of chromosome 5q [del(5q)], either independently (5q- syndrome)
or in conjunction with additional chromosomal abnormalities (see Figure 1-1). The agent received FDA approval after a phase II, open-label investigation demonstrated cytogenetic remission in 45% of low-risk patients with MDS with del(5q); 67% of patients achieved transfusion independence (List 2005).

Subsequently, a phase III double-blind study randomized 205 transfusion-dependent, low- and intermediate-1-risk del(5q) patients to lenalidomide 10 mg/day on days 1–21, lenalidomide 5 mg per day on days 1–28, or placebo for 28-day cycles (Fenaux 2011). Crossover was allowed at week 16 if minor erythroid response was not achieved. The primary end point of RBC transfusion independence for 26 weeks or longer saw statistically significant improvement in 56%, 43%, and 6% of patients in the 10 mg, 5 mg, and placebo groups, respectively. Complete cytogenetic response rates were 29% and 16% in the 10-mg and 5-mg groups, respectively. Despite excellent response rates, differences in overall survival between groups was not statistically significant. Crossover from placebo to lenalidomide by 80% of participants confounded the ability to thoroughly assess lenalidomide’s impact on mortality or leukemic progression. Patients with either isolated del(5q) or a single additional cytogenetic abnormality had a rate of progression to AML of 24% and 21%, respectively. However, in patients with del(5q) and two or more additional abnormalities, the rate of progression to AML was 47%.

Treatment success with lenalidomide in low-risk patients prompted evaluation in higher-risk patients despite preliminary evidence that responses may not be durable. A phase II trial of lenalidomide 10 mg daily in 47 patients with intermediate-2- or high-risk MDS with del(5q), reported hematologic response in 13 of 47 patients (27%) (Ades 2009). Complete remission was isolated to patients with only del(5q) or a single additional cytogenetic abnormality and absence of baseline thrombocytopenia. Significant myelosuppression was reported, and most patients in the study (67%) required hospitalization. Response duration (median 6.5 months) was significantly less than studies with lower-risk del(5q) patients. Lenalidomide is a viable option for patients with del(5q); however, high-risk features such as pancytopenia, complex cytogenetics, and elevated marrow blasts suggest that durability of response remains low, and guidelines recommend use of alternative agents such as azacitidine or decitabine (NCCN 2014).

Lenalidomide has also been evaluated in patients without del(5q). In a phase II study of 214 transfusion-dependent patients with low or intermediate-1-risk MDS, one group received lenalidomide 10 mg daily on days 1–21 of a 28-day cycle (Raza 2008). Overall hematologic improvement was 33%, with 17% of patients achieving transfusion independence. Among those who achieved transfusion independence, 80% had good cytogenetics per IPSS, and only 4 patients achieved a complete cytogenetic response. The success of lenalidomide in these patients despite the absence of del(5q) is likely attributable to lenalidomide’s effects on the bone marrow microenvironment rather than the alteration of the MDS clone.

Pharmacy Practice
Lenalidomide undergoes substantial renal elimination and requires dose adjustment if CrCl is below 50 mL/minute (see Table 1-4). Neutropenia and thrombocytopenia are dose-limiting toxicities, and the manufacturer recommends dose reduction if the platelets decrease by greater than 50% from baseline or to less than 30,000/mm³. If neutrophils fall below 500 to 750 cells/mm³, adjustment is also recommended. However, neutropenia and thrombocytopenia may act as a surrogate marker for suppression of the MDS clone. Low- and intermediate-1-risk patients with del(5q) who had a decrease in WBC greater than 75% and in platelets by greater than 50% had a higher likelihood of developing transfusion independence than those with a small decrease or stable laboratory values (Sekeres 2008).

Lenalidomide is prescribed and dispensed under an FDA REMS program to prevent embryo/fetal exposure. Any violation of the REMS terms of agreement or known or suspected pregnancy must be reported to the manufacturer for mandatory submission to the FDA through the MedWatch Online Mandatory Reporting Form. Providers may also report directly to the FDA using the MedWatch Online Voluntary Reporting Form.

Combination Therapy
Success with immunomodulators, DNA hypomethylating agents, and ESAs as monotherapy prompted evaluation of combination therapy. Two trials evaluated lenalidomide and epoetin in patients with low-risk MDS that failed to improve on ESAs alone (Komrokji 2012; Sibon 2012). Evaluation of 31 low-risk patients without del(5q) and with disease refractory to ESA monotherapy demonstrated transfusion independence in 37% of previously dependent patients. Erythroid response rates were more robust in patients who continued ESAs (55% vs. 36%), and median duration of response was 24 months (Sibon 2012). In the second study, 39 patients with low- and intermediate-1-risk MDS were initiated on lenalidomide 10 or 15 mg daily. At week 16, patients that did not have an erythroid response were eligible to receive epoetin 40,000 units/week (Komrokji 2012). Twenty-three patients proceeded to combination therapy, 22 of whom were non-del(5q) patients. Of the combination therapy patients, 26% achieved erythroid hematologic improvement. A phase III study is currently under investigation to further evaluate this unique combination.

Lenalidomide has also been evaluated in combination with azacitidine in a phase II study of 36 patients with higher-risk MDS who were not candidates for HSCT (Sekeres 2012). Patients received azacitidine 75 mg/m²/day for 5 days and lenalidomide 10 mg daily for 21 days of
a 28-day cycle. The overall response rate was 72%. Sixteen patients (44%) had a complete response, and another 10 patients (28%) had hematologic improvement. The rate of febrile neutropenia was 22%, and median decreases in neutrophils (35%) and platelets (15%) were mild. Although this overall response rate is markedly improved over azacitidine monotherapy in a similar patient population, this study did include some intermediate-1 patients and had a significantly shorter follow-up (11.5 vs. 21.1 months).

Thrombopoiesis-stimulating agents are being evaluated in combination with lenalidomide, decitabine, and azacitidine. Preliminary results indicate combination therapy can modestly reduce the need for platelet transfusions and has the potential to avoid dose reductions or delays in therapy caused by thrombocytopenia (Greenberg 2013; Wang 2012; Kantarjian 2010).

**Immunosuppressive Therapy**

Immunosuppressive therapy, including cyclosporine and both equine and rabbit antithymocyte globulin (ATG), has been evaluated in MDS patients. Horse and rabbit ATG result in modest response rates, with about one-third of patients achieving transfusion independence within 8 months (Garg 2009; Stadler 2004). Treatment with ATG may not benefit all patients because of the potential for infectious and infusion-reaction complications (e.g., serum sickness).

Cyclosporine monotherapy with therapeutic drug monitoring to a target level 100–400 ng/mL has had modest success in patients with isolated refractory anemia (Shimamoto 2003). A retrospective review of several clinical trials from the National Institutes of Health found a combination of equine ATG and cyclosporine to be an independent factor associated with response to therapy compared with either agent alone (Sloand 2008). A phase III study evaluated equine ATG 15 mg/kg/day for 5 days and oral cyclosporine versus best supportive care in 45 patients with all levels of IPSS risk categories (Passweg 2011). At 6 months, 29% of patients had achieved hematologic response in the ATG group versus 9% for BSC; however, at 2 years the transformation-free and overall survival rates had no statistically significant difference. It is noteworthy that this study did not select patients based on a high likelihood of responding to ATG. Patients were not tested for HLA DR15, the median age was 62 years, and only 13 patients demonstrated a hypoplastic bone marrow, likely contributing to the lower than expected overall response rate.

**Intensive Chemotherapy**

Patients with intermediate-2 or high-risk disease may benefit from intensive chemotherapy with AML-type induction regimens (anthracycline and cytarabine). Remission rates with intensive chemotherapy are 40%–60%, but treatment-related mortality can be as high as 42% (Malcovati 2013). Patients younger than 55 years with normal cytogenetics and a good performance status are most likely to benefit, but the likelihood of cure is less than 15% (Beran 2001). Induction chemotherapy is reserved for patients with good performance status and few comorbidities awaiting allogeneic HSCT who may require a reduction in tumor burden (Malcovati 2013; NCCN 2014).

**Allogeneic HSCT Candidates**

Allogeneic HSCT is currently the only curative therapy for MDS. Patient age, comorbidities, and IPSS risk are considered when determining whether patients should undergo allogeneic HSCT. Comorbidities in HSCT are assessed by a hematopoietic cell transplant comorbidity index (HCT-CI) with points assigned for each of 15 different comorbidities (Sorror 2013). The HCT-CI is predictive of both nonrelapse mortality and overall survival in HSCT; patients with three comorbidities have almost double the risk of nonrelapse mortality (15% vs. 28%) compared with those who have no comorbidities (Raimondi 2012).

Patients up to age 70 with IPSS intermediate-2 or high-risk MDS who are healthy enough for allogeneic HSCT, as well as those with intermediate-1 risk IPSS with excess blasts or poor-risk cytogenetics, are candidates for allogeneic HSCT (Malcovati 2013). On the basis of data from the European Group for Blood and Marrow Transplantation registry, the overall survival for patients older than 50 at 4 years after allogeneic HSCT is 31%, with a 36% risk of death from transplant-related complications (Lim 2010). Patients with tMDS have a poor prognosis with conventional therapy, and therefore should receive an allogeneic HSCT if healthy enough to tolerate the procedure.

**Reduced-Intensity vs. Myeloablative Chemotherapy**

Given that the median age of patients with MDS is 76 years, the use of reduced-intensity chemotherapy before allogeneic HSCT has been employed to improve the tolerability of HSCT and allow a graft-versus-leukemia effect with lower treatment-related mortality. Unfortunately, retrospective comparisons of reduced intensity and myeloablative chemotherapy regimens have shown higher rates of relapse or of late nonrelapse mortality, resulting in no difference in overall survival between regimens (Luger 2012; Martino 2006). The determination of the intensity of the chemotherapy regimen should be individualized based on performance status, comorbidity index, and disease status at the time of transplantation. An ongoing prospective, randomized controlled trial is comparing myeloablative and reduced-intensity chemotherapy regimens in patients with MDS undergoing allogeneic HSCT. Autologous HSCT is not recommended because it confers no survival benefit over intensive chemotherapy (de Witte 2010).
**Emerging Therapies**

As understanding of MDS biology evolves, new therapeutic options are targeting alternative mechanisms of action. Alemtuzumab, a monoclonal antibody with immunosuppressive properties, was evaluated in a case series and demonstrated hematologic improvement in 77% of intermediate-1-risk patients and 57% of intermediate-2-risk patients (Sloand 2010). Clofarabine, an antimetabolite used in acute leukemia, has been evaluated intravenously and orally in higher-risk MDS patients who have failed DNA hypomethylating agents, but extensive cytopenias have limited use in this population (Faderl 2012; Faderl 2010; Lim 2010). Newly developed histone deacetylase inhibitors have attempted to alter disease biology. Limited success has been seen with monotherapy; combination therapy is currently being evaluated in multiple trials (Cashen 2012; Dimicoli 2012). Lastly, oral azacitidine has been successfully trialed in extended dosing strategies of 14 or 21 days, which have correlated with high levels of demethylation (Garcia-Manero 2012).

**Treatment Approach**

See Figure 1-1 for a description of the management of a patient with MDS. In general, patients are designated as having lower- or higher-risk MDS. Lower-risk patients include those with IPSS low and intermediate-1 risk, as well as IPSS-R very low and low risk MDS. Higher risk will include IPSS intermediate-2 and high risk, as well as IPSS-R high and very high risk MDS. Patients with IPSS-R intermediate-risk MDS can be either high or low risk, treatment should be based on performance status, symptoms, comorbidities, and transfusion requirements. Caution should be exercised in patients with pre-existing profound neutropenia (absolute neutrophil count less than 500 cells/mm³) or thrombocytopenia (platelets less than 25,000/mm³) because most of these patients were excluded from clinical trials.

Low-risk, asymptomatic patients may benefit from watchful waiting. Minimally symptomatic patients with multiple comorbidities who would likely suffer complications from treatment may also benefit from a period of observation (Stone 2009). Symptomatic patients with

---

**Patient Care Scenario**

Five months ago, an 80-year-old woman who resides in an assisted living center presented to her primary care provider with progressive dyspnea on exertion, exercise intolerance, and pallor. Her medical history was significant for a recent occurrence of gastrointestinal bleeding because of ulcerations. Her CBC demonstrated a hemoglobin of 7.9 g/dL, absolute neutrophil count 3930 cells/mm³, and platelets 447,000/mm³. Her bone marrow biopsy was consistent with myelodysplastic syndrome, refractory cytopenia with multilineage dysplasia. Less than 5% bone marrow blasts were demonstrated and karyotype was normal. Since diagnosis, she has received two units of packed red blood cells roughly every 2 weeks but still has persistent fatigue. Her erythropoietin level is 741 mU/mL today. Upon clinical examination, her European Cooperative Oncology Group (ECOG) performance score is 2. What would be best to recommend for this patient’s myelodysplastic syndrome?

**Answer**

Although this patient type may appear difficult to categorize per the algorithm, they are common in the myelodysplastic patient population. Her IPSS is 0 and therefore she would be low risk with a median overall survival without treatment of 5.7 years. Re-evaluation with IPSS-R demonstrates intermediate risk with a median overall survival of 3 years. Current guidelines recommend against the use of ESAs for the management of anemia when erythropoietin levels are > 500 mU/mL, regardless of prognostic score. This patient’s IPSS-R stratification of intermediate indicates that either the low-risk branch or high-risk branch would be feasible. Given her age, performance status, and recent history of gastrointestinal bleeding, this patient would be an excellent candidate for best supportive care. Active chemotherapeutic intervention with azacitidine or decitabine is likely to decrease her overall quality of life, and a normal karyotype diminishes her likelihood of response to lenalidomide. Her age and performance status indicate she is not a candidate for allogeneic HSCT.

---

serum erythropoietin concentrations less than 500 mU/mL are candidates for ESAs with or without G-CSF. If erythropoietin concentrations are greater than 500 mU/mL, DNA hypomethylating agents or lenalidomide are appropriate. Patients with a hypocellular marrow and HLA DR15 should receive up-front immunosuppressive therapy.

High-risk patients should be evaluated for allogeneic HSCT early in treatment so an appropriate donor can be identified. Azacitidine is the treatment of choice in patients unable to undergo HSCT and may be used as a bridge to HSCT or as cytotherapeutic therapy.

**Conclusion**

Significant advances in the management of MDS have allowed for improvements in symptom management and for modification of disease history. Providers must assist patients in weighing the pros and cons of aggressive therapies that may prolong time to AML transformation and overall survival balanced with quality of life. In the future, genome-wide diagnostics, novel drug mechanisms of action, and combination therapies are likely to play larger roles in the management of this complex patient population.

**References**


Dimicoli S, Jabbour E, Borthakur G, et al. Phase II study of the histone deacetylase inhibitor panobinostat (LBH589) in


NCI. National Cancer Institute’s Surveillance Epidemiology and End Results 18 (SEER 18) Database. 2013.


Nilsson-Ehle H, Birgegard G, Samuelsson J, et al. Quality of life, physical function and MRI T2* in elderly low-risk MDS patients treated to a haemoglobin level of ≥/≤120 g/L with darbepoetin alfa +/- filgrastim or erythrocyte transfusions. Eur J Haematol 2011;87:244-52.


Stauder R. Myelodysplastic Syndrome.

SELF-ASSESSMENT QUESTIONS

Questions 1 and 2 pertain to the following case.
R.P. is a 46-year-old woman with a history of stage 2B breast cancer. She underwent radical mastectomy, radiation, and adjuvant chemotherapy with doxorubicin, cyclophosphamide, and paclitaxel. She has received 2 years of tamoxifen and on routine follow-up was found to have a hemoglobin of 9.8 g/dL, absolute neutrophil count of 1300 cells/mm³, and platelets of 87,000/mm³. Bone marrow biopsy was consistent with myelodysplastic syndrome (MDS) refractory cytopenia with multilineage dysplasia and she had 3% blasts. R.P.’s cytogenetics revealed a t(8;21).

1. Which one of the following is most likely responsible for R.P.’s therapy-related MDS?
   A. Doxorubicin.
   B. Cyclophosphamide.
   C. Paclitaxel.
   D. Tamoxifen.

2. R.P. has normal organ function and no significant comorbidities. Her breast cancer has a low risk of recurrence. R.P. has a matched sibling donor. Which one of the following is best for R.P.?
   A. Autologous stem cell transplantation.
   B. Allogeneic stem cell transplantation.
   C. Azacitidine.
   D. Decitabine.

Questions 4–6 pertain to the following case.
K.H. is a 54-year-old man with complaints of increasing fatigue, shortness of breath on exertion, and two recent sinus infections treated with azithromycin. His CBC reveals a hemoglobin of 7.8 g/dL with an absolute neutrophil count of 750 cells/mm³ and a platelet count of 19,000 cells/mm³. Bone marrow biopsy reveals MDS refractory cytopenia with multilineage dysplasia with 3% blasts. K.H. has normal cytogenetics and a matched sibling donor.

4. Which one of the following best describes K.H.’s predicted overall survival on the basis of the International Prognostic Scoring System (IPSS)?
   A. 5.7 years.
   B. 3.5 years.
   C. 1.2 years.
   D. 0.4 years.

5. Which one of the following best describes K.H.’s predicted overall survival on the basis of the International Prognostic Scoring System-Revised (IPSS-R)?
   A. 5.3 years.
   B. 3 years.
   C. 1.6 years.
   D. 0.8 years.

6. Which one of the following is the best therapy for K.H.?
   A. Lenalidomide.
   B. Autologous stem cell transplantation.
   C. Allogeneic stem cell transplantation.
   D. Decitabine.

7. A 69-year-old man with intermediate -1 risk MDS presents with hematuria. His laboratory evaluation shows absolute neutrophil count of 3700 cells/mm³, hemoglobin 8.4 g/dL, and platelets 18,000/mm³. A baseline erythropoietin level is 587 mU/mL. Which one of the following is best to recommend for this patient?
   A. Romiplostim.
   B. Eltrombopag.
   C. Platelet transfusion.
   D. Epoetin.

8. Which one of the following statements best characterizes the risk versus benefit of allogeneic hematopoietic stem cell transplant (HSCT) in patients with MDS?
   A. Allogeneic HSCT is curative therapy; however, patients have a similar risk of treatment-related mortality and for cure.
   B. Randomized trials have demonstrated improvement in overall survival after allogeneic
HSCT with minimal risk of treatment-related mortality.
C. Patients benefit from an allogeneic HSCT regardless of the number of comorbidities or IPSS risk of their disease.
D. Myeloablative chemotherapy and allogeneic HSCT decreases the risk of treatment-related mortality in elderly patients and is recommended to improve overall survival.

9. Which one of the following statements best characterizes the risk versus benefit of iron chelation in patients with MDS?
   A. Iron chelation improves overall survival; however, treatment is limited by renal and hepatic toxicity.
   B. Iron chelation is well tolerated; however, reversal of organ dysfunction related to iron overload has not been demonstrated.
   C. Iron chelation has been shown to reduce ferritin and hepatic iron concentration; however, treatment is limited by renal and hepatic toxicity.
   D. Iron chelation is associated with hematologic improvement in most patients and treatment is well tolerated.

10. A 71-year-old woman presents with complaints of increasing fatigue and shortness of breath. Her CBC reveals a hemoglobin of 8.2 g/dL with an absolute neutrophil count of 5600 cells/mm³ and a platelet count of 104,000/mm³. Bone marrow biopsy reveals MDS, refractory anemia with 3% blasts. She has normal cytogenetics. Her baseline erythropoietin concentration is 87 mU/mL. She has normal kidney and liver function. She has received a total of four RBC transfusions in the past 6 months. Her ferritin is 1200 ng/mL. Which one of the following is best to recommend for this patient?
   A. Decitabine.
   B. Deferasirox.
   C. Romiplostim.
   D. Epoetin.

11. A 76-year-old man presents with complaints of fatigue and lightheadedness. His CBC reveals a hemoglobin of 9.4 g/dL with an absolute neutrophil count of 4600 cells/mm³ and a platelet count of 129,000/mm³. Bone marrow biopsy reveals MDS, refractory anemia with 2% bone marrow blasts and 20% ringed sideroblasts. He has normal cytogenetics. A baseline erythropoietin level is 163 mU/mL. He has a Scr of 2.3 mg/dL and normal liver function. His medical history includes hypertension and type 2 diabetes. Which one of the following is best to recommend for this patient?
   A. Epoetin and filgrastim.
   B. Azacitidine and filgrastim.
   C. Azacitidine and epoetin.
   D. Epoetin and lenalidomide.

Questions 12–14 pertain to the following case.
H.P. is a 78-year-old man with a history of atrial fibrillation and hypertension. His heart rate and blood pressure are well controlled with metoprolol succinate, and he is anticoagulated with warfarin. Over the past several months he has been fatigued, short of breath, and had intermittent gum bleeding despite a therapeutic INR. His laboratory evaluation shows a neutrophil count of 2500 cells/mm³, hemoglobin 7.4 g/dL, and platelets 65,000/mm³. H.P.’s baseline erythropoietin level is 603 mU/mL. His physical examination is notable for persistent atrial fibrillation. He is diagnosed with MDS refractory anemia with excess blasts-1 with 7% blasts. Cytogenetic analysis shows deletion 20q. H.P.’s Eastern Cooperative Oncology Group performance status is 2.

12. Which one of the following best describes H.P.’s IPSS classification?
   A. Low-risk disease.
   B. Intermediate-1 risk.
   C. Intermediate-2 risk.
   D. High risk.

13. Which of the following is the best goal of therapy for H.P.?
   A. Cure of his myelodysplastic syndrome.
   B. Prolonging overall survival.
   C. Improvement in quality of life.
   D. Maintaining concurrent warfarin therapy.

14. Which one of the following is the best therapy for H.P.?
   A. Antithymocyte globulin.
   B. Lenalidomide.
   C. Darbepoetin.
   D. Best supportive care.

15. A 63-year-old man with intermediate-2 risk MDS is started on azacitidine. He presents before cycle 2 today. His hemoglobin has not increased above his baseline of 9.0 g/dL, and he has required three RBC transfusions during the cycle. His platelets are stable at 93,000/mm³ and absolute neutrophil count is 2700 cells/mm³. His physician is concerned that the patient has not seen a significant response to therapy. Which one of the following is best to recommend for this patient?
   A. Switch to decitabine.
   B. Add filgrastim.
16. A 25-year-old woman presents with new-onset anemia over the past 3 weeks. Bone marrow biopsy demonstrates a hypoplastic bone marrow with dysplastic changes. Cytogenetic analysis reveals HLA DR-15. Which one of the following is best to recommend for this patient?
A. Azacitidine.
B. Lenalidomide.
C. Antithymocyte globulin.
D. Epoetin.

17. A 59-year-old man presents with profound hypoxia and syncope. His CBC reveals a hemoglobin of 6.6 g/dL with an absolute neutrophil count of 1900 cells/mm³ and a platelet count of 85,000 cells/mm³. A bone marrow biopsy reveals MDS, refractory anemia with excess blasts-1, and del 20q. A baseline erythropoietin level is 770 mU/mL. The patient’s medical history includes mild hypertension managed with hydrochlorothiazide. Which one of the following is best to recommend for this patient?
A. Decitabine.
B. Epoetin.
C. Antithymocyte globulin.
D. Best supportive care.

18. A 62-year-old woman with newly diagnosed MDS associated with isolated deletion of 5q is found to be intermediate-1 risk by IPSS and intermediate risk by IPSS-R. She has received two transfusions since her diagnosis, and her symptoms have been minimal. Her serum erythropoietin concentration is 155 mU/mL. Which one of the following would be best to recommend for this patient?
A. Azacitidine.
B. Lenalidomide.
C. Filgrastim.
D. Romiplostim.

Questions 19 and 20 pertain to the following case.
Two months ago J.B., a 51-year-old man, presented with new-onset fatigue and shortness of breath. Laboratory results were hemoglobin 8.2 g/dL, absolute neutrophil count 7300 cells/mm³, and platelets 145,000 cells/mm³. Six weeks ago J.B. was initiated on lenalidomide 10 mg orally once daily. Today he presents with the following laboratory values: hemoglobin 9.3 g/dL, absolute neutrophil count 1800 cells/mm³, and platelets 98,000/mm³. J.B. has required one transfusion since initiating therapy.

19. Which one of the following is the best to recommend for J.B.?
A. Add filgrastim.
B. Decrease lenalidomide to 5 mg.
C. Continue current lenalidomide dose.
D. Add eltrombopag.

20. J.B. confides in his provider that his current sexual partner is pregnant. He admits to inconsistently following the latex condom requirements in the Risk Evaluation and Mitigation Strategies program. Which one of the following would be best to notify about J.B.'s circumstances?
A. Organization of Teratology Information Specialist.
B. Agency for Healthcare Quality.
C. FDA Safety Information and Adverse Event Reporting Program.
Chronic Myeloid Leukemia

By Marc A. Earl, Pharm.D., BCOP

Reviewed by David S. Bateshansky, Pharm.D., BCPS; and Ulfat Usta, Pharm.D., BCNS, BCPS

**Learning Objectives**

1. Analyze available evidence to recommend a first-line therapy for chronic myeloid leukemia (CML).
2. Assess patient response to therapy to determine whether alternative CML treatment options are necessary.
3. Distinguish common adverse events with CML and design appropriate management strategies.
5. Detect drug-drug interactions common in CML and design a management plan for affected patients.

**Introduction**

Chronic myeloid leukemia (CML) is a myeloproliferative malignancy involving the hematopoietic stem cells. The median age at diagnosis of CML is 67 years, and an estimated 5920 U.S. patients (15% of leukemia cases) received a diagnosis of CML in 2013 (Siegel 2013). The cause of CML is often uncertain, and there appears to be no genetic predisposition. However, radiation exposure seems to increase the risk (e.g., survivors of radiation disasters, those receiving therapeutic radiation).

Chronic myeloid leukemia is characterized by a chromosomal translocation called the Philadelphia chromosome; it involves the breakpoint cluster region (BCR) gene on chromosome 22 and the Abelson murine leukemia (ABL) gene on chromosome 9. This translocation, designated t(9;22), produces the fusion protein BCR-ABL, which leads to the uncontrolled growth of white blood cells (WBCs) including neutrophils, basophils, and eosinophils.

The Philadelphia chromosome results from and leads to the unregulated proliferation of malignant myeloid cells and some lymphoid cells. Eventually, the BCR-ABL cells predominate because of the lack of apoptosis in them and their precursors. Yet these cells do not function like normal myeloid cells. The excess of BCR-ABL cells also causes a decrease in the number of normal functioning cells. Patients may be in any of the three CML phases at the time of diagnosis (chronic phase, accelerated phase, or blast crisis), depending on the percentage of immature myeloid cells. Patients generally receive a diagnosis in chronic phase, which can progress to the accelerated and blast phases. The BCR-ABL protein becomes more unstable as the disease progresses. Additional genetic mutations are common and can lead to treatment failure as well as disease progression to more aggressive forms of CML, including accelerated phase and blast crisis.

**Baseline Knowledge Statements**

Readers of this chapter are presumed to be familiar with the following:

- Common cytochrome P450–interacting medications
- General adverse events of tyrosine kinase inhibitors
- General response criteria for patients having a diagnosis of chronic myeloid leukemia

**Additional Readings**

The following free resources are available for readers wishing additional background information on this topic.

The 10-year overall survival (OS) rate for CML has dramatically increased since the advent of targeted therapy (tyrosine kinase inhibitors [TKIs]). The OS is 86% for ages 15–44 years; 76% for ages 45–64 years; 51% for ages 65–74 years; and 36% for ages 75–84. This represents an increase of 8%–17% from patients who did not receive targeted therapy (Brunner 2013). Novel oral targeted agents have played a large role in transforming CML to a disease that can be managed in the outpatient environment like other chronic conditions. However, the cost of these agents can be a problem for patients and is an important consideration for disease management because CML is fatal if it progresses.

**Presentation and Diagnosis**

**Clinical Features**

Patients are often asymptomatic and receive a CML diagnosis after an incidental finding on a general physician visit. When symptoms are present, they are often nonspecific. Common complaints include unexplained weight loss, abdominal pain, fatigue, and bone pain. Splenomegaly is present in 50% of patients at diagnosis, which leads to early satiety and weight loss. Symptoms of leukostasis (defined as a WBC count greater than $10 \times 10^3$ cells/mm$^3$) include respiratory distress and mental status changes. These symptoms are rare in the chronic phase but may be present in advanced phases.

**Laboratory Abnormalities**

The median WBC count at presentation is greater than $10 \times 10^3$ cells/mm$^3$. The differential routinely shows cells from most stages of myeloid development. Myeloid blasts typically are less than 2% in the chronic phase. Platelet counts tend to be normal or above normal and are almost never low. More than 50% of patients have anemia.

**Diagnosis**

Diagnosis occurs by identifying t(9;22) through cytogenetic analysis, fluorescence in situ hybridization, or reverse transcriptase polymerase chain reaction. Ninety-five percent of patients are positive for this chromosomal translocation. The remaining patients usually have some variant of this translocation and may require additional molecular testing to confirm the diagnosis.

**Phases of Disease**

Most patients present in the chronic phase. The World Health Organization (WHO) defines chronic phase as less than 10% immature myeloid cells (blasts). With time, the disease tends to progress to more aggressive phases (i.e., accelerated and blast phases). Box 2-1 lists the definitions according to the WHO (Baccarani 2013). The most important laboratory value to review is the percentage of blasts; accelerated phase relates to a blast percentage of 10%–19%, whereas blast crisis is a blast percentage greater than 20%.

**Prognosis Scoring**

Various scoring systems are available to predict patient outcome. The two most common are the Sokal and the Euro scores. The Sokal score considers spleen size, age, platelet count, and percentage of blasts. The Euro score adds the percentage of basophils and eosinophils to these end points. These scoring systems help identify high-risk patients who may have a lower chance of experiencing a complete cytogenetic response (CCyR) with therapy (Hasford 2011; Sokal 1984).

---

**Box 2-1. WHO Definitions of CML Accelerated and Blast Phases**

**Presence of one or more**

**Accelerated phase:**
- Peripheral or bone marrow blasts 10%–19%
- Persistent thrombocytopenia (<100,000/L) not related to therapy
- Thrombocytosis (>1,000,000/L) despite drug therapy
- Peripheral basophilia > 20%
- Increasing spleen size and WBC count despite drug therapy
- Evidence of progression of leukemic clone or new cytogenetic abnormalities

**Blast phase:**
- Peripheral or bone marrow blasts > 20%
- Extramedullary disease apart from spleen
- Large clusters of blasts in bone marrow

---

### Abbreviations in This Chapter

- **ABL** Abelson murine leukemia
- **BCR** Breakpoint cluster region
- **CCyR** Complete cytogenetic response
- **CHR** Complete hematologic response
- **CML** Chronic myeloid leukemia
- **HSCT** Hematopoietic stem cell transplantation
- **MCyR** Major cytogenetic response
- **MMR** Major molecular response
- **OS** Overall survival
- **TKI** Tyrosine kinase inhibitor
Treatment Response Goals and Criteria

The goal of initial therapy varies depending on the disease phase when the CML diagnosis is given. For patients in chronic phase, the goal is to prevent progression to either accelerated phase or blast phase. If patients are in accelerated or blast phase at diagnosis, or if they progress while on therapy, the goal is for them to return to a chronic-phase state. With all phases of CML, the goal is to minimize toxicity while achieving a response. The response to therapy is measured at various time points, with different goals at each end point, which are achieved through hematologic, cytogenetic, and molecular responses (Box 2-2). It appears most advantageous to have a major cytogenetic response (MCyR) at 3 months, a CCyR by 6 months, and a complete molecular response by 12 months (Baccarini 2013).

Treatment Overview

The only treatment option that provides a cure for patients with CML is allogeneic hematopoietic stem cell transplantation (HSCT). Therapy has been revolutionized by targeted oral agents that offer long-term chronic therapy for CML. Goals include obtaining a complete hematologic response (CHR), a CCyR, and a major molecular response (MMR) within prespecified periods (Baccarini 2013). These responses lead to a decrease in disease progression to accelerated or blast phase. Patients who have resistance to or disease progression on targeted therapy may be treated with cytotoxic agents. However, these agents have lower cytogenetic and molecular responses.

Historical Treatment Options

Past treatment included cytotoxic therapy with busulfan and hydroxyurea. Although both agents controlled WBC count and led to a reduction in spleen size, neither led to cytogenetic responses or a decrease in progression to blast phase. Hydroxyurea is still sometimes used for an immediate reduction in WBC count in patients with leukostasis or CML in the accelerated or blast phase. Leukapheresis may also be an option for patients presenting with leukostasis.

Interferon alfa plus subcutaneous cytarabine was the first therapy to show an increased CHR. Patients receiving interferon also had an increased OS. Interferon-based therapy became the standard of treatment for CML until the evolution of oral targeted therapy (Guilhot 1997). Interferon therapy is currently recommended only in patients who cannot tolerate TKI therapy.

First-Generation TKI

Imatinib

A major advance in the treatment of CML was the discovery of the oral TKI imatinib. By preventing phosphorylation of the BCR-ABL tyrosine kinase, cell proliferation is “shut off” and apoptosis is induced.

Compared with interferon alfa and subcutaneous cytarabine therapy, imatinib has higher a CHR (95.3% vs. 55.5%, p<0.001) and CCyR (73.8% vs. 8.5%, p<0.001). Many patients taking interferon alfa cross over to the imatinib arm, making OS difficult to evaluate (O’Brien 2003). However, patients receiving imatinib in one trial had OS rates at 8 years of 85% and 93% when non-CML deaths were excluded. Because of these results, imatinib 400 mg orally (with food) daily was recommended for initial CML therapy (Jabbour 2011). Studies have investigated the use of higher imatinib doses (400 mg vs. 600 mg or 800 mg), but results do not appear to show any major advantages for an imatinib dose greater than 400 mg in initial therapy (Cortes 2010).

Box 2-2. CML Response Criteria

<table>
<thead>
<tr>
<th>Complete hematologic response:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Normal WBC counts</td>
</tr>
<tr>
<td>• No blasts</td>
</tr>
<tr>
<td>• Leukocytes &lt; 10 x 10⁹/L</td>
</tr>
<tr>
<td>• Platelet count &lt; 450,000/mm³</td>
</tr>
<tr>
<td>• No signs and symptoms of disease</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Partial hematologic response:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Presence of blasts and/or</td>
</tr>
<tr>
<td>• Platelet decrease &lt; 50% but &gt; 450,000/mm³ and/or</td>
</tr>
<tr>
<td>• Persistent splenomegaly &lt; 50% of pretreatment size</td>
</tr>
<tr>
<td>• No Philadelphia-positive metaphases</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Partial cytogenetic response:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 1%–34% Philadelphia-positive metaphases</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Major cytogenetic response:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 0%–35% Philadelphia-positive metaphases</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Minor cytogenetic response:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 35% Philadelphia-positive metaphases</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Complete molecular response:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• No detectable BCR-ABL by PCR</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Major molecular response:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• A 3-log reduction or greater in BCR-ABL from baseline</td>
</tr>
</tbody>
</table>

CML = chronic myeloid leukemia; PCR = polymerase chain reaction.
Second- and Third-Generation TKIs

**Nilotinib**
Nilotinib was designed to be more selective and a better geographic fit for the BCR-ABL tyrosine kinase than imatinib. This design was theorized to have a more potent inhibition of BCR-ABL. In a phase III trial, nilotinib was more effective than imatinib (400 mg orally daily), with higher MMR rates at 24 months (44% imatinib and 67% nilotinib 400 mg vs. 71% nilotinib 300 mg; p<0.001) and higher CCyR rates at 24 months (77% imatinib and 85% nilotinib 400 mg vs. 87% nilotinib 300 mg; p=0.0018). Despite these advantages, OS was not significantly different at 24 months (96.7% imatinib and 97.8% nilotinib 400 mg vs. 97.4% nilotinib 300 mg; p=NS) (Kantarjian 2011a). This led to U.S. Food and Drug Administration (FDA) label approval for nilotinib 300 mg orally twice daily for initial CML therapy. Unlike imatinib, nilotinib should be taken on an empty stomach.

**Dasatinib**
When compared with imatinib (400 mg orally daily) in a phase III trial, dasatinib 100 mg was more effective with respect to CCyR at 24 months (86% dasatinib vs. 82% imatinib; p=NS) and MMR at 24 months (64% dasatinib vs. 46% imatinib). Similar to nilotinib, dasatinib caused no significant differences in progression-free survival (93.7% dasatinib vs. 92.1% imatinib; p=NS) or OS (95.3% dasatinib vs. 95.2% imatinib; p=NS). These data led to FDA approval of dasatinib for initial CML therapy (Kantarjian 2012). The starting daily dosage of dasatinib is 100 mg orally.

**Bosutinib**
Bosutinib 500 mg daily has results similar to imatinib on end points related to CCyR (70% bosutinib vs. 68% imatinib; p=0.601). Bosutinib is superior to imatinib in MMR only at 12 months (41% bosutinib vs. 27% imatinib; p<0.001). The bosutinib toxicity profile is greater than that of imatinib (see Box 2-1), which leads to higher discontinuation rates (19% bosutinib vs. 6% imatinib) (Cortes 2012b). These results have led to FDA label approval of bosutinib, but only in patients who have not responded to initial therapy. Bosutinib dosage is 500 mg orally daily. Bosutinib is not an option for first-line therapy except in patients with an intolerance to imatinib, dasatinib, and nilotinib.

**Ponatinib**
Ponatinib is the only first third-generation TKI available, and it is the only TKI with activity against some resistant forms of CML (i.e., the T315I mutation). Patients who do not respond to initial therapy at 3 months may undergo mutational analysis to detect evidence of TKI-resistant subtypes. In a phase II study of patients with resistant/intolerant CML (70% with the T315I mutation), ponatinib produced MCyR in 56%, CCyR in 46%, and MMR in 34%. Despite this success, 9% of patients experienced serious arterial thrombotic events (Cortes 2013a). This led to ponatinib label approval only for patients intolerant of any other TKI or who are T315I positive.

Ponatinib is dosed at 45 mg orally daily. The drug has a boxed warning regarding the incidence of arterial and vascular thrombosis. Patients experiencing this adverse effect and having the T315I mutation have few options for treatment. However, omacetaxine (see the following) may be an option, together with HSCT.

**Choice of Initial TKI**
Although time to CCyR and MMR are potential advantages of nilotinib and dasatinib over imatinib, second-generation TKIs demonstrate no substantial difference in OS. Many clinicians recommend either nilotinib or dasatinib because of their better CCyR and MMR rates; however, nilotinib and dasatinib have not been compared in a randomized trial. The choice of agent is most influenced by the cost of therapy and the adverse effect profile. One month of imatinib costs about $9000, whereas 1 month of nilotinib or dasatinib costs about $10,000. This dynamic is projected to change in 2015 when imatinib becomes available generically. At that time, clinicians will have to evaluate whether the clinical benefit of nilotinib and dasatinib justifies the cost difference. Table 2-1 lists the dosing of these agents in the initial treatment of chronic-phase CML.

### Table 2-1. Dosage for Chronic-, Accelerated-, and Blast-Phase Treatment of Chronic-Phase CML

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Chronic-Phase Dosing (mg orally/day)</th>
<th>Accelerated/Blast-Phase Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib</td>
<td>400</td>
<td>600 mg orally daily; may be increased to 800 mg</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>300</td>
<td>400 mg orally twice daily</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>100</td>
<td>140 mg orally daily; may be increased to 180 mg</td>
</tr>
<tr>
<td>Bosutinib</td>
<td>500</td>
<td>Not indicated</td>
</tr>
</tbody>
</table>

CML = chronic myeloid leukemia.
Resistence or Intolerance to Initial Therapy

Although resistance to CML therapy is rare, some patients do not respond to initial therapy, or they lose the response at some point during therapy. Resistance can be caused by the evolution of the BCR-ABL fusion protein or by point mutations that result in lack of response to most TKIs (i.e., T315I). Various strategies have been investigated to eliminate resistance, including dose escalation of a given TKI or switching to an alternative agent.

For patients who have had a cytogenetic response to imatinib, increasing the dosage to 600 mg or 800 mg daily is an option (Jabbour 2009), although the subsequent-generation TKIs offer more benefit with respect to hematologic, cytogenic, and molecular response. A phase II study comparing dasatinib with imatinib 800 mg showed higher CHR rates (82% imatinib vs. 93% dasatinib, p=0.034), higher MCyR rates (33% imatinib vs. 53% dasatinib, p=0.017), and higher CCyR (18% imatinib vs. 44% dasatinib, p=0.0025) (Kantarjian 2009). Nilotinib (MCyR 59% and CCyR 44%) and bosutinib (MCyR 53% and CCyR 41%) have shown similar results (Kantarjian 2011b).

Before these subsequent-generation agents became available, the only option for imatinib resistance was HSCT. Success of the new TKIs has led some clinicians to postpone HSCT unless there is a lack of response to the TKI, particularly given the toxicity associated with HSCT. Patients ineligible for HSCT may require a trial with another TKI, omacetaxine, or a clinical trial.

Strategies for Overcoming TKI Resistance

Omacetaxine, a protein synthetase inhibitor, is another option for patients with CML. This agent is given for 2 weeks in induction therapy (1.25 mg/m² subcutaneously twice daily) and then at the same dose during maintenance for 1 week every 28 days. Omacetaxine is indicated in patients with resistance to therapy after at least two TKIs (Cortes 2012c). In a phase II study that included patients with a T315I mutation, 77% achieved CHR, 23% MCyR, and 16% CCyR. Toxicities were mainly hematologic, including thrombocytopenia (76%), neutropenia (44%), and anemia (39%). Progression-free survival was 7.7 months, showing that omacetaxine remains an option for patients with resistant disease. Similar data exist for patients who have shown resistance to several TKIs (Cortes 2012).

Accelerated Phase

Patients may receive a diagnosis of accelerated-phase disease initially or after resistance to therapy. For patients with resistance to a TKI, a mutational analysis should be done. These patients need to be treated more aggressively than those in chronic phase. Most clinicians initially treat with a TKI and evaluate for response (see Table 2-1). Progression-free survival at 12 months can be as high as 70% with TKIs (Apperley 2009). Despite these positive results, this percentage continues to decline with time. Therefore, patients with a good performance status and no significant comorbidities may be candidates for HSCT.

Blast Crisis

Patients with blast crisis have a poor prognosis. Eligibility for HSCT should be determined depending on the diagnosis of blast-phase disease. Patients taking a TKI should have their therapy evaluated and be switched to an alternative agent while a mutational analysis is performed. The process for HSCT should begin immediately.

Studies have evaluated giving chemotherapy to achieve a response in blast crisis. These regimens are a combination of oral TKI and intravenous chemotherapy. Regimens including mitoxantrone, etoposide, and cytarabine or idarubicin, cytarabine, and etoposide have been studied with overall response rates of 48%. Many of these patients returned to a chronic phase of CML (Axdorph 2002). Patients ineligible for HSCT may be tried on a TKI at the accelerated dosing levels (Table 2-2).

| Table 2-2. Common Adverse Events with Bosutinib vs. Imatinib |
|---------------------------------|------------|----------|---|
| Adverse Event | Bosutinib (%) | Imatinib (%) | p-value |
| Diarrhea | 68 | 21 | x |
| Vomiting | 32 | 13 | x |
| Edema | 11 | 38 | x |
| Muscle spasm | 2 | 20 | x |
| Total grade 3/4 | 64 | 48 | < 0.001 |
Hematopoietic Stem Cell Transplantation

Allogeneic stem cell transplantation remains the only curative therapy for CML. In one study, patients undergoing a transplant in the chronic phase of disease had long-term remission rates of 50%–75% (Goldman 1986). Because of the morbidity and mortality associated with HSCT, the number of patients who undergo a transplant is limited. Patients considered eligible for HSCT are usually younger than 50, lack significant comorbidities (e.g., hepatic toxicity, cardiac or severe hypertension issues, renal dysfunction), and have a good performance status. The overwhelming success of TKIs to treat chronic-phase disease, combined with the low toxicity of these agents, has further decreased the use of HSCT for CML.

The success of HSCT depends on the patient’s disease phase at the time of the transplant. Overall survival at 3 years was 58% for chronic phase, 41% for accelerated phase, and 25% for blast phase (Biggs 1992). For patients whose disease has relapsed, it may be more beneficial to initiate therapy with chemotherapy or TKIs so that the patient may undergo transplantation in the chronic phase. The most common conditioning regimen used for HSCT is busulfan and cyclophosphamide. With targeted busulfan dosing, the 3-year OS can be as high as 85% (Radich 2003). Despite these successes, the incidence of death within 100 days of HSCT remains 10%–20%. Because the mortality risk is almost zero with TKIs, most clinicians still recommend TKI therapy before considering HSCT.

Monitoring

Adverse Events with CML Therapy

Imatinib

Common adverse events with imatinib are primarily gastrointestinal (GI) complaints (e.g., nausea, vomiting, diarrhea); these may be decreased by taking the agent with food or dividing the dose.

Myelosuppression can occur with any of the TKIs, and is likely caused by the eradication of malignant cells rather than the suppressed production of normal cells. Patients are generally monitored weekly for 1 month, every 2 weeks for 1 month, and then every few months.

Patient Care Scenario

F.P. is a 47-year-old man who presents to his physician for a yearly physical examination. On reviewing his CBC, F.P.’s WBC count is 10.5 x 10^3 cells/mm^3. He undergoes PCR testing, which verifies that he is positive for BCR-ABL. A bone marrow biopsy shows his blast percentage to be 4%. F.P. is started on imatinib 400 mg orally daily. He has some issues with nausea on starting therapy but is able to manage this and is now tolerating therapy well. Two months later he returns to clinic; his WBC count is 5 x 10^3 cells/mm^3 and a bone marrow biopsy reveals 25% of his metaphases positive for the Philadelphia chromosome. What is best to recommend for F.P.?

A. He has not responded hematologically or cytogenically and should be evaluated for omacetaxine therapy.
B. He has not responded molecularly and should be evaluated for increasing his dose of imatinib.
C. He has completely responded hematologically but not cytogenically and should be evaluated again at 6 months.
D. He has completely responded hematologically and molecularly and should be evaluated again at 12 months.

Answer

The correct answer is option C. A complete hematological response is a WBC less than 10 x 10^3 cells/mm^3. Technically, he has had a major cytogenetic response, which is appropriate at this time. The goal at 6 months would be a CCyR. Option A is incorrect because he has had a complete hematological response. Option B is incorrect because a complete molecular response is not evaluated until 12 months. Option D is incorrect, again because of the molecular response.

After 14 months of therapy, F.P.’s WBC count is 24 x 10^3 cells/mm^3. What is best to recommend for this patient?

A. Increase his dose of imatinib to 600 mg orally daily
B. Continue imatinib at 400 mg orally daily
C. Switch to omacetaxine 1.25 mg/m^2 subcutaneously twice daily x 14 days.
D. Switch to nilotinib 300 mg orally twice daily.

Answer

At this point in therapy, the patient’s disease can be considered resistant. He should be evaluated for alternative TKI therapy. From what he has received in the past, his therapy should be transitioned to nilotinib (option D is correct). Option A and option B are incorrect because he is resistant to imatinib. Option C is incorrect because omacetaxine is not indicated unless two TKIs have failed. Depending on his age and comorbidities, it would be appropriate to consider HSCT because this would be the only chance for a cure for his CML.

If a patient experiences a decrease in absolute neutrophil count (ANC) to less than 1000 cells/mm$^3$ or a decrease in platelet count to less than 50,000/mm$^3$, the offending drug can be held. When the count recovers, the drug can then be reintroduced at full dose. Filgrastim 5 mcg/kg subcutaneously (given daily, every other day, or two or three times weekly during treatment) has been used to assist in maintaining an ANC greater than 1000 cells/mm$^3$.

Imatinib is reported to cause muscle spasm and pain, usually in the upper and lower extremities, in up to one-half of patients. This pain is theorized to result from alterations in electrolyte levels. Despite normal magnesium and calcium levels, supplementation may be beneficial. Hepatotoxicity is also a concern, with reports of elevated serum bilirubin and/or liver enzymes.

**Dasatinib**

Up to one-third of patients treated with dasatinib have reported some type of pleural effusion, which is usually exudative. Early studies using dasatinib 70 mg twice daily had a higher incidence of pleural effusion than those using the currently recommended dosage of 100 mg daily. Many different procedures have been used to resolve these symptoms, but drug discontinuation is usually the only successful method.

Bleeding with normal platelet counts has been reported in to one-fourth of patients receiving dasatinib; this bleeding usually affects the GI tract. Coagulation studies are also typically normal in this situation. This adverse event appears to be related to impaired platelet aggregation. If the platelet count falls to less than 50,000/mm$^3$ therapy should be withheld until the count rises above this level. Then, if it is the first occurrence, the full dasatinib dose can be restarted; if the platelet count falls again, dasatinib should be discontinued and another TKI started. Caution should be used when administering dasatinib with other drugs that affect platelet function. For patients who experience bleeding issues, the drug should be withheld and transfused with platelets.

**Nilotinib**

Nilotinib appears to carry more concerns with cardiovascular issues than other TKIs. Less than 10% of patients experience corrected QT (QTc) prolongation, but it can be severe, including reports of death. Electrocardiography should be done at baseline, at 7 days, with all dose changes, and periodically during therapy. Special concern should be paid to potassium and magnesium levels during therapy. Potassium should be targeted above 4.0 mEq/L and magnesium above 1.8 mg/dL. Prolonged QTc interval may lead to arrhythmias, seizures, and death. Cardiovascular events related to atherosclerosis have been reported, as have stenosis and cerebrovascular events. Caution should be used in patients with preexisting cardiovascular disease. A boxed warning exists for these issues, which should be evaluated before starting therapy.

**Bosutinib**

Gastrointestinal events (e.g., nausea, vomiting, diarrhea) tend to be common during bosutinib therapy. Edema has also been described, which may also present as pleural effusions. Treatment discontinuation may be necessary to eliminate this latter adverse effect.

**Ponatinib**

The biggest concern with ponatinib is the incidence of arterial and venous occlusion events. This has presented as arterial thrombosis in around 10% of patients in clinical trials. The FDA temporarily withdrew ponatinib from the market because of this concern. More recently, after the safety information for the drug was updated, it was approved for return to the market.

**Drug Interactions**

**CYP System**

All TKIs interact with the cytochrome P450 (CYP) system as a substrate, an inhibitor, or an inducer (Box 2-3). Each drug has a slightly different metabolic profile; therefore, each patient’s medication list should be reviewed before TKI therapy is initiated and before a drug is initiated or discontinued (Haouala 2011).

An example of the difference between metabolic profiles of TKIs is that between dasatinib and nilotinib. The area under the curve (AUC) of dasatinib increases by 5-fold when exposed to CYP3A4 inhibitors and decreases by 80% in the presence of CYP3A4 inducers. In contrast, the AUC of nilotinib increases by 3-fold when exposed to CYP3A4 inhibitors and decreases by 5-fold when given with CYP3A4 inducers. The dasatinib dose should be decreased to 20 mg daily in combination with a CYP3A4 inhibitor. Nilotinib should be decreased to 300 mg daily for resistant CML and to 200 mg daily for chronic CML. Neither drug should be combined with CYP3A4 inducers. Patients should be closely monitored for response and toxicity, with a dose reduction if appropriate. Table 2-3 lists the CYP characteristics of these drugs; see Box 2-3 for the common drugs that affect CYP3A4.

**Absorption**

Nilotinib, dasatinib, bosutinib, and ponatinib all appear to have pH-dependent absorption. When dasatinib is given within 2 hours of famotidine, dasatinib exposure decreases by 61%. Dasatinib absorption is not affected when this agent is given with antacids separated by at least 2 hours. Ideally, patients should avoid histamine-2 (H$_2$)-antagonists and proton pump inhibitors while taking TKIs. Patients should try to separate antacids use by 2 hours from the TKI dose. If this solution does not suffice, an H$_2$-antagonist or a proton pump inhibitor may be tried and should be scheduled to avoid a gastric pH increase when the TKI is taken. For instance, dasatinib may be taken at 6:00 a.m., followed by an H$_2$-antagonist at 7:00 a.m. This will allow dasatinib absorption while the patient continues acid suppression therapy. Patients should be followed closely for response to therapy.
Because nilotinib and dasatinib can increase the QT interval, any medications that affect the QT interval should be added cautiously. Drugs like fluoroquinolones, digoxin, and some antipsychotics can have an additive effect on the QT interval. Patients should be monitored closely with periodic ECGs.

**Conclusion**

Pharmacists have a responsibility to understand the intricacies of and differences between the various TKI agents and the ways in which they correspond with individual patients. By knowing the adverse events and drug interaction profiles, the pharmacist can assist in identifying the most appropriate agent for each patient. The pharmacist can also assist in helping each patient individualize his or her other drug therapies, given the differences between each agent. The biggest impact in the coming years will be cost management. With imatinib projected to become available as a generic in 2015, many patients will have the opportunity to choose between TKIs, not only according to effectiveness but also according to how much they are willing to pay for the potential increase in efficacy related to quicker CCyR and MMR.

Adherence plays a primary role in the success of oral TKI therapy in CML. Pharmacists can interact with patients throughout this chronic disease process. Because patients may be taking these agents for many years, pharmacists will have more opportunities to evaluate adverse events and drug interactions.

Treatment of CML has progressed dramatically in the past 15 years. Treatment options have gone from mostly symptomatic management to disease-modifying therapy. As a result, CML is now similar to other chronic disease states that are managed throughout decades. The availability of many TKIs makes it harder than ever for the health care professional to stay up to date on each drug. This allows the pharmacist yet another opportunity to show expertise in managing adverse events and drug interactions.

**Table 2-3. Common Major CYP Characteristics of CML agents**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Substrate</th>
<th>Inhibits</th>
<th>Induces</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib</td>
<td>3A4</td>
<td>2C9, 2D6, 3A4</td>
<td>N/A</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>3A4</td>
<td>2C8, 2C9, 2D6</td>
<td>2B6, 2C8, 2C9</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>3A4</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Bosutinib</td>
<td>3A4</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

CML = chronic myeloid leukemia; N/A = not applicable.

**Box 2-3. Common Inhibitors and Inducers of CYP3A4**

**Strong CYP3A4 inhibitors**
- Atazanavir
- Clarithromycin
- Indinavir
- Itraconazole
- Ketoconazole
- Nefazodone
- Nelfinavir
- Posaconazole
- Ritonavir
- Saquinavir
- Telithromycin
- Voriconazole
- Grapefruit juice

**Strong CYP3A4 inducers**
- Carbamazepine
- Dexamethasone
- Phenobarbital
- Phenytoin
- Rifabutin
- Rifampin

**QT Prolongation**

Because nilotinib and dasatinib can increase the QT interval, any medications that affect the QT interval should be added cautiously. Drugs like fluoroquinolones, digoxin, and some antipsychotics can have an additive effect on the QT interval. Patients should be monitored closely with periodic ECGs.
**Practice Points**

- The availability of TKIs has changed the way CML has been managed in the past 15 years.
- Current therapy options have transformed CML into a chronic disease that can be managed with oral TKIs.
- As more TKIs have been approved, it is important to know the distinct adverse effect and drug interaction profile of each agent.
- Dasatinib and nilotinib appear to be more effective than imatinib in the initial treatment of CML with respect to MMR and CCyR.
- Imatinib becoming generic may influence the initial treatment choice because of its reduced cost.
- HSCT remains the only proven cure for CML.

**References**


Kantarjian HM, Shah NP, Cortes JE, et al. Dasatinib or imatinib in newly diagnosed chronic-phase chronic myeloid


Self-Assessment Questions

21. A 47-year-old man presents with complaints of early satiety. The patient has a WBC count of 12.5 x 10^3 cells/mm^3 and splenomegaly, and a bone marrow biopsy reveals a blast count of 12%. Which one of the following best describes this patient’s phase of chronic myeloid leukemia (CML)?
   A. Blast phase.
   B. Accelerated phase.
   C. Chronic phase.
   D. Chronic/accelerated phase.

22. A 37-year-old woman receives a diagnosis of chronic-phase CML. She is beginning therapy with a tyrosine kinase inhibitor (TKI). Which one of the following best describes the optimal response to therapy for this patient?
   A. A complete hematologic response (CHR) by 12 months.
   B. A major cytogenetic response (MCyR) by 6 months.
   C. A complete molecular response by 12 months.
   D. A complete cytogenetic response (CCyR) by 12 months.

23. A 54-year-old man presents for his annual physical examination. His laboratory values are as follows: WBC count 9 x 10^3 cells/mm^3, platelet count 200,000/mm^3, and hemoglobin 14.1 g/dL. The patient is referred to a hematologist, from whom he receives a diagnosis of chronic-phase CML. Which one of the following is the best initial treatment for this patient?
   A. Omacetaxine 1.25 mg/m^2 subcutaneously twice daily for 14 days.
   B. Bosutinib 500 mg orally daily.
   C. Ponatinib 45 mg orally daily.
   D. Nilotinib 300 mg orally twice daily.

24. A 57-year-old woman receives a diagnosis of chronic-phase CML, and therapy is initiated with imatinib 400 mg once daily. Three months later, follow-up studies show a loss of major molecular response (MMR). Further molecular testing concludes that she is positive for a T315I mutation. Which one of the following is best to recommend for this patient?
   A. Ponatinib 45 mg once daily.
   B. Bosutinib 500 mg once daily.
   C. Allogeneic stem cell transplantation.
   D. Dasatinib 140 mg once daily.

25. A 67-year-old woman receives a diagnosis of chronic-phase CML. Her medical history includes diabetes, hypertension, hypercholesterolemia, and atrial fibrillation. Which one of the following is the best treatment option for this patient?
   A. Nilotinib 300 mg orally twice daily.
   B. Bosutinib 500 mg orally daily.
   C. Imatinib 400 mg daily.
   D. Ponatinib 45 mg orally daily.

26. A 62-year-old man with CML treated with dasatinib recently saw an infectious diseases physician because of pulmonary nodules. The physician confirms the diagnosis of pulmonary aspergillosis and wants to use voriconazole to treat the patient. Which one of the following would be best to recommend for this patient?
   A. Increase the dasatinib dose.
   B. Increase the voriconazole dose.
   C. Discontinue dasatinib and initiate omacetaxine.
   D. Decrease the dasatinib dose.

27. A 68-year-old woman recently received a diagnosis of CML. Her medical history is significant for diabetes, asthma, and chronic obstructive pulmonary disease. Which one of the following is best to recommend for this patient?
   A. Dasatinib 140 mg orally daily.
   B. Imatinib 400 mg orally daily.
   C. Ponatinib 300 mg orally twice daily.
   D. Bosutinib 500 mg orally daily.

28. A 59-year-old woman begins treatment for chronic-phase CML with imatinib 400 mg daily. Three months later, she has a CHR, with a minor cytogenetic response after 17 months of imatinib therapy. This prompts the physician to investigate adherence. The patient now reports low-grade malaise and back pain. Supportive care initiatives and their appropriate management are reviewed with the patient, and her regimen is altered to include scheduled nonsteroidal anti-inflammatory drugs (NSAIDs) together with a GI-protective agent to manage low-grade bone pain, vasodilators for migraine headaches, and tramadol for pain unalleviated by NSAIDs. Which one of the following is best to recommend for this patient?
   A. Aluminum hydroxide 600 mg 2 hours before or after imatinib.
   B. Famotidine 10 mg twice daily 2 hours before or after imatinib.
C. Lansoprazole 30 mg daily 2 hours before or after imatinib.
D. All types of acid suppression therapy are contraindicated with TKIs.

29. A 47-year-old man presents with a WBC count of 21.2 x 10^3 cells/mm^3. He is positive for t(9;22). A bone marrow biopsy reveals 17% blasts in the bone marrow. Which one of the following is best to recommend for this patient?
A. Nilotinib 300 mg orally twice daily.
B. Dasatinib 140 mg orally daily.
C. Imatinib 400 mg orally daily.
D. Omacetaxine 1.25 mg/m^2 subcutaneously twice daily.

30. A 47-year-old man presents with a WBC count of 2.5 x 10^3 cells/mm^3. He is positive for t(9;22). His blast count on bone marrow biopsy is 22%. Which one of the following is best to recommend for this patient?
A. Imatinib 400 mg orally daily.
B. Hematopoietic stem cell transplantation.
C. Nilotinib 400 mg orally twice daily.
D. Bosutinib 500 mg orally daily.

31. A 57-year-old woman is being treated with imatinib for chronic-phase CML. She has been treated for 8 months and has been in a CCyR. At her last visit, her WBC count was 10.5 x 10^3 cells/mm^3. A bone marrow biopsy reveals a blast count of 14%. Which one of the following is best to recommend for this patient?
A. Switch to omacetaxine 1.25 mg/m^2 subcutaneously twice daily x 14 days.
B. Increase the imatinib dose to 500 mg orally daily.
C. Switch to ponatinib 45 mg orally daily.
D. Switch to dasatinib 140 mg orally daily.

32. You are reviewing a patient’s medication history before initiating a TKI for the first time. The patient’s current regimen includes risperidone, docusate, cyclobenzaprine, candesartan, and acyclovir. Which one of the following TKIs is most appropriate to initiate in this patient?
A. Nilotinib 300 mg orally twice daily.
B. Bosutinib 500 mg orally daily.
C. Omacetaxine 1.25 mg/m^2 subcutaneously twice daily x 14 days.
D. Imatinib 400 mg orally daily.

33. One month ago, a patient with chronic-phase CML began treatment with imatinib 400 mg twice daily. Today, he presents to the outpatient clinic with an ANC of 750 cells/mm^3. Which one of the following is best to recommend for this patient?
A. Decrease imatinib to 300 mg orally twice daily.
B. Start filgrastim 5 mcg/kg subcutaneously daily.
C. Switch to dasatinib 100 mg orally daily.
D. Hold therapy until the ANC recovers and reinitiate at the current dose.

34. A 50-year-old woman is receiving treatment with nilotinib for chronic-phase CML. She has taken the drug for 6 months and is in a CCyR. During her therapy, she receives a diagnosis of arterial thrombosis. Which one of the following is best to recommend for this patient?
A. Continue nilotinib.
B. Discontinue nilotinib and initiate omacetaxine.
C. Discontinue nilotinib and initiate ponatinib 45 mg orally daily.
D. Discontinue nilotinib and initiate imatinib 400 mg orally daily.

35. Two weeks ago, a 30-year-old patient received a diagnosis of deep venous thrombosis in her right calf and began taking enoxaparin 60 mg subcutaneously twice daily. Today, she receives a diagnosis of chronic-phase CML. Which one of the following is best to recommend for this patient?
A. Dasatinib 100 mg orally daily.
B. Ponatinib 45 mg orally daily.
C. Nilotinib 300 mg orally twice daily.
D. Bosutinib 500 mg orally daily.

36. A 38-year-old man receives a diagnosis of chronic-phase CML, and he comes to the clinic for counseling on his therapy. He brings with him printouts from the Internet on describing many of the drugs used to treat CML over the years (e.g., hydroxyurea, busulfan, cytarabine, interferon, imatinib). The patient is curious about the ways in which therapy for his disease has evolved over the years. Which one of the following is the best response to this patient’s question?
A. Busulfan is still considered an option for CML therapy because of its ease of administration.
B. Hydroxyurea is an option for therapy initially to decrease WBC count.
C. Imatinib was the first drug therapy to modify the cytogenetics of CML.
D. Interferon is more effective than imatinib, but its toxicity prevents its use in most patients.

37. A 48-year-old man with no significant medical history is brought to the hospital with generalized weakness. A CBC reveals the following: hemoglobin 12.4 g/dL, platelet count 159,400/mm^3, WBC...
count 16.5 x 10^3 cells/mm^3, segmented neutrophils 65%, lymphocytes 26%, monocytes 3%, eosinophils 2%, and atypical lymphocytes 4%. The Philadelphia chromosome is detected in 19 of 20 bone marrow metaphase cells analyzed. Subsequently, BCR/ABL1 FISH (fluorescence in situ hybridization) analysis yields a positive result. An RT-PCR analysis for the BCR/ABL1 rearrangement shows the presence of the b3a2 fusion gene. The patient receives a diagnosis of CML, and treatment with dasatinib 100 mg daily is initiated. Four months later, the patient’s WBC count is 8 x 10^3 cells/mm^3, and a bone marrow biopsy shows 22% Philadelphia-positive metaphases. Which one of the following best describes this patient’s response?

A. Partial hematologic response and CCyR.
B. CHR and MMR.
C. Partial hematologic response and partial cytogenetic response (PCyR).
D. CHR and PCyR.

38. A 45-year-old man is being treated with imatinib 400 mg daily for chronic CML. He is experiencing a great deal of nausea and some vomiting when taking his doses. Which one of the following is best to recommend for this patient?

A. Decrease the imatinib dose to 300 mg daily.
B. Take a proton pump inhibitor with the dose.
C. Take imatinib with meals.
D. Initiate ondansetron 4 mg orally daily.

39. A 40-year-old man with CML and no other significant medical history presents to the clinic. He currently takes dasatinib 140 mg daily. His WBC count is 12 x 10^3 cells/mm^3 with a blast count of 7%. The patient has five siblings, and a donor search is planned. Which one of the following is best to recommend for this patient?

A. Switch the patient to ponatinib 45 mg daily.
B. Switch to omacetaxine 1.25 mg/m^2 subcutaneously twice daily x 14 days.
C. Evaluate the patient for an allogeneic stem cell transplant.
D. Switch the patient to nilotinib 400 mg orally twice daily.

40. A 59-year-old man has the T315I mutation. His medical history includes hypertension and diabetes. Which one of the following toxicities to TKI therapy is most likely to require therapy discontinuation in this patient?

A. Arterial thrombosis.
B. Hyperglycemia.
C. Myelosuppression.
D. Rash.
Pharmacology of New Targeted Therapies

By Salvatore M. Bottiglieri, Pharm.D., BCOP

Reviewed by Gabriel T. Bartoo, Pharm.D., BCOP, BCPS; and Kathryn A. Wheeler, Pharm.D., BCPS

Learning Objectives

1. Evaluate the clinical efficacy and optimal use of targeted therapies in the hematology/oncology patient setting.

2. Assess common adverse effects and monitoring parameters associated with the treatment of newly approved targeted therapies.

3. Account for key drug interactions and appropriate medication management with newly approved targeted therapies in the hematology/oncology patient setting.

4. Develop key patient counseling points on newly approved targeted agents.

5. Evaluate the appropriate dosing of targeted therapies in the setting of impaired organ function or drug-related toxicities.

Introduction

The management of malignancies has dramatically changed in recent years with additional pharmacologic options, including an array of nontraditional cytotoxic agents. As cancer research progresses, so has the recognition of the role of various receptors, enzymes, and complex pathways in the promotion, growth, and metastasis of malignancies. With this better understanding, several targets have been identified as key areas of drug research and development of new pharmacologic agents.

Newly developed targeted therapies include an assortment of monoclonal antibodies, tyrosine kinase inhibitors, hormonal therapy, and immune modulating agents. Since 2010 the U.S. Food and Drug Administration (FDA) has approved 27 new drug entities for malignancies; 22 of

Baseline Knowledge Statements

Readers of this chapter are presumed to be familiar with the following:

- Basic mechanisms of cancer development, promotion, angiogenesis, and metastasis
- Foundational understanding of cancer and chemotherapy effects on the immune system
- Pharmacology and structural relationships of monoclonal antibodies to their targets
- General pharmacologic strategies and therapeutic modalities in the management of advanced malignancies
- Pharmacology and toxicity of traditional cytotoxic chemotherapy agents in the management of hematologic and oncologic malignancies
- Supportive management of cancer patients as described in The National Comprehensive Cancer Network’s treatment guidelines

Additional Readings

The following free resources are available for readers wishing additional background information on this topic.

these are targeted therapies. Many drug companies have a large pipeline of targeted molecular entities in development, and many additional approvals are expected in the coming years. The clinical pharmacotherapy specialist requires an understanding of the utility, pharmacology, and toxicity of these agents as they become integrated into the standard treatment of malignancies.

Monoclonal Antibodies

Antitumor effects may be delivered to cancer cells by monoclonal antibodies (MAbs) that target the receptors, surface proteins, or antigens involved in the pathways that promote cancer growth, survival, angiogenesis, or metastasis. The MAbs are immunoglobulins composed of two identical antigen binding (Fab) domains connected to a constant domain (Fc) by a flexible hinge sequence (Figure 3-1). They were first developed through hybridoma technology, which made it possible to produce large quantities of antibodies with high purity and monospecificity for a single binding region on an antigen. First-generation MAbs were produced and formulated as fully murine products. These were found to provoke significant immunogenicity reactions and were relatively ineffective because of anti-mouse antibody responses in patients. New technology has led to the development of chimeric, humanized, and fully human MAbs that have less immunogenicity, improved tolerability, and greater efficacy. Chimeric MAbs are composed of 30% mouse protein with a human constant region and murine variable region, whereas humanized MAbs are composed of 5% mouse protein with murine complementarity determining regions grafted into human immunoglobulin G. Human MAbs are made from a human hybridoma, resulting in a 100% human protein product.

Monoclonal antibodies act in several ways to combat malignancy. One described mechanism is antibody-dependent cellular cytotoxicity, in which MAbs bind to tumor cells and the MAb Fc domain interacts and engages with Fc receptors on the surface of immune effector cells. This activity mediates cytotoxicity because the MAb tags tumor cells for destruction by macrophages and natural killer cells. Another mechanism is complement-dependent cytotoxicity, in which MAb binding to a tumor cell activates complement binding and the development of membrane attack complexes, thereby leading to the lysis of tumor cells. There are several agents that also serve as conjugated treatment delivery devices. These MAbs are linked by the Fc portion to radioactive substances or traditional cytotoxic chemotherapy agents; this allows for localized and selective delivery to tumor cells, improving tolerability and efficacy of tumor cell kill.

Tyrosine Kinase Inhibitors

Tyrosine kinase inhibitors (TKIs) are another option to preferentially target and alter cellular signals in malignant cells. Tyrosine kinases catalyze the transfer of phosphates from adenosine triphosphate (ATP) to polypeptides. This process mediates cellular signals controlling proliferation, survival, differentiation, function, and motility. The use of TKIs has greatly expanded since the concept was proved by the success of imatinib in chronic myeloid leukemia. Tyrosine kinase inhibitors inhibit two major types of tyrosine kinases: (1) transmembrane proteins with a

---

**Abbreviations in This Chapter**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALK</td>
<td>Anaplastic lymphoma kinase</td>
</tr>
<tr>
<td>ATP</td>
<td>Adenosine triphosphate</td>
</tr>
<tr>
<td>BCC</td>
<td>Basal cell carcinoma</td>
</tr>
<tr>
<td>EGFR</td>
<td>Epidermal growth factor receptor</td>
</tr>
<tr>
<td>HER2</td>
<td>Human epidermal growth factor</td>
</tr>
<tr>
<td>LVEF</td>
<td>Left ventricular ejection fraction</td>
</tr>
<tr>
<td>MAb</td>
<td>Monoclonal antibody</td>
</tr>
<tr>
<td>MAPK</td>
<td>Mitogen-activated protein kinase</td>
</tr>
<tr>
<td>MBC</td>
<td>Metastatic breast cancer</td>
</tr>
<tr>
<td>MET</td>
<td>Hepatocyte growth factor receptor</td>
</tr>
<tr>
<td>MTC</td>
<td>Medullary thyroid cancer</td>
</tr>
<tr>
<td>NSCLC</td>
<td>Non–small cell lung cancer</td>
</tr>
<tr>
<td>ORR</td>
<td>Objective response rate</td>
</tr>
<tr>
<td>OS</td>
<td>Overall survival</td>
</tr>
<tr>
<td>PFS</td>
<td>Progression-free survival</td>
</tr>
<tr>
<td>PR</td>
<td>Progesterone receptor</td>
</tr>
<tr>
<td>RCC</td>
<td>Renal cell carcinoma</td>
</tr>
<tr>
<td>RET</td>
<td>Rearranged during transfection</td>
</tr>
<tr>
<td>SRE</td>
<td>Skeletal-related events</td>
</tr>
<tr>
<td>TKI</td>
<td>Tyrosine kinase inhibitor</td>
</tr>
<tr>
<td>VEGF</td>
<td>Vascular endothelial growth factor</td>
</tr>
<tr>
<td>VEGFR</td>
<td>Vascular endothelial growth factor receptor</td>
</tr>
</tbody>
</table>

---

**Figure 3-1:** Monoclonal antibody structure.

CH = Constant heavy chain; CL = constant light chain; Fab = antigen binding domain; Fc = constant domain; VH = variable heavy chain; VL = variable light chain.
ligand-binding extracellular domain and catalytic intracellular kinase domain; and (2) nonreceptor proteins that are free floating in the cytoplasm of the cell. There are many tyrosine kinases that can be dysregulated in various types of malignancies and thus serve as areas of targeted therapy. Some of these targets include the BCR-ABL and epidermal growth factor receptor (EGFR). Cancers involving the EGFR tyrosine kinase have known deletion and point mutations that lead to constitutive kinase activity. Other tyrosine kinases are overexpressed, such as the human epidermal growth factor receptor 2 (HER2)/neu receptor, where increased tyrosine kinase signaling is caused by receptor over-expression.

Tyrosine kinase inhibitor pharmacology is actually quite simple compared with that of the MAbs. The TKIs are small molecules that directly inhibit the catalytic activity of the kinase by occupying the binding pockets in the kinase, thereby interfering with the binding of ATP or a substrate. As small molecules, the majority of TKIs are available for oral administration; however, many undergo first-pass metabolism and are highly metabolized by cytochrome P450 (CYP) enzymes. Many agents are CYP 3A4 substrates (e.g., erlotinib, everolimus, imatinib) and have several clinically significant drug interactions. In addition, many of these agents require strict administration in relation to meals.

Therapy with TKIs can be complex for patients and providers because of drug interaction potential, tolerability, and administration. Pharmacists are in the ideal position to assist with optimizing oral TKI therapy. This chapter discusses the pharmacology and therapeutic role of new TKIs; for more on the use of TKIs in cancer therapy, see the Oral Chemotherapy chapter.

**Pharmacology of Targeted Therapies**

**Epidermal Growth Factor Receptors**

Targeted therapies in oncology now include EGFRs, vascular endothelial growth factors, and kinases along the mitogen-activated protein kinase pathway (Table 3-1). The EGFRs are a key group of receptors identified in epithelial cancers. There is a functional activation of growth factors and overexpression of the EGFR found in many solid tumor malignancies. Epidermal growth factor receptor is a transmembrane receptor belonging to a family of four related proteins (i.e., EGFR, HER2, HER3, and HER4). After a ligand binds to a single-chain EGFR, the receptor forms a dimer that signals within the cell by activating receptor autophosphorylation through tyrosine kinase activity. Anti-EGFR MAbs bind to the extracellular domain of the EGFR when it is in the inactive configuration and compete for receptor binding by occluding the ligand-binding region. Anti-EGFR TKIs compete reversibly with ATP to bind to the intracellular catalytic domain of the EGFR tyrosine kinase; this inhibits EGFR autophosphorylation and downstream signaling.

Anti-EGFR MAbs include cetuximab, panitumumab, and the HER2-directed MAb trastuzumab. Anti-EGFR TKIs include erlotinib and lapatinib (a selective HER2 and EGFR TKI). Since their development, additional therapies have been approved for various indications. These include the anti-HER2–directed MAbs pertuzumab and ado-trastuzumab emtansine, as well as afatinib, a newly approved EGFR TKI. Pertuzumab is a humanized MAb that binds the HER2 at a different epitope of the HER2 extracellular domain than trastuzumab. Trastuzumab binds to subdomain IV of the HER2 receptor and exerts its antitumor effects by stimulating antibody-dependent cellular cytotoxicity and inhibiting ligand-independent signaling. Pertuzumab blocks subdomain II of the HER2 receptor, which prevents HER2 from dimerizing with other ligand-activated HER receptors including HER3. Ado-trastuzumab emtansine is an antibody-drug conjugate composed of the anti-HER2 agent trastuzumab linked to a cytotoxic microtubule inhibiting agent. Finally, afatinib is a second-generation EGFR TKI that is an irreversible inhibitor of this kinase. Afatinib has shown activity in wild-type and mutated EGFR tyrosine kinases in lung cancer patients.

**Cytotoxic T-Lymphocyte Antigen-4**

Previous sections discussed MAbs with regards to complement-dependent and antibody-dependent cellular cytotoxicity, which uses the immune system to help clear tumor cells. However, new MAbs have been developed that use the adaptive immune system against tumor cells. Ipilimumab specifically targets T-cells in the immune system to attack melanoma cancer cells. Ipilimumab is an immunoglobulin G MAb that targets and blocks the cytotoxic T-lymphocyte antigen-4 (CTLA-4) (Figure 3-2).

**Vascular Endothelial Growth Factor**

Vascular endothelial growth factor (VEGF) refers to a family of molecules that mediate tumor angiogenesis. Vascular endothelial growth factor receptors (VEGFRs) are found on endothelial cells. Binding of VEGF to the VEGFR promotes vasculature growth around the tumor. During angiogenesis, tumor hypoxia leads to production of VEGF and endothelial cell production and growth around tumors. Drugs targeting this system include MAbs, VEGF decoy receptor agents, and TKIs that enter endothelial cells and inhibit the VEGFR tyrosine kinase tails.

In addition to pure anti-angiogenesis agents, there has been a flurry of mixed TKIs that include VEGF activity in addition to other sites of action (see Table 3-1). Anti-angiogenesis agents that bind to the VEGF protein include bevacizumab and ziv-aflibercept. Bevacizumab is a recombinant humanized MAb that binds all VEGF-A isoforms, and was the first developed anti-angiogenesis agent. Ziv-aflibercept is a newly approved agent that acts as a VEGF decoy receptor, or VEGF-trap. Ziv-aflibercept is a fusion
<table>
<thead>
<tr>
<th>Target</th>
<th>Drug</th>
<th>Indication</th>
</tr>
</thead>
</table>
| EGFR            | Cetuximab                   | Squamous cell carcinoma of the head and neck  
K-ras wild type metastatic colorectal cancer (CRC)                                           |
|                 | Panitumumab                 | K-ras wild type metastatic CRC                                                                 |
|                 | Erlotinib                   | Metastatic non-small cell lung cancer (NSCLC)                                                   
Metastatic pancreatic cancer                                                                  |
|                 | Afatinib                    | EGFR mutated metastatic NSCLC                                                                  |
| HER2            | Trastuzumab                 | HER2 overexpressed local or metastatic breast cancer  
HER2 overexpressed gastric cancer                                                            |
|                 | Pertuzumab                  | HER2 overexpressed metastatic breast cancer                                                      |
|                 | Ado-trastuzumab emtansine   | HER2 overexpressed metastatic breast cancer                                                      |
|                 | Lapatinib                   | HER2 overexpressed metastatic breast cancer (MBC)                                                |
| CTLA-4          | Ipilimumab                  | Advanced or metastatic melanoma                                                                |
| RANKL           | Denosumab                   | Bone metastasis from solid tumors                                                                
Giant cell tumor of the bone                                                                   
Men and women with osteoporosis                                                                 
Men on androgen deprivation therapy for prostate cancer                                          
Women on adjuvant aromatase inhibitor therapy for breast cancer                                 |
| VEGF            | Bevacizumab                 | Metastatic colorectal cancer (mCRC)                                                               
Metastatic non-small cell lung cancer (NSCLC)                                                  
Glioblastoma (GBM)                                                                             
Metastatic renal cell carcinoma (mRCC)                                                          |
|                 | Ziv-aflibercept             | mCRC                                                                                           |
| VEGFR (PDGFR, Flt-3, c-Kit) | Sunitinib                  | Gastrointestinal stromal tumor (GIST)                                                            
mRCC                                                                                            
Pancreatic neuroendocrine tumor (pNET)                                                          |
| (PDGFR, Flt-3, c-Kit, BRAF) | Sorafenib                  | Hepatocellular carcinoma                                                                       mRCC                                                 |
| (PDGFR, Flt-3, c-Kit) | Pazopanib                  | mRCC                                                                                            
Soft tissue sarcoma (STS)                                                                        |
|                 | Axitinib                    | mRCC                                                                                           |
| (MET, RET)      | Cabozantinib                | Metastatic medullary thyroid cancer (MTC)                                                         |
| (RET, EGFR)     | Vandetanib                  | Metastatic MTC                                                                                  |
| (TIE2, PDGFRb, FGFR, c-Kit, RET, RAF1, BRAF) | Regorafenib                | Metastatic CRC                                                                                  |
| ALK             | Crizotinib                  | Metastatic NSCLC                                                                                |
| BRAF            | Vemurafenib                 | Unresectable or metastatic melanoma                                                              |
|                 | Dabrafenib                  | Unresectable or metastatic melanoma                                                              |
protein that consists of the binding domains of VEGFR-1 and VEGFR-2 fused to the Fc portion of human immunoglobulin G. Ziv-aflibercept has a higher affinity to VEGF-A than bevacizumab, and it also inhibits VEGF-A, VEGF-B, and plactenta growth factor-2. The VEGFR TKIs bind to the ATP binding site of multiple receptors; many affect angiogenesis in addition to other cell signaling pathways, and many have off-target effects. The VEGFR TKIs include sunitinib, sorafenib, pazopanib, and axitinib (see Table 3-1). Axitinib is a novel second-generation TKI that inhibits VEGFR-1, VEGFR-2, and VEGFR-3 only and does not have off-target effects. This potent and selective inhibition is thought to enhance efficacy and tolerability of therapy.

Other oncologic agents have emerged that inhibit multiple key tyrosine kinases involved in the cell signaling of tumors in addition to VEGF (see Table 3-1). Cabozantinib is a newly approved multi-targeted oral TKI with potent inhibition of hepatocyte growth factor receptor (MET), VEGFR-2, and rearranged during transfection (RET) kinases. The RET kinase encodes a transmembrane tyrosine kinase that comprises an extracellular, transmembrane, and cytoplasmic domain. Mutations of RET are found in various malignancies, making it a key target of new therapies. The MET is a tyrosine kinase receptor that mediates invasive growth of epithelial cells. Vandetanib is a TKI that inhibits VEGFR-2, VEGFR-3, RET, and EGFR. Regorafenib is an orally available agent with the broadest of TKI coverage; it inhibits multiple cellular signals including VEGF, platelet-derived growth factor receptor-beta (PDGFRb), KIT, RET, and BRAF. The anaplastic lymphoma kinase (ALK) is a mutated kinase that has been detected in several tumor types including non–small cell lung cancer. Crizotinib is an oral ATP competitive selective inhibitor of the ALK and MET kinases and inhibits tyrosine phosphorylation of activated ALK and subsequent cellular signaling.

### Mitogen-Activated Protein Kinase

The Raf family of enzymes includes three isoforms, ARAF, BRAF, and CRAF. Activated Raf kinase triggers the phosphorylation of the MEK and ERK kinases of

---

**Table 3-1. Agents Used in Solid Tumor Targeted Therapies (continued)**

<table>
<thead>
<tr>
<th>Target</th>
<th>Drug</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEK</td>
<td>Trametinib</td>
<td>Unresectable or metastatic melanoma</td>
</tr>
<tr>
<td>mTOR</td>
<td>Temsirolimus</td>
<td>mRCC</td>
</tr>
<tr>
<td>Hedgehog</td>
<td>Vismodegib</td>
<td>Metastatic or advanced basal cell carcinoma</td>
</tr>
</tbody>
</table>

---

**Information from:** U.S. National Library of Medicine, [DailyMed](https://dailymed.nlm.nih.gov) [homepage on the internet].

---

**Figure 3-2:** Mechanism of action of ipilimumab.

T-cell activation occurs when a receptor is activated by antigen on the HLA receptor of a presenting cell, as well as B7 interaction with CD28 on the T-cell. To maintain homeostasis in the immune system, the T-cell generates CTLA-4, which competitively binds with B7 and makes the T-cell anergic or inactivated. Because ipilimumab directly blocks CTLA-4, it enhances B7 to CD28 interactions. This increases T-cell activation to the antigen being presented to fight melanoma cells.
the mitogen-activated protein kinase (MAPK) pathway (Figure 3-3); these kinases play an important role in cellular proliferation and survival. Activating mutations have been discovered in the BRAF kinase in about half of melanomas. The most common BRAF mutation, V600E, is a missense mutation generated by a substitution of glutamic acid with valine at position 600. This translocation leads to constitutive activation of the BRAF kinase and subsequent activation of MEK and ERK, leading to downstream signaling. Vemurafenib was the first in class TKI of mutated BRAF V600E. Since the approval of vemurafenib, a second-generation BRAF TKI (dabrafenib) has also been approved. The last agent to be recently approved along the MAPK pathway is trametinib. Trametinib is an orally available, small-molecule, selective inhibitor of MEK1 and MEK2. Trametinib is an allosteric, second-generation, ATP noncompetitive inhibitor against MEK1 and MEK2. The inhibition of MEK inhibits downstream signaling in the MAPK (see Figure 3-3).

Hedgehog Pathway

The hedgehog pathway is a complex pathway involving multiple signals active in embryonal cells. Smoothened homologue (SMO) is a G-coupled protein that mediates gene transcription by activation of the Gli family of transcription factors. These transcriptional factors are key regulators of growth and angiogenesis and subsequent cancer development. The hedgehog pathway is inactive in adult tissues because SMO is typically inhibited by a transmembrane receptor called patched homologue 1 (PTCH1). However, many basal cell tumors have mutations to PTCH1 that render it incapable of inhibiting SMO, resulting in SMO activation and subsequent tumor development. Vismodegib is a first in class inhibitor of the hedgehog pathway, where it binds and inhibits the extracellular domain of SMO and is available for the treatment of basal cell tumors.

Receptor Activator for Nuclear Factor β Ligand

The final targeted therapy to discuss is the receptor activator for nuclear factor κβ ligand (RANKL), a protein that binds to the RANK receptor and mediates bone turnover. When RANKL binds with the RANK receptors on osteoclast precursors in the bone, it induces the formation of osteoclasts and promotes their survival and activation, thereby promoting bone resorption and bony lesion development. Denosumab is a newly approved, fully human MAb that binds to and inhibits the activity of RANKL, effectively reducing the formation of osteoclasts and bone breakdown. Denosumab is now a commonly used agent in the management of bone metastasis or decreased bone mineral density for patients on adjuvant hormonal therapy.

Therapeutics of Targeted Therapy

Breast Cancer

Breast cancer is the leading cancer in women in the United States and is second only to lung cancer as a cause of cancer death. For 2013, the estimated number of new cases is 232,340 with an expected 39,620 breast cancer deaths. Unlike many other types of cancers, breast cancer presents most commonly as a localized disease (61% of patients), whereas metastatic disease presents in only 5% of patients (Howlader 2012).

Breast cancer markers that are commonly tested include estrogen receptor (ER) expression, progesterone receptor (PR) expression, and HER2 receptor expression. About 70% of breast cancer tumors are ER/PR positive, which is a good prognostic factor because of the slower growth of these tumors and the ability to use hormonal therapy (Hammond 2010). About 20% of tumors are HER2 positive, which has traditionally been considered a poor prognostic factor. However, improved targeting of this receptor as resulted in better outcomes for patients who are HER2 positive (Wolff 2007).

The treatment of early stage breast cancer is based on stage and receptor status but generally includes a multimodal approach including surgery, chest wall radiation, chemotherapy, hormonal therapy (if ER or PR positive), and trastuzumab (if HER2 positive). Although the management of each stage of breast cancer is beyond the scope of this chapter, management of metastatic breast cancer (MBC) is pertinent in reviewing the role of new targeted therapies.

The approach to managing MBC or recurrent breast cancer is based on stage and receptor status but generally includes a multimodal approach including surgery, chest wall radiation, chemotherapy, hormonal therapy (if ER or PR positive), and trastuzumab (if HER2 positive). Although the management of each stage of breast cancer is beyond the scope of this chapter, management of metastatic breast cancer (MBC) is pertinent in reviewing the role of new targeted therapies.

The approach to managing MBC or recurrent breast cancer is based on ER/PR and HER2 status as well as symptoms and sites of disease as seen in Figure 3-4. For patients who require chemotherapy, treatment options vary with HER2 status: if HER2 negative, single agent or combination chemotherapy can be initiated; if HER2 positive, combination chemotherapy and targeted therapy is preferred. Treatment options in HER2-positive MBC have significantly changed with the advent and
development of the newly approved agents pertuzumab and ado-trastuzumab emtansine.

**Pertuzumab**

Pertuzumab, in combination with trastuzumab and docetaxel, has been approved for patients with MBC who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease; it is also approved for neoadjuvant therapy in locally advanced HER2-positive breast cancer.

Pertuzumab was evaluated in a randomized, double-blind, placebo-controlled phase III study of HER2-positive MBC patients who had not received prior chemotherapy or biologic therapy for their metastatic disease (Baselga 2012). Patients were randomized in a 1:1 ratio to standard of care therapy (placebo plus trastuzumab plus docetaxel) or to pertuzumab plus trastuzumab plus docetaxel. Patients were given a loading dose of trastuzumab 8 mg/kg, then 6 mg/kg every 3 weeks; and docetaxel 75 mg/m² every 3 weeks, with the option to increase to 100 mg/m² by physician discretion. Pertuzumab or placebo was given as a flat 840-mg loading dose and then 420 mg every 3 weeks. The median progression-free survival (PFS) was greater with the pertuzumab combination (18.5 months)
<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication and Role in Therapy</th>
<th>Dosing and Administration</th>
<th>Adverse Events</th>
<th>Renal or Hepatic Adjustments</th>
<th>Drug Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pertuzumab</td>
<td>Indication: HER2 over-expressed metastatic breast cancer (MBC)</td>
<td>840 mg loading dose followed by 420 mg every 3 weeks plus trastuzumab 8 mg/kg then 6 mg/kg every 3 weeks and docetaxel 75 mg/m² every 3 weeks</td>
<td>Diarrhea (66.8%)</td>
<td>No renal or hepatic adjustment</td>
<td>No drug interactions</td>
</tr>
<tr>
<td></td>
<td>Role in therapy: MBC in combination with trastuzumab and docetaxel chemotherapy in patients who have not received prior anti-HER2 therapy or chemotherapy for metastatic HER2 positive disease</td>
<td>Intravenous infusion over 60 minutes for the first dose then 30 minute infusion if tolerated Pre-medications are not required for pertuzumab, however additional pre-medications are commonly used with docetaxel/ trastuzumab therapy Pertuzumab and trastuzumab should be given before the docetaxel chemotherapy</td>
<td>Railroad (33.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Indication: HER2 over-expressed locally advanced breast cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Role in therapy: neo-adjuvant therapy in locally advanced HER2 positive breast cancer in combination with trastuzumab and docetaxel chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ado-trastuzumab</td>
<td>Indication: HER2 over-expressed metastatic breast cancer</td>
<td>3.6 mg/kg intravenous infusion every 3 weeks The first infusion is administered over 90 minutes, where patients should be observed during and 90 minutes after the first infusion. Subsequent infusions can be given over 30 minutes if tolerated</td>
<td>Nausea (39.8%)</td>
<td>Avoid use in patients with baseline impairment with serum transaminases &gt;2.5 times the upper limit of normal or bilirubin &gt; 1.5 times the upper limit of normal</td>
<td></td>
</tr>
<tr>
<td>Emtansine</td>
<td>Role in therapy: Treatment of HER2-positive MBC who previously received trastuzumab and a taxane in the metastatic setting with disease progression</td>
<td></td>
<td></td>
<td>If AST or ALT elevation &gt;5 to £ 20 times the upper limit of normal treatment should be temporarily held If the AST/ALT is &gt; 20 times the upper limit of normal permanently discontinue</td>
<td></td>
</tr>
<tr>
<td>Afatinib</td>
<td>Indication: EGFR mutated metastatic NSCLC</td>
<td>See oral chemotherapy chapter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Role in therapy: First line treatment of metastatic NSCLC with EGFR mutations including exon 19 deletion or exon 21 substitutions.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crizotinib</td>
<td>Indication: Metastatic NSCLC that is ALK positive</td>
<td>See oral chemotherapy chapter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Role in therapy: Patients who have metastatic NSCLC with ALK positive disease should be placed on treatment at some point during their therapy either in the first line setting if known to be ALK positive or second or third line settings.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ziv-aflibercept</td>
<td>Indication: Metastatic colorectal cancer (mCRC)</td>
<td>4 mg/kg intravenous infusion over 1 hour on day 1 every 2 weeks with concurrent FOLFIRI chemotherapy</td>
<td>Diarrhea (69%)</td>
<td>No renal or hepatic adjustment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Role in therapy: ziv-aflibercept is an option to be utilized in combination with FOLFIRI based chemotherapy in patients who have progressed on first line therapy for mCRC. Patients must have progressed on oxaliplatin based chemotherapy with or without bevacizumab or other upfront targeted therapy.</td>
<td></td>
<td>Asthenia (18%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Stomatitis (50%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hypertension (41%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Neutropenia (67%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Thrombocytopenia (48%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regorafenib</td>
<td>Indication: Metastatic CRC</td>
<td>See oral chemotherapy chapter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Role in therapy: last line treatment option in advanced metastatic CRC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Indication and Role in Therapy</td>
<td>Dosing and Administration</td>
<td>Adverse Events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>-----------------------------------------------------------------------------------------------</td>
<td>---------------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>Indication: Advanced unresectable or metastatic melanoma Role in therapy: Utilized in first or subsequent lines of advanced unresectable or metastatic melanoma with or without BRAF mutations</td>
<td>3 mg/kg intravenously over 90 minutes every 3 weeks for four doses</td>
<td>Diarrhea (32%) Pruritus (31%) Rash (29%) Hypopituitarism (4%) Adrenal insufficiency (1%) Hepatotoxicity (1%) No renal or hepatic adjustment Corticosteroids and immunosuppressants may blunt the effects of ipilimumab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>Indication: Unresectable or metastatic melanoma with BRAF mutation Role in therapy: may be utilized in first of subsequent lines of therapy for metastatic melanoma</td>
<td>See oral chemotherapy chapter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dabrafenib</td>
<td>Indication: Unresectable or metastatic melanoma with BRAF mutation Role in therapy: may be used in first of subsequent lines of therapy for metastatic melanoma</td>
<td>See oral chemotherapy chapter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trametinib</td>
<td>Indication: Unresectable or metastatic melanoma with BRAF mutation Role in therapy: may be used in first of subsequent lines of therapy for metastatic melanoma</td>
<td>See oral chemotherapy chapter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vismodegib</td>
<td>Indication: Metastatic or recurrent basal cell carcinoma Role in therapy: only systemic therapy for advanced or recurrent disease where surgery or radiation therapy is no longer an option</td>
<td>See oral chemotherapy chapter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vandetanib</td>
<td>Indication: Metastatic medullary thyroid cancer (MTC) Role in therapy: metastatic or unresectable MTC as either first- or subsequent line of therapy</td>
<td>See oral chemotherapy chapter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cabozantinib</td>
<td>Indication: Metastatic medullary thyroid cancer (MTC) Role in therapy: metastatic or unresectable MTC as either first- or subsequent line of therapy</td>
<td>See oral chemotherapy chapter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Axitinib</td>
<td>Indication: Metastatic renal cell carcinoma (mRCC) Role in therapy: second line systemic therapy for advanced or mRCC where patients had progressed on previously therapy including bevacizumab, sunitinib, temsirolimus, or cytokine treatment</td>
<td>See oral chemotherapy chapter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Denosumab</td>
<td>Bone metastasis from solid tumors Giant cell tumor of the bone Men and women with osteoporosis Men on androgen deprivation therapy (ADT) for prostate cancer Women on adjuvant aromatase inhibitor (AI) therapy for breast cancer</td>
<td>Bone metastasis and giant cell tumor of the bone: 120 mg subcutaneously every 4 weeks Osteoporosis, ADT, and AI therapy: 60 mg subcutaneously every 6 months</td>
<td>Nausea (31%) Fatigue (45%) Hypocalcemia (18%) Hypophosphatemia (32%) Headache (13%) Dyspnea (21%) Use with caution in renal function less than 30 mL/min No drug interactions</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
versus the control (12.4 months) (hazard ratio [HR] 0.62; 95% CI, 0.51–0.75; p<0.001). Follow-up revealed a median overall survival (OS) of 37.6 months in the control group had not been reached in the pertuzumab group (HR 0.66; 95% CI 0.52–0.84; p=0.0008) (Swain 2013).

The pertuzumab arm reported a higher incidence of diarrhea, rash, mucosal inflammation, febrile neutropenia, and dry skin (Table 3-2). Grade three or higher toxicities reported with the combination regimen included neutropenia (48.9%), febrile neutropenia (13.8%), and diarrhea (7.9%). Left ventricular systolic dysfunction was reported more often in the control group (8.3%) than in the pertuzumab arms (4.4%). Grade three or higher left ventricular systolic dysfunction was reported in 2.8% of the control group and 1.2% of the pertuzumab group. Other toxicities with pertuzumab include pleural effusion (5.2% of patients) and hypersensitivity reactions (10.1% of patients).

Pertuzumab is an effective, well-tolerated MAb in the management of first-line HER2-positive MBC. In cases of chemotherapy-related toxicity (e.g., neutropenia), docetaxel could be held on treatment days, but trastuzumab and pertuzumab therapy are generally continued. Indications to hold pertuzumab include hypersensitivity reactions, left ventricular ejection fraction (LVEF) less than 45% or a LVEF of 45% to 49% with a 10% or greater decline from baseline. If trastuzumab needs to be withheld, pertuzumab should also be withheld or discontinued. After a lapse of 6 weeks or more in pertuzumab dosing, the patient should receive another loading dose. Monitoring on pertuzumab therapy primarily involves assessment of LVEF at baseline and every 9 weeks, pulmonary evaluation for pneumonitis, pregnancy testing, and physical examination.

**Ado-trastuzumab Emtansine**

The management of HER2-positive MBC involves continued HER2-blocking therapy plus key chemotherapy agents with activity in MBC. Ado-trastuzumab emtansine is a single agent approved for the treatment of HER2-positive MBC in patients who previously received trastuzumab and a taxane and experienced disease progression. Ado-trastuzumab emtansine label approval was based on data from a phase III, randomized, open-label trial of HER2-positive MBC patients (n=991) previously treated with trastuzumab and a taxane (Verma 2012). The study compared ado-trastuzumab emtansine 3.6 mg/kg intravenously every 21 days with a commonly used regimen of lapatinib 1250 mg orally daily plus capecitabine 1000 mg/m² orally twice daily on days 1–14 every 21 days. A majority of patients enrolled had visceral metastasis, and 61% had received at least one prior chemotherapy regimen in the metastatic setting. The median PFS was 9.6 months in the ado-trastuzumab emtansine group and 6.4 months in the lapatinib/capecitabine treatment arm (HR 0.65; 95% CI, 0.55–0.77; p<0.001). The median OS was also improved with ado-trastuzumab emtansine (30.9 months) versus lapatinib/capecitabine (25.1 months) (HR 0.68; 95% CI, 0.55–0.85; p<0.001).

Toxicities commonly associated with ado-trastuzumab emtansine treatment are nausea, fatigue, thrombocytopenia, diarrhea, and AST and ALT elevations (see Table 3-2). The most common grade 3 or 4 adverse events associated with treatment were thrombocytopenia (12.9%), elevated AST (4.3%), and elevated ALT (2.9%). It appears the dose-limiting toxicity of this agent is thrombocytopenia, because the incidence of bleeding was also higher with ado-trastuzumab emtansine treatment (29.8%) versus lapatinib/capecitabine (15.8%). The LVEF was maintained above 45% in 97.1% of patients, with three patients in each group experiencing a significant decline in LVEF to less than 40%. The overall incidence of left ventricular dysfunction in the ado-trastuzumab emtansine group was 1.8% versus 3.3% in the lapatinib/capecitabine groups. As a result, ado-trastuzumab emtansine has a boxed warning regarding hepatotoxicity and LVEF reductions, as well as risk of fetal harm.

Ado-trastuzumab emtansine is administered according to the phase III dosing as a 3.6-mg/kg intravenous infusion every 3 weeks. Ado-trastuzumab emtansine should be initiated only with a LVEF of 50% or greater; the agent should be held with an LVEF decline to less than 40% or with an LVEF of 40%–45% when there has been a decline of 10% or more from baseline. To continue ado-trastuzumab emtansine therapy, the platelet count should be 75,000/mm² or greater. Finally, ado-trastuzumab emtansine should be permanently discontinued in patients with interstitial lung disease and temporarily discontinued for severe peripheral neuropathy. Monitoring parameters while on ado-trastuzumab emtansine include a metabolic panel before each dose to evaluate liver function, complete blood count to evaluate platelets before each dose, LVEF at baseline and every 3 months while on treatment, pregnancy testing, signs and symptoms of pneumonitis, and neurotoxicity.

**Lung Cancer**

Lung cancer is the leading cause of cancer death in the United States, with an estimated 228,190 new cases and 159,480 deaths in 2013. There are two clear delineations of lung cancer: small cell lung cancer (SCLC) and non–small cell lung cancer (NSCLC). Non–small cell lung cancer is the most common form and is sub-classified based on the histology of the malignancy. Non–small cell lung cancer can present as adenocarcinoma (40% of patients) or as a squamous cell carcinoma (25%), large cell carcinoma (10%), or other less common types. About 57% of patients present with advanced or metastatic lung cancer because most don’t have symptoms until the disease is more widespread; this limits the 5-year survival to 5.7% (Howlader 2013). Stage IV NSCLC is managed with either targeted therapy or systemic chemotherapy based on tumor histology and mutation status (Figure 3-5).
**Afatinib**

Afatinib has been studied in several different settings of lung cancer as part of the LUX-Lung study series. The LUX-Lung 1 was a phase IIb/III study that included patients who had one or two prior chemotherapy regimens for metastatic lung cancer with disease progression after at least 12 weeks of treatment of erlotinib or gefitinib (Miller 2012). No OS benefit was demonstrated with this study; however there was a median PFS benefit of 3.3 months in the afatinib group versus 1.1 months with placebo. Of note, 67% and 71% of patients in this study had EGFR mutations.

The LUX-Lung 2 was a phase II study that demonstrated the efficacy of afatinib in EGFR mutated patients (Yang 2012). This study enrolled patients who had no more than one previous chemotherapy regimen and no previous EGFR TKI therapy. The objective response rate (ORR) while on afatinib was 61%, with 82% of patients having an exon 19 or 21 mutation and the rest having less common mutations. This evaluation led to LUX-Lung 3, a phase III study of untreated EGFR mutation–positive patients with locally advanced or metastatic NSCLC (Sequist 2013). Patients were randomized to afatinib 40 mg by mouth daily or cisplatin 75 mg/m² and pemetrexed 500 mg/m² intravenously every 21 days. The median PFS was 11.1 months for the afatinib group and 6.9 months for the chemotherapy groups (p=0.0004). Afatinib, like erlotinib, is now recommended as a first-line treatment in metastatic NSCLC with an EGFR mutation; however, afatinib may have a role in other lines of therapy because it may overcome additional forms of drug resistance.

**Crizotinib**

The ALK mutation occurs in 2%–3% of NSCLC when a chromosomal rearrangement generates a fusion gene between EML4 and ALK. This results in a constitutive

---

**Figure 3-5.** Approach to managing metastatic NSCLC.

Patients with squamous subtypes of NSCLC typically do not harbor EGFR or ALK mutations and are not regularly tested. These patients are not candidates for up front targeted therapy but may have some benefit of second- or third-line erlotinib. Patients with adenocarcinoma subtype of NSCLC can use three different first-line therapies including chemotherapy, afatinib or erlotinib if an EGFR mutation is present, or crizotinib if an ALK rearrangement is present.

Cytoplasmic kinase that sends growth signals to the cell, leading to cancer development. Crizotinib was first evaluated in a phase I study of patients with metastatic NSCLC in which 94% of patients had received at least one previous treatment for metastatic lung cancer. The ORR was 57%, a significant finding considering most of these patients had prior therapy. A recent phase III study compared crizotinib 250 mg by mouth twice daily with chemotherapy in 347 patients with ALK-positive disease who had received one prior platinum-based regimen in an open-label trial (Shaw 2013). The standard of care chemotherapy arm was either pemetrexed 500 mg/m² intravenously or docetaxel (Shaw 2013). The standard of care chemotherapy arm was either pemetrexed 500 mg/m² intravenously or docetaxel 75 mg/m² intravenously every 3 weeks. Docetaxel was given if the patient received pemetrexed in the first-line setting. The median PFS was 7.7 months and 3 months in the crizotinib and chemotherapy groups, respectively (HR 0.49; 95% CI, 0.37–0.64). The ORR was 65% with crizotinib and 20% with the chemotherapy arm; however, OS data was not significant (HR 1.02; 95% CI, 0.68–1.54). Current guidelines recommend the use of crizotinib in all patients with an ALK mutation as first-line or as a subsequent line of treatment if mutation testing was not available upon initial diagnosis.

Colorectal Cancer

Colorectal cancer is the third leading cause of cancer and cancer deaths among men and women in the United States (Siegel 2013). The 2013 estimates are 142,820 new cases of colorectal cancer and 50,830 deaths. About 75% of patients present with localized disease, with either a single primary tumor or tumor involving the lymph nodes, and in many cases are curative. The primary method of treatment for stages I, II, and III is surgical resection. In addition to surgical treatment, chemotherapy can be provided in the adjuvant setting for stage III disease and in some high-risk stage II cases. The treatment of metastatic colorectal tumors is based on the use of systemic chemotherapy. Targeted therapy has expanded treatment options that can be used after progression on first-line chemotherapy (Figure 3-6).

Ziv-aflibercept

Ziv-aflibercept was evaluated in a multinational, randomized, double-blind, parallel-arm, phase III study of patients with metastatic colorectal cancers whose disease had progressed on or after treatment with an oxaliplatin-based first-line regimen (Van Cutsem 2012). Patients were allowed to have prior bevacizumab therapy but not prior irinotecan-based therapy. Patients were randomized in a 1:1 fashion to ziv-aflibercept plus FOLFIRI chemotherapy or placebo and FOLFIRI chemotherapy. Of the total 1226 patients, about 30% in each arm had prior bevacizumab therapy and 43% had prior hypertension. The median survival in the ziv-aflibercept arm was 13.5 months compared with 12.06 months in the placebo plus chemotherapy arm (HR 0.817, p=0.0032). The median PFS was 6.9 months and 4.67 months in the ziv-aflibercept and placebo arms, respectively (HR 0.758, p< 0.0001). When evaluating patients who had previously received bevacizumab, the OS was not statistically significant (HR 0.862, 95% CI, 0.673–1.104); however, the PFS was significant (HR 0.661; 95% CI, 0.512–0.852).

The most common adverse events associated with the ziv-aflibercept and chemotherapy arm, but not the placebo and chemotherapy arm, were diarrhea, asthenia, stomatitis, infections, hypertension, and hemorrhage (see Table 3-2). Grade three and four toxicities with a higher incidence in the ziv-aflibercept arm included hypertension, hemorrhage, and arterial and venous thromboembolic events. The risk of fistula formation, proteinuria, and ALT increase were higher in the ziv-aflibercept arm; however, the risk of GI perforation was not different in the two treatment arms. Ziv-aflibercept carries boxed warnings for several conditions including hemorrhage, GI perforation, and compromised wound healing.

Ziv-aflibercept should be suspended at least 4 weeks before elective surgery and suspended in recurrent severe hypertension or for proteinuria measuring 2 g during 24 hours. Ziv-aflibercept should be permanently discontinued for hemorrhage, GI perforation, fistula formation, compromised wound healing, arterial thromboembolic events, and nephritic syndrome. Monitoring while on treatment should include complete blood counts and complete metabolic panel before each dose, especially when used in combination with chemotherapy. Additional monitoring parameters may include blood pressure, urine protein levels, wound healing, and signs of bleeding. Ziv-aflibercept is now an option with FOLFIRI-based chemotherapy in the second-line setting. Toxocities associated with this agent are very similar to other anti-VEGF therapy and include hypertension, hemorrhage, thromboembolic events, and proteinuria.

Regorafenib

Regorafenib was evaluated in a placebo-controlled, phase III trial of 760 metastatic colorectal cancer patients (Grothey 2013). Patients included in this study either progressed on currently approved standard therapies or were intolerant to such therapy. Standard therapies varied from country to country but had to include the following agents (if commercially available): fluorouracil, oxaliplatin, irinotecan, bevacizumab, and cetuximab or panitumumab. These highly treatment-refractory patients were randomized in a 2:1 ratio to regorafenib 160 mg orally on days 1–21 every 28 days plus best supportive care; or to placebo plus best supportive care. The median OS was 6.4 months and 5 months in the regorafenib and placebo treatment arms (HR 0.77; 95% CI, 0.64–0.94). Regorafenib also improved PFS with a median of 1.9 and 1.7 months in the regorafenib and placebo groups, respectively (HR 0.49; 95% CI, 0.42–0.58).
There are currently three main classifications of skin cancers: squamous cell carcinomas, basal cell carcinomas (BCCs), and melanoma. The most common form of skin cancer, BCC is composed of nonkeratinizing cells that originate in the basal cell layer of the epidermis. Melanoma is a form of malignancy that arises from the melanocytes in the epidermis. The most recent estimates reveal that melanoma is the fifth leading cause of cancer in men and

Regorafenib should be considered in patients with a good performance status whose disease has failed to respond to all other conventional cytotoxic chemotherapy and targeted therapy agents. In addition to the approved indication of regorafenib in metastatic colorectal cancer, the agent was recently approved in locally advanced, unresectable or metastatic gastrointestinal stromal tumor in patients with disease that has not responded to imatinib and sunitinib therapy (Demetri 2013).

Melanoma and Basal Cell Skin Cancers
There are currently three main classifications of skin cancers: squamous cell carcinomas, basal cell carcinomas (BCCs), and melanoma. The most common form of skin cancer, BCC is composed of nonkeratinizing cells that originate in the basal cell layer of the epidermis. Melanoma is a form of malignancy that arises from the melanocytes in the epidermis. The most recent estimates reveal that melanoma is the fifth leading cause of cancer in men and

---

**Figure 3-6.** Treatment regimens for advanced or metastatic colorectal cancer.

FOLFOX = fluorouracil, leucovorin, oxaliplatin; CapeOX = capecitabine, oxaliplatin; FOLFIRI = fluorouracil, leucovorin, irinotecan. Preferred first-line chemotherapy is FOLFOX or CapeOX ± bevacizumab or FOLFOX and panitumumab for patients with KRAS wild-type tumors. Information from: National Comprehensive Cancer Network Clinical Practice Guidelines in Colon Cancer. Colon Cancer. NCCN 2014; V2:COL-C.
seventh leading cause of cancer in women (Siegel 2013). Fortunately, most melanoma cancers are diagnosed with early stage disease (84%) with a 5-year survival of 98.3% (Howlader 2013). Stage I and II tumors are localized tumors that involve lesions up to 4 mm in thickness with no nodal involvement, whereas stage III tumors can be any thickness but have nodal involvement. Patients who present with stages I, II, and III cutaneous melanoma require a wide excision, with the widest excisions given to patients whose tumors are more than 4 mm thick. Systemic therapy is generally used as the mainstay of therapy for disseminated or metastatic disease. Traditional drug therapy has included high-dose IL-2, a very toxic regimen, as well as several cytotoxic agents such as dacarbazine, biochemotherapy, and temozolomide. Newly approved targeted therapies for melanoma include ipilimumab, vemurafenib, dabrafenib, and trametinib (Figure 3-7).

**Ipilimumab**

Ipilimumab is currently a National Comprehensive Cancer Network category one recommendation for the treatment of metastatic melanoma. Ipilimumab may be used up front for patients who do not harbor BRAF mutations or those who progress through BRAF or MEK inhibitors; however, sequencing and head-to-head studies are not available (see Figure 3-7). Ipilimumab was approved after a phase III study that included HLA-A*0201-positive patients (Hodi 2010). Patients (n=676) had unresectable stage III or IV melanoma that progressed despite therapy for metastatic disease. Patients were randomly assigned in a 3:1:1 ratio to ipilimumab 3 mg/kg intravenously every 3 weeks plus gp100 every 3 weeks, ipilimumab alone, or gp100 alone. Patients were screened for the HLA subtype because of the administration of the gp100 vaccine, which is a peptide consisting of amino acid residues of a melanoma antigen. This study was the first in the history of advanced melanoma to demonstrate an OS benefit with therapy. The median OS was 10 months, 6.4 months, and 10.1 months for the ipilimumab plus gp100 arm, gp100 arm, and ipilimumab alone arm, respectively. Both ipilimumab arms demonstrated statistically significant OS benefit compared with the gp100 arm.

Although the clinical benefit is significant with ipilimumab-based treatment, it does come with some risks. The toxicity of ipilimumab is well described, with immune-related adverse events (IRAE) occurring in up to 60% of patients. The most common IRAE were diarrhea, pruritus, rash, hypothyroidism, hypopituitarism, hypophysitis, adrenal insufficiency, and hepatotoxicity (Table 3-2). Of note, in the study described there were 14 deaths related to ipilimumab, with seven deaths directly associated with IRAE. Thus, the FDA has required extensive REMS program for ipilimumab that involves a health care provider letter, IRAE management guide, nursing patient assessment checklist, and a patient wallet card to identify patients currently on ipilimumab. The pharmacist can assist with management of ipilimumab-associated IRAE. Typically, skin-related effects present within 2 to 3 weeks of treatment; GI and hepatic effects present after 6 to 7 weeks; and endocrine effects present after 9 weeks (Weber 2012). Skin toxicity can be treated with topical corticosteroids, and oral antipuritis can treat limited rashes (grade one or two). However, in the case of severe skin reactions (grade three or higher), ipilimumab should be permanently discontinued and the patient treated with a 4-week taper of prednisone with a starting dose of 1 mg/kg daily. In a similar fashion, patients who develop immune-related diarrhea should receive loperamide and oral hydration for low-grade diarrhea. For grade two diarrhea, diphenoxylate and atropine four times daily and budesonide 9 mg by mouth once daily can be used. For serious diarrhea (grade three or four), ipilimumab should be permanently discontinued and the patient started on systemic corticosteroids, with a steroid taper over 4 weeks. In patients whose diarrheal symptoms are not resolved within 48 to 72 hours, treatment with infliximab is recommended.

Because of the significant toxicity associated with ipilimumab therapy, an extensive patient assessment is required before dispensing each dose. Regular laboratory testing is required, including assessment of liver function, as well as thyroid function tests at baseline and before each dose. Additional testing for endocrinologic effects is also warranted based on the patient’s symptoms.

**Vemurafenib**

A BRAF mutation occurs in about 50% of melanomas, with the most common being a V600E mutation that constitutively activates the MAPK pathway. Vemurafenib was approved after a series of phase II and III studies demonstrated improved survival and tumor response. The phase III study randomized patients with previously untreated, metastatic melanoma with BRAF V600E mutations to dacarbazine 1000 mg/m² intravenously every 3 weeks or vemurafenib 960 mg by mouth twice daily (Chapman 2011). The 6-month OS was 84% and 64% in the vemurafenib and dacarbazine treatment arms, with a 63% reduction in the risk of death associated with vemurafenib.

**Dabrafenib**

Dabrafenib is the second selective BRAF V600E oral inhibitor approved in the setting of BRAF V600E mutation metastatic melanoma. This agent received approval based on single agent phase III data in patients with previously metastatic or advanced unresectable melanoma. The study randomized 250 patients in a 3:1 ratio to dabrafenib 150 mg by mouth twice daily or dacarbazine 1000 mg/m² intravenously every 3 weeks (Hauschild 2012). The median PFS was significantly improved in the dabrafenib group (5.1 months) versus the dacarbazine group (2.7 months) (HR 0.30; 95 CI, 0.18–0.51). The findings of the study did not confirm an OS benefit on treatment.
Trametinib

Trametinib was evaluated in a phase III study of 322 patients with metastatic BRAF V600E or V600K mutation melanoma (Flaherty 2012). Patients were randomized in a 2:1 fashion to receive trametinib 2 mg by mouth daily or dacarbazine 1000 mg/m² intravenously or paclitaxel 175 mg/m² every 3 weeks. Patients enrolled could have received one previous chemotherapy regimen in the metastatic setting but not previous treatment with ipilimumab, BRAF inhibitors, or MEK inhibitors. The median PFS was 4.8 months in the trametinib group and 1.5 months in the chemotherapy group (HR 0.45; 95% CI, 0.33–0.63). The 6-month OS rate was 81% in the trametinib group and 67% in the chemotherapy group (HR 0.54; 95% CI, 0.32–0.92).

Since the phase III study of trametinib, subsequent combination and sequencing studies have been studied. One option that has been explored is the combination of BRAF and MEK inhibitor to enhance the response to therapy. Patients with metastatic BRAF V600 mutations were randomized to receive dabrafenib 150 mg by mouth twice daily plus trametinib 1 or 2 mg once daily, or dabrafenib monotherapy (Flaherty 2012). The median PFS in the dabrafenib and trametinib 2 mg combination was 9.4 months compared with 5.8 months in the dabrafenib monotherapy arm (HR 0.39; 95% CI, 0.25–0.62). A doubling in the duration of response was also observed with combination therapy (an important observation because BRAF inhibitors have typically demonstrated a limited duration of response). A sequencing study also revealed...

Figure 3-7. Treatment regimens for advanced or metastatic melanoma.

'aSystemic chemotherapy = dacarbazine, temozolomide, albumin-bound paclitaxel, paclitaxel, or paclitaxel/carboplatin.
'bBio-chemotherapy = chemotherapy + interleukin-2 (IL-2), interferon alfa
'cIpilimumab is a preferred option for patients with low disease burden or asymptomatic disease

Information from: NCCN Clinical Practice Guidelines in Melanoma. Melanoma. NCCN 2014; V2: ME-E.
that failure of a BRAF inhibitor in the first-line setting imparts resistance to trametinib (Kim 2013). In summary, trametinib is an overall safe and well-tolerated therapy that may be used in the management of metastatic BRAF mutation melanoma; however, trametinib should not be used after the failure of a BRAF inhibitor. Combination therapy may also be another consideration in the management of metastatic BRAF mutation melanoma.

**Vismodegib**

Basal cell carcinoma is usually a slow-growing disease that invades locally with a low metastatic potential. Drug therapy has a limited role in BCC with the exception of vismodegib, a newly approved agent for recurrent or advanced BCC. Vismodegib was evaluated in a phase I study in which 33 patients with metastatic or locally advanced BCC were randomized to escalating doses of vismodegib. In the dose evaluation study, 55% of patients had an objective response to drug therapy (Von Hoff 2009). Subsequently, an international double cohort non-randomized study was conducted in patients with either metastatic or locally advanced BCC who were started on oral vismodegib 150 mg daily (Sekulic 2012). In the metastatic cohort, the ORR was 30%; in the locally advanced BCC cohort, the ORR was 43%. A median duration of response of 7.6 months was seen in both cohorts.

**Medullary Thyroid Cancer**

Thyroid cancer is the fifth leading cause of cancer in women; in 2013, it was expected to affect 60,220 patients and cause death in 1850 patients (Siegel 2013). The subtypes of thyroid cancer include papillary thyroid cancer, follicular thyroid cancer, and medullary thyroid cancer. Medullary thyroid cancer (MTC) is a rare form of thyroid cancer that accounts for about 5%–10% of thyroid cancers; it develops from the C cells of the thyroid, which normally make calcitonin. This form of thyroid cancer can be more aggressive and can present in the lymph nodes, lung, or even liver before a thyroid nodule is discovered. The management of MTC for localized disease is typically a total thyroidectomy and neck dissection. Radioactive iodine is not typically used because the tumor cells do not take up iodine. External-beam radiation therapy has a limited role in advanced MTC, and conventional cytotoxic chemotherapy has not proved to prolong survival. Mutations in the RET proto-oncogene are typically found in hereditary MTC and up to 50% of sporadic MTC. Hence, targeted therapy in advanced or metastatic MTC has been focused on the RET kinase and VEGF because these tumors tend to be highly vascularized.

**Vandetanib**

When evaluated in patients with unresectable locally advanced and metastatic hereditary MTC, vandetanib achieved a partial response in the tumor size in 20% of patients and stable disease in 23% of patients (Wells 2010). A subsequent phase III study in advanced MTC assigned patients randomly in a 2:1 ratio to vandetanib 300 mg by mouth once daily or placebo (Wells 2012). The median PFS was significantly prolonged with vandetanib versus placebo (HR 0.46; 95% CI, 0.31–0.69; p<0.001), where the median PFS was not reached in the observation period for vandetanib and was 19.3 months in the placebo arm. Overall survival data, although not mature to present a significant improvement, trended toward vandetanib therapy.

**Cabozantinib**

The approval of cabozantinib was based on the improvement in PFS from an international, randomized (2:1), placebo-controlled trial enrolling 330 patients with metastatic MTC (Elisei 2013). Patients were randomized to receive cabozantinib 140 mg by mouth daily or placebo. Of enrolled patients, 25% received two or more prior systemic therapies and 21% had been previously treated with a TKI. The median PFS was 11.2 months for the cabozantinib arm and 4 months for the placebo arm (HR 0.28; 95% CI, 0.19–0.40). Overall survival data from this study is not yet mature to demonstrate an improvement in survival. In summary, vandetanib and cabozantinib are new targeted therapies with activity in MTC and may have future use in additional malignancies or thyroid cancer types.

**Renal Cell Carcinoma**

Renal cell carcinoma (RCC) is the sixth leading cause of cancer in men and eighth leading cause of cancer in women; is the tenth leading cause of cancer death in men. An estimated 65,150 new cases were expected in 2013 (Siegel 2013). A majority of patients (63%) present with localized disease and typically have hallmark symptoms of RCC such as hematuria, flank pain, and a palpable abdominal mass (Howlader 2013). Renal cell carcinoma presents with a clear cell histology in 70%–80% of patients; however, there are other types including papillary (15%) and chromophobe (5%). The primary management of RCC involves surgical intervention with a partial or radical nephrectomy and follow-up observation for stages I-III. In patients with stage IV RCC, systemic therapy is the primary mode of treatment. First-line systemic therapy and additional therapy after progression with metastatic disease are described in Figure 3-8. Targeted therapy is now the main treatment modality; however, limited treatment options are available in progressive disease.

**Axitinib**

Axitinib was evaluated in 723 patients with metastatic RCC who had progressed on either sunitinib, bevacizumab plus interferon-α, temsirolimus, or cytokine-based therapy (Rini 2011). Patients were randomized to either axitinib 5 mg by mouth twice daily or sorafenib 400 mg by mouth twice daily. A majority of patients received prior therapy with sunitinib (54%) or cytokine therapy (35%). Follow-up results revealed a median PFS of 8.3 months...
with axitinib and 5.7 months with sorafenib (HR 0.656; 95% CI, 0.552–0.770) (Motzer 2013). The median OS was similar in both groups (20.1 months with axitinib; 19.2 months with sorafenib). Axitinib has a clear role in the management of metastatic RCC in the refractory setting. This is one of very few studies that has evaluated TKI-based therapy after failure of other TKI-based regimens, comparing it to a previous standard of care (i.e., second-line sorafenib).

**Bone Metastasis**

Bone metastasis is a common complication of malignancy that can lead to fracture, spinal cord compression, need for radiation or surgery, or hypercalcemia. This collection of complications, known as *skeletal-related events* (SRE), can lead to pain and decreased quality of life. Bisphosphonates are often administered as part of the management of patients with bone metastasis to delay or prevent a SRE. Zoledronic acid and pamidronate are potent intravenous bisphosphonates that are effective in prolonging time to SRE or reducing SRE in patients with advanced cancer and bone metastasis. Despite treatment, SRE still occur, and there are several key toxicities associated with bisphosphonate treatment including nephrotoxicity, flu-like syndromes, and osteonecrosis of the jaw. Newer agents are needed with improved efficacy and tolerability in the prevention of SRE.

**Denosumab**

Denosumab has been approved for the prevention of SRE in patients with solid tumor bone metastasis as the branded name Xgeva. The same agent is approved at a lower dosage as the branded name Prolia for several indications including postmenopausal osteoporosis, osteoporosis in men, high fracture risk from androgen deprivation therapy in men, and high fracture risk from aromatase inhibitor therapy in women.

Denosumab was compared with zoledronic acid in three key phase III evaluations in patients with bone metastasis from three different cancer populations: breast cancer, prostate cancer, and advanced cancer patients (excluding breast and prostate cancer but including multiple myeloma). In the breast cancer study, 2046 patients with active bone metastasis were randomized to receive either denosumab 120 mg subcutaneously and intravenous placebo or intravenous zoledronic acid 4 mg and subcutaneous placebo every 4 weeks (Stopeck 2010). All patients were advised to take daily calcium and vitamin D supplements. Denosumab was superior to zoledronic acid in delaying time to first SRE (HR 0.82; 95% CI, 0.71–0.95). The median time to first SRE was 26.4 months with zoledronic acid and was not reached during the observation period in the denosumab group.

A similar study was conducted in 1904 men with castrate-resistant prostate cancer with bone metastasis; patients were randomized to denosumab therapy or zoledronic acid therapy for the prevention of SRE (Fizazi 2011). The median time to first SRE was 20.7 months with denosumab and 17.1 months with zoledronic acid, demonstrating that denosumab was statistically superior to zoledronic acid for the time to first SRE (HR 0.82; 95% CI, 0.71–0.95). The last evaluation of denosumab in bone metastasis was in a population of 1776 patients with multiple myeloma or advanced solid tumor cancer, excluding the breast and prostate cancer population (Henry 2011). The study was conducted in the same fashion as those described above. Denosumab was noninferior to zoledronic acid in delaying the time to first SRE, with the median time to first SRE being 20.6 months in the denosumab group and 16.2 months in the zoledronic acid group (HR 0.84; 95% CI, 0.71–0.98).

---

**Metastatic or recurrent RCC**

- Sunitinib
- Bevacizumab + interferon
- Pazopanib
- High-dose IL-2 for selected patients
- Temsirolimus (for patients with poor prognosis)

**Preferred options after progression on TKI therapy**
- Everolimus
- Axitinib

**Additional options after progression on TKI therapy**
- Sorafenib
- Sunitinib
- Temsirolimus
- Bevacizumab
- Pazopanib
- IL-2 for selected patients

**Preferred options after progression on cytokine therapy**
- Axitinib
- Sorafenib
- Sunitinib
- Pazopanib

*Figure 3-8. Treatment of advanced or metastatic renal cell carcinoma.*

As a result of these evaluations, denosumab 120 mg received approval for the management of bone metastasis in all patients with advanced cancer. This agent is an option in the prostate and breast cancer population and is an acceptable agent in other solid tumors, although not considered to be superior to bisphosphonate therapy. Because of the limited number of patients with myeloma in the clinical studies, denosumab is not currently approved for use in multiple myeloma.

Toxicities associated with denosumab include nausea, fatigue, hypocalcemia, hypophosphatemia, headache, dyspnea, and cough. Some patients experienced hypocalcemia and hypophosphatemia, especially those with poor renal function (see Table 3-2). Osteonecrosis of the jaw has also been reported at a rate of 2% in denosumab and 1.4% in zoledronic acid (p=0.39). Denosumab should not be initiated in patients with pre-existing hypocalcemia, and calcium and vitamin D supplementation should be started. Denosumab has not been evaluated in patients with a CrCl less than 30 mL/minute, and it should be used with caution because of the risk of hypocalcemia.

Denosumab 60 mg every 6 months can be used in women with breast cancer on aromatise inhibitor therapy or in men on androgen deprivation therapy to prevent thinning of bone, osteoporosis, and/or bone fractures. In a recent study, 252 patients with hormone-positive non-metastatic breast cancer on adjuvant aromatase inhibitors and low bone mass were randomized to placebo or subcutaneous denosumab 60 mg subcutaneously every 6 months (Ellis 2008). At 12 and 24 months, the lumbar spine bone mineral density (BMD) increased by 5.5% and 7.6% from baseline, and this increase was superior to the placebo groups (p<0.0001 at both time points). In a similarly designed study, denosumab was evaluated in 1468 prostate cancer patients on androgen deprivation therapy for prostate cancer (Smith 2009). At 24 months,

Patient Care Scenario

Several months ago, a 34-year-old man underwent resection of an 8-mm melanoma lesion on his neck. Today he presents to the clinic for routine follow-up. On examination, it is noted that he has several cutaneous masses on his legs, trunk, and chest. The patient notes that the masses itch a bit but otherwise are not bothersome. Further workup reveals BRAF V600E mutated, metastatic melanoma to the lung and liver.

Answer

There is no one correct answer to this patient scenario; however, some characteristics of the patient presentation make certain options more preferable than others. For patients who have BRAF mutation melanoma, any of the BRAF or MEK inhibitors could be used. However, many of these agents provide a quick response to therapy but have a limited duration of response. Therefore BRAF inhibitors are generally recommended for patients who have large diffuse and symptomatic disease, which this patient does not have. Combination dabrafenib/trametinib could be offered in an attempt to increase his duration of response (studies comparing combination BRAF/MEK inhibition suggest an increased duration of response over single-agent therapy). An alternative approach to treating this patient would be to provide immunotherapy with either ipilimumab or IL-2. This patient is young, in good health, with relatively few comorbidities, making him an ideal candidate for either ipilimumab or IL-2 therapy. The benefit of front-line immunotherapy is that the patient is free of toxicity from any previous lines of therapy and will likely tolerate treatment better than if you waited after other treatments. Ipilimumab therapy and IL-2 may not provide an immediate response or benefit for his disease; however, if the patient responds to therapy, he can be maintained in a durable disease response for a longer period. This has been demonstrated with long-term data from IL-2 as well as more recent but shorter follow-up with ipilimumab data. The BRAF or MEK inhibitor treatments could be offered if his tumors progress and become symptomatic. Once a patient progresses on BRAF therapy, the disease may become more resistant, as demonstrated with the second-line use of trametinib after BRAF therapy progression. In summary, the consensus would be to initiate immunotherapy in this patient. However, as described above, there may be variations in this decision process because no double-blind, parallel studies have compared these relatively new treatment options for melanoma.

Conclusion

Targeted therapy has had significant growth over the past several years in the management of malignancies. Targeted therapies continue to be used across pharmacy practice settings such as ambulatory care clinics, hospital inpatient, and community practice. Targeted therapies are expected to continue to contribute to the management of malignancy and will see increased usage in various settings of cancer care. As we continue to understand and identify new targets in malignancy, the development of new agents will only continue to grow. The pipeline of targeted therapies is rich and the future is bright as we continue to improve tolerability as well as efficacy in the management of cancer.

References


41. An 80-year-old woman with stage IV colorectal cancer metastatic to the liver has been on several chemotherapy regimens. She presented with metastatic disease about 18 months ago and received a diagnosis of KRAS wild type adenocarcinoma of the colon. Initial chemotherapy consisted of bevacizumab +FOLFOX (fluorouracil/leucovorin/oxaliplatin) every 2 weeks. Eight months ago, she had progression of her liver lesion and was started on FOLFIRI (fluorouracil/leucovorin/irinotecan) + bevacizumab. Since then, she developed a local recurrence and fistula formation in her descending colon and is currently admitted for surgical intervention and supportive care. The patient asks to see her oncologist to discuss future planning of therapy once the fistula is repaired. The oncologist has thought of several treatment options for the patient after fistula repair. Which one of the following would be best to recommend for this patient?

A. Ziv-aflibercept and FOLFIRI.
B. Panitumumab and FOLFOX
C. Cetuximab and irinotecan.
D. Capecitabine and bevacizumab.

Questions 42 and 43 pertain to the following case.

B.Z. is a 62-year-old woman who presents with recurrent metastatic breast cancer. At age 44 she received a diagnosis of stage II localized disease in the right breast that was ER/PR negative and HER2 positive. She underwent a right breast mastectomy with standard AC (doxorubicin/cyclophosphamide)→paclitaxel + trastuzumab, followed by 1 year of trastuzumab and continued follow-up. B.Z. now has a new left breast mass and metastasis in the femoral bone. The left breast biopsy was ER/PR negative and HER2 positive ductal carcinoma. The patient’s AST is 23 units/L, ALT is 33 units/L, total bilirubin is 0.7 mg/dL, and CrCl is 40 mL/minute. The patient is seeing the breast oncologist for consultation to start treatment of her metastatic disease. Which one of the following would be best to recommend as a first-line treatment option for B.Z.’s metastatic breast cancer?

A. Ado-trastuzumab emtansine.
B. Carboplatin/paclitaxel/trastuzumab.
C. Capecitabine/trastuzumab.
D. Docetaxel/pertuzumab/trastuzumab.

Which of the following adjunct therapies would be best to manage B.Z.’s bone metastasis?

A. Zoledronic acid 4 mg intravenously every 4 weeks.
B. Denosumab 120 mg subcutaneously every 4 weeks.
C. Pamidronate 90 mg intravenously every 4 weeks.
D. Zoledronic acid 5 mg intravenously every year.

44. A 62-year-old man is hospitalized with shortness of breath. A CT scan reveals a right, lower lung mass with pleural effusion as well as a right adrenal mass. The patient undergoes tissue biopsy and pleural fluid draining that reveals stage IV non-small cell lung cancer. Further testing on the biopsy revealed a well-differentiated EGFR-negative, ALK-positive adenocarcinoma. He now presents to the oncologist office for further treatment planning. Which one of the following would be best to recommend for this patient?

A. Crizotinib.
B. Carboplatin, paclitaxel and bevacizumab.
C. Aftatinib.
D. Cisplatin and pemetrexed.

45. A 68-year-old woman with metastatic breast cancer is currently on ado-trastuzumab emtansine for her metastatic disease. The patient has breast cancer in her bones that started some time ago and has been on denosumab since the development of her bone metastasis. The patient’s comorbidities include cardiovascular disease, hypertension, and hypercholesterolemia. Her current drugs include: ado-trastuzumab emtansine, metoprolol, rosuvastatin, and hydrochlorothiazide. You have completed a medication review and prepare for follow-up education with the patient. Which one of the following education points is most pertinent for this patient?

A. There is minimal risk of osteonecrosis of the jaw compared with bisphosphonate treatment.
B. A baby aspirin will reduce her risk of a myocardial infarction.
C. She should start calcium and vitamin D supplementation.
D. Use of an emollient cream can prevent hand foot syndrome.

46. A 48-year-old woman has metastatic breast cancer with disease in her liver and lungs. Five years ago she received a diagnosis of stage II breast cancer that was ER/PR negative and HER2 positive. She was treated with adjuvant therapy that included a right breast lumpectomy, chemotherapy, and chest wall radiation. The patient also completed 1 year of adjuvant trastuzumab targeted therapy. One year ago she presented...
with shortness of breath and a pulmonary mass that was diagnosed as a recurrent metastatic breast cancer. Pathology revealed the same type of breast cancer from 5 years before, ER/PR negative, and HER2 positive. The patient was started on TCH (carboplatin, paclitaxel, trastuzumab) regimen. The patient tolerated treatment for some time but was later found to have developed liver metastasis after 8 months of TCH chemotherapy. She was switched to capecitabine and lapatinib therapy, but this was poorly tolerated and she continues to show progressive disease after 2 months of therapy. The patient has now been recommended to start ado-trastuzumab emtansine. The patient is trying to understand the toxicities of this treatment because she was told this was a targeted therapy that did not work like chemotherapy and would not have toxicities similar to chemotherapy like thrombocytopenia and nausea. Which one of the following would best explain the mechanism of action for ado-trastuzumab emtansine to this patient?

A. This medication is considered a form of chemotherapy like several other forms of chemotherapy that you have received. This is just a newly approved chemotherapy agent for your breast cancer.
B. This medication is considered a form of targeted therapy as it targets the HER2 receptor on the breast cancer cells, similar to trastuzumab therapy that you have received for your breast cancer.
C. This medication is considered a form of targeted therapy that targets the HER2 receptor, but the medication is linked to a chemotherapy drug that selectively delivers chemotherapy to the breast cancer cells.
D. This medication is considered a form of targeted therapy that targets the HER2 receptor. However this agent binds to a different portion of the HER2 receptor that trastuzumab binds to.

Questions 47 and 48 pertain to the following case.

F.G. is a 43-year-old man with metastatic cutaneous melanoma; he has disease in the lung and a distant cutaneous metastasis. Three weeks ago he was started on ipilimumab therapy, and today he presents for his second dose of ipilimumab. The nurse assessing F.G. notices a diffuse skin rash covering his trunk, arms, and legs with about 60% of the surface area affected (grade three skin rash). The patient reports some mild diarrhea as well (about one loose bowel movement daily). The oncologist asks for your opinion on the management of the patient’s immune-related adverse events.

47. Which one of the following would be best to recommend for F.G.?
A. Hold ipilimumab therapy today then re-attempt ipilimumab after 1 week and initiate prednisone 1 mg/kg by mouth daily with a 1-week taper for skin rash, and loperamide as needed for diarrhea.
B. Continue ipilimumab therapy and initiate topical hydrocortisone for skin rash, loperamide as needed and encourage oral hydration for diarrhea.
C. Continue ipilimumab therapy, initiate prednisone 1 mg/kg by mouth daily with a 2-week taper for skin rash, and loperamide as needed for diarrhea.
D. Permanently discontinue ipilimumab therapy and initiate prednisone 1 mg/kg by mouth daily with a 1-month taper, loperamide as needed, and encourage oral hydration for diarrhea.

48. Which one of the following would be best to complete before dispensing each dose of ipilimumab to F.G.?
A. Complete metabolic panel (CMP), thyroid stimulating hormone (TSH), and physical examination.
B. Complete blood count (CBC) with differential, CMP, physical examination, and TSH.
C. CMP, TSH, physical examination, and cortisol stimulation test.
D. CBC, physical examination, and TSH if symptomatic.

49. You are working on a drug monograph for afatinib in consideration of adding this agent to your formulary. Your recommendation will be to restrict this agent to outpatient use only and to patients who have an exon 19 or 21 EGFR mutation in the first-line setting. When patients are admitted to an inpatient service, the oncology service may write to continue afatinib, but because of drug costs will require that patients continue to use their own supply. You review this proposal because of drug costs will require that patients continue to use their own supply. You review this proposal with your colleagues, who ask if there are any other potential settings in which this drug may be used. Based on current data, which one of the following best describes possible future uses for afatinib?
A. Metastatic non-small cell lung cancer in the second- or third-line setting for patients who have progressed on erlotinib or gefitinib treatment.
B. Metastatic non-small cell lung cancer in the first-line setting without an exon 19 or 21 EGFR mutation.
C. Metastatic non-small cell lung cancer in the second- or third-line setting for patients who have progressed on chemotherapy only.
D. Metastatic non-small cell lung cancer with squamous cell type in the second or third line setting for patients who have progressed on chemotherapy only.
50. An 82-year-old woman has metastatic breast cancer with metastasis to the bone and lungs. The patient’s medical history consists of a previous heart attack with bypass, congestive heart failure with significant edema, hypertension, dyslipidemia, and glaucoma. Her ejection fraction was 51% when she was started on pertuzumab/trastuzumab/docetaxel treatment. She has been getting treatment every 3 weeks for the past 4 months. On a repeat MUGA, the patient’s ejection fraction was 46%. Which one of the following would be best to recommend for this patient?

A. Withhold pertuzumab but continue trastuzumab and docetaxel.
B. Continue treatment with all three agents with continued ejection fraction monitoring.
C. Withhold trastuzumab but continue pertuzumab and docetaxel.
D. Withhold pertuzumab and trastuzumab but continue with docetaxel chemotherapy.

51. A patient receives a new diagnosis of metastatic melanoma with cutaneous metastasis as well as lung metastasis. The patient’s pathology and mutational testing reveals a BRAF V600E mutation, and the oncologist would like to initiate systemic therapy. The patient’s performance status is marginal; he uses a wheelchair to get around and currently needs oxygen because he is symptomatic from his lung metastasis. The patient would benefit from therapy that will have a rapid debulking effect for his melanoma. Which one of the following would be best to recommend for this patient?

A. Vemurafenib single-agent therapy.
B. High dose IL-2 single agent therapy.
C. Vismodegib single-agent therapy.
D. Ipilimumab single-agent therapy.

52. A 45-year-old man has metastatic melanoma with metastases to the bone and a BRAF V600E mutation. The patient has been on first-line treatment with dabrafenib 150 mg by mouth twice daily for about 5 months and most recently has developed disease progression. The patient is young and healthy and is willing to try any other treatments that might provide additional benefit. Which one of the following would be best to recommend for this patient?

A. Add trametinib therapy to dabrafenib.
B. Switch to trametinib.
C. Switch to ipilimumab therapy.
D. Increase the dose of dabrafenib.

53. A man has been on temsirolimus therapy for his metastatic renal cell carcinoma (mRCC). He now is progressing on temsirolimus therapy with tumor growth in the pelvis and new bone metastasis. Which of the following would be the best second-line therapy for this patient?

A. Everolimus.
B. Sorafenib.
C. Vandetanib.
D. Axitinib.

54. A 67-year-old man with stage IV colorectal cancer metastatic to the liver has been on several chemotherapy regimens. He presented with metastatic disease about 22 months ago and received a diagnosis of KRAS mutated adenocarcinoma of the colon. Initial chemotherapy consisted of bevacizumab + FOLFOX (fluorouracil/leucovorin/oxaliplatin) every 2 weeks. Eight months ago he had progression of his liver lesion and was started on FOLFIRI (fluorouracil/leucovorin/irinotecan) + bevacizumab. Since then, he developed a recurrence in his pelvis. Which one of the following would be best to recommend for this patient?

A. FOLFOX alone.
B. Cetuximab + FOLFIRI.
C. Panitumumab alone.
D. Regorafenib.

55. A 65-year-old woman presents with recurrent metastatic ER/PR negative HER2 positive breast cancer. The patient was diagnosed with stage IV disease 2 years ago and has undergone several treatment options including trastuzumab/carboplatin/paclitaxel and lapatinib/capecitabine. She now has progression of disease in her liver and bones. The patient’s AST is 350 units/L, ALT is 370 units/L, total bilirubin is 1.8 mg/dL, and CrCl is 35 mL/minute. The patient is seeing the breast oncologist for consultation to start treatment of her metastatic disease. The oncologist would like to initiate ado-trastuzumab emtansine; however, the oncologist would like to know if this is safe given the patient’s current organ function. Which one of the following is best to recommend for this patient?

A. Proceed with full doses of ado-trastuzumab emtansine.
B. Proceed with half dose of ado-trastuzumab emtansine.
C. Considering withholding therapy until the patient’s liver function improves.
D. Considering withholding therapy until the patient’s renal function improves.

56. A patient receives a new diagnosis of metastatic renal cell carcinoma (mRCC) with pelvis and bone metastasis. The patient has a good performance status, is relatively asymptomatic, and is considered to have an overall good prognosis. Which one of the following would be best to recommend for this patient?
would be the best to recommend as first-line therapy for this patient?
A. Everolimus.
B. Temsirolimus.
C. Sunitinib.
D. Axitinib.

57. A 43-year-old woman recently received a diagnosis of localized basal cell carcinoma. She is being seen by her primary care physician, who is going to refer the patient to a dermatologist for assessment of a lesion that he believes could be either radiated or removed. The physician asks you if there is any current medication therapy that could be used to treat basal cell carcinomas that do not respond to local therapies. Which one of the following would be best to recommend for this patient?
A. Vemurafenib.
B. Vismodegib.
C. Vandetanib.
D. Cabozantinib.

Questions 58 and 59 pertain to the following case.
W.Z. is a 60-year-old woman who presents with diffusely metastatic medullary thyroid cancer. She has metastasis to the bone and lungs and is being seen by the endocrine clinic. She has normal liver function but has experienced slight rises in her serum creatinine over the past few months. You also note that W.Z. presents today with a corrected calcium level of 14 mg/dL.

58. Which one of the following would be most appropriate for W.Z.’s type of thyroid cancer?
A. Vandetanib.
B. Surgical resection.
C. Trametinib.
D. Cetuximab and irinotecan chemotherapy.

59. Given her current presentation, which one of the following is best to initiate as an adjunct medication in W.Z.?
A. IV fluids and denosumab 120 mg.
B. IV fluids and zoledronic acid 4 mg.
C. IV fluids and intranasal calcitonin.
D. Furosemide 20 mg IV.

60. A 62-year-old woman presents to the ER with hemoptysis and shortness of breath. Tissue biopsy reveals stage IV non-small cell lung cancer, adenocarcinoma, with metastasis to the adrenal glands and brain. The patient is significantly short of breath and requires urgent treatment. Mutational testing is currently not available. Which one of the following would be best to recommend for this patient?
A. Crizotinib.
B. Cisplatin and gemcitabine.
C. Erlotinib.
D. Cisplatin and pemetrexed.
Oral Chemotherapy

By Margaret M. Charpentier, Pharm.D., BCPS; and Karen R. Smethers, Pharm.D., BCOP

Reviewed by John B. Bossaer, Pharm.D., BCPS, BCOP; and Kimberly N. Flynn, Pharm.D., BCPS

Learning Objectives

1. Distinguish the common adverse drug effects (ADEs) associated with oral chemotherapy agents.
2. Develop strategies to prevent and manage ADEs.
3. Compose counseling points for patients and caregivers regarding the use of oral chemotherapy.
4. Apply best practices to improve safety in the medication use process for oral chemotherapy.
5. Justify the pharmacist’s role in improving outcomes for patients receiving oral chemotherapy agents.

Introduction

There are more than 50 orally administered cancer drugs agents currently available, and an estimated 250 agents are under investigation. The National Comprehensive Cancer Network Oral Chemotherapy Task Force estimates that 25% of cancer therapy is provided to patients in an oral formulation, an increase from 10% during the past 5 years (Weingart 2008). With the wider availability of both cytotoxic and targeted antineoplastic oral chemotherapy, patients and their caregivers face new challenges in ensuring safe dosing, handling, and administration. In addition, because administration is occurring outside a controlled setting, it is paramount to provide effective patient education and close monitoring for adverse drug effects (ADEs). This chapter reviews safe practices in the prescribing, dispensing, administering, and monitoring of oral chemotherapy agents/drugs.

Baseline Knowledge Statements

Readers of this chapter are presumed to be familiar with the following:

- FMEA (failure mode and effects analysis) proactive risk assessment process
- Safe chemotherapy dispensing guidelines by the American Society of Health-System Pharmacists
- Management of typical adverse events associated with traditional chemotherapy
- Monitoring of patients on hormonal therapies for cancer treatment (except for newer prostate agents)
- Pharmacology of oral chemotherapy (see chapter on targeted therapy in this edition)
- Management of nonspecific conditions associated with chemotherapy-related toxicities such as QT prolongation or hypertension

Additional Readings

The following free resources are available for readers wishing additional background information on this topic.

- ISMP International Medication Safety Self-Assessment for Oncology
- ASCO/ONS Oral Chemotherapy Administration Safety Standards
- International Pharmacy Panel on Safe Handling of Oral Chemotherapy
- Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0
- ECOG-ACRIN Cancer Research Group, Eastern Cooperative Oncology Group Scales and Criteria [homepage on the Internet].
Safe Practices in the Medication Use Process

The Institute for Safe Medication Practices (ISMP) recommends that the same safety checks used for parenteral chemotherapy be followed when orders for oral antineoplastic agents are processed (Shastay 2013). However, this practice has not been viewed as necessary and/or fully implemented in oral chemotherapy treatment (Shastay 2013; Johnson 2008). In current practice, a prescription may be written by a licensed clinician without specialty board certification and called into a retail pharmacy by a designee. A nurse may not have the opportunity to verify the order before the prescription transmission.

The pharmacist filling the oral chemotherapy order often lacks access to the patient’s medical history and may not have the specialty training needed to perform all the necessary checks. A nurse is not involved in verifying the drug before administration. Therefore, the patient is responsible for safely administering and managing supportive therapy and for understanding when to contact a health care practitioner for ADE management (Birmer 2003). This places patients at increased risk of medication events.

The ISMP and the American Society of Clinical Oncology (ASCO), in collaboration with the Oncology Nursing Society, recently published safe practices to reduce the risk of error in the hematology/oncology setting (Neuss 2013; Shastay 2013). Practices specific to oral chemotherapy safety are highlighted in Box 4-1.

Prescribing

High-risk failure modes in the prescribing process were identified by an analysis of five oral chemotherapy agents (Weingart 2011). The failure modes described included errors caused by shortcuts, miscalculations, and illegible handwriting. This analysis is consistent with ISMP reports of prescribing errors associated with the use of hyphenation as a shortcut (e.g., “days 1-8”) (Shastay 2013) or the failure to specify the exact dose on a prescription (e.g., “take as directed”). Also reported as a failure mode were errors during transmission of the prescription to the pharmacy (Weingart 2011).

Dispensing Medication Errors

High-risk failure modes identified in the dispensing phase include the wrong drug, wrong dose, and incorrect quantity (Weingart 2011). One example is a mistake in which Matulane (procarbazine) was dispensed instead of Materna (prenatal vitamin) to a pregnant woman, resulting in a miscarriage. Other examples include dispensing propylthiouracil for mercaptopurine (and vice versa); Tessalon instead of temozolomide (both available as a 100-mg dose); and mercaptopurine instead of metoclopramide (to a patient with nausea) (Weingart 2010). Forty percent of dispensing-related ADEs are attributed to providing the wrong quantity (Weingart 2010). (See Box 4-1 for dispensing recommendations.)

Protecting the Health Care Worker

Adequate training for health care practitioners who are exposed to hazardous drugs is important to provide a safe work environment (i.e., standard processes to prevent exposure, actions to take if an accidental exposure occurs). An applicable program that is regularly updated is important in ensuring that health care practitioners are familiar with the most recent lists of hazardous drugs such as those provided by the National Institute for Occupational Safety and Health or the Occupational Safety and Health Administration.

In hospital and clinic practices, the Oncology Nursing Society, collaboratively with ASCO and the American Society of Health-System Pharmacists (ASHP), has developed detailed guidelines on the safe preparation and administration of chemotherapy (Neuss 2013; ASHP 2006). Each step in the process includes a double check to ensure safety. Although the focus is clinical- and hospital-based practice, the guidelines also include information on safety measures for oral agents. The practitioner may also refer to the ASHP guidelines on handling hazardous medications.

In 2010, an international expert panel convened to review policies and guidelines from Europe and North America and to create a set of recommendations for the safe handling of oral chemotherapy (Goodin 2011). This document was created by pharmacists in a variety of settings related to oncology practice. Participants provided guidelines and recommendations on handling oral chemotherapy from their respective institutions and countries. The group identified best practices and gaps in current practice guidelines and developed a working draft of recommendations specific to the handling of oral chemotherapy for the inclusion in institutions and practices.

In health-system practice, staff wear personal protective equipment (PPE) when handling chemotherapy; this includes disposable gowns, mask, gloves, and head and shoe covers, especially when handling injectable agents.
Box 4-1. Oral Chemotherapy Safe Medication Practices by Medication Use Process

**All Health Care Practitioners:**

Health care practitioners in each stage of the medication use process have formal training in hematology/oncology (e.g., board certification, therapy specific certification) and complete an orientation, baseline competency assessment, and annual competency.

Health care practitioners are trained to anticipate, identify, and manage chemotherapy-induced toxicities.

Health care practitioners and supportive staff are educated about actual medication errors at their practice site and other institutions and about corresponding system-based risk reduction strategies.

Current drug information references are readily available to all health care practitioners.

The following information is readily available after collection in a standardized manner:

- First and last name and second unique identifier (e.g., date of birth, medical record number)
- Hematology/oncology diagnosis including stage, goal of therapy (e.g., curative, palliative)
- Current (measured) height and weight in metric units; identified prescribing weight
- Calculated body surface area (BSA), if appropriate
- Comorbid and/or chronic conditions and performance status
- Allergies (e.g., drug, food, contrast media)
- Adverse drug reaction history
- List of current medications (including over-the-counter drugs, vitamins, herbal, recreational drugs, and homeopathic drugs)
- Current laboratory values and organ function tests
- Cumulative medication dose information (e.g., doxorubicin, bleomycin)
- Regimen-specific maximum and minimum dose limit checks

**In Prescribing:**

Patient, family, or caregivers are educated in their primary language and comprehension level about recommended treatment and therapy alternatives, including anticipated ADEs before treatment selection and initiation.

A patient-specific education and monitoring plan is established before treatment initiation.

Patient is provided with written materials on treatment plan. Informed consent for chemotherapy is obtained before treatment, when the risks and benefits of treatment change, or if the treatment changes.

A standard template is used to ensure that all the following medication order elements are included:

- Regimen or reference, date prescribed, date to start therapy, cycle number, generic medication name (brand included for look-alike, sound-alike [LASA] risk), methodology used for dose calculation, dose in metric units, dosage form, route, frequency, therapy duration, schedule, exact quantity for prescribed treatment, number of refills
- Tall man lettering is used to clearly distinguish LASA medication names.

Doses are rounded to commercially available strengths/concentrations, whenever possible.

Leading zeros are always used, trailing zeros are never used, and insignificant integers are not used.

Specific days of treatment are written explicitly (e.g., days 1, 2, 3; daily for 14 consecutive days, followed by no medication for 7 consecutive days).

Orders are entered into a computer system that directly interfaces with nursing and pharmacy computer systems.

Verbal or telephone orders are never accepted unless they are to hold or discontinue chemotherapy/biotherapy.

Clinical decision support is in place to identify potential cross-reactivity with current allergies and drug interactions and requirements for dose modification because of abnormal laboratory values.

A process is identified to immediately communicate order changes and/or clarifications.

**In Dispensing:**

Both nursing and pharmacy practitioners verify the patient’s oral chemotherapy medication order following the same system-based checks completed for parenteral chemotherapy (e.g., correct patient, diagnosis, indication for use, regimen for diagnosis, height and weight values, BSA, date to start therapy, dose calculation, dosage form, route, frequency, duration, schedule, and exact quantity).

Nursing and pharmacy practitioners also verify adjunctive therapy and ensure the dose is adjusted for performance status, comorbid disease, organ function, and concomitant medications according to established values.

Chemotherapy medications are purchased from authorized distributors or manufacturers.

If patient’s own medication is used in the inpatient setting to ensure treatment continuation, an order is written to specify the use of the home medication, and the medication is identified and documented by a pharmacist before administration. Home medications must not be stored at the bedside.

Appropriate PPE is used when handling chemotherapy, including during receipt, stocking, and preparation activities.

Medication preparation areas are clearly designated and relatively free of distractions, interruptions, and noise (no more than 50 decibels).

Chemotherapy is stored in separate designated areas of the pharmacy with appropriate signage, adequate space, and in an environment with 12 air changes per hour.

Appropriate PPE is used when handling chemotherapy. Chemotherapy requiring manipulation from its original form is done according to published literature and in a Strategies are in place to prevent LASA confusion (e.g., segregated storage, use of tall man lettering).

Bar code verification technology is used during medication receipt, stocking, preparation, and dispensing.

When medication solution or suspension is compounded, a second licensed health care clinician verifies the
When admixing chemotherapy, many clinics and hospitals use closed-system devices to prevent vapor or fluid from escaping into the environment. These systems are also “needleless,” ensuring that staff members do not receive any inappropriate needlesticks during admixture, transportation, or administration.

Pharmacists in community-based practice are less aware of recommendations for dispensing hazardous drugs. A survey of pharmacy practitioners at several New England continuing education programs found that few were using any protection when dispensing oral chemotherapy. At the end of the hour-long continuing education program, provided to pharmacists working mainly in community settings, many agreed to change their practices; however, no follow-up was conducted to determine whether these changes were implemented (Charpentier 2012).

The ASHP guide for medication error prevention with chemotherapy describes safe practices for dispensing oral chemotherapy. All guidelines recommend against using automated counting machines for hazardous drugs. Any compounding, splitting, or crushing of drugs should involve the use of PPE and be performed in a biological safety cabinet.

All recommendations are for those handling oral chemotherapy (e.g., nursing staff, pharmacy staff, caregivers) to wear gloves. Individuals dispensing oral chemotherapy should also wash their hands before and after using gloves.

Use of alcohol-based sanitary hand wash is not adequate because the contaminant is only displaced, not removed. Use of a separate counting tray, as well as other dispensing equipment dedicated to oncology products, is necessary to avoid contamination. The counting tray, tools, and any other surfaces that may have been exposed to hazardous material should be washed with sodium hypochlorite solution and neutralizer, then rinsed.

At the manufacturing level, guidelines suggest that drug makers provide unit of use packaging whenever possible, or at least provide commonly prescribed quantities. For example, an agent dosed once daily for 21 of every 28 days should be provided in 21 units per package. Liquid formulations are also recommended to avoid any compounding and crushing by pharmacists, nurses, or caregivers.

**Administration**

Guidelines suggest that health care professionals provide counseling to patients and caregivers regarding proper handling (Neuss 2013; Goodin 2011). Although many practice sites rely on nursing for the counseling component, others have pharmacists who provide counseling. Pharmacists dispensing chemotherapy are uniquely suited to provide detailed information. Patients and caregivers often make several visits to the pharmacy for supplies, where pharmacists are easily accessible without an appointment. Some patients using mail order for

---

**Box 4-1. Oral Chemotherapy Safe Medication Practices by Medication Use Process (continued)**

<table>
<thead>
<tr>
<th>Controlled Environment</th>
<th>In Administering:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medications dispensed in ready-to-administer form.</td>
<td>Patients are educated on the importance of adherence to chemotherapy and are given tools to assist in taking their medication (e.g., pillbox, calendar, automated reminder systems, journal).</td>
</tr>
<tr>
<td>Medication labels are typed, not handwritten.</td>
<td>Patients are educated on what to do if they miss their scheduled dose of medication.</td>
</tr>
<tr>
<td>Auxiliary warning labels are placed on the primary container (e.g., Chemotherapy).</td>
<td>Appropriate PPE is used when administering chemotherapy (e.g., gloves).</td>
</tr>
<tr>
<td>Before administration of the first dose, patients, family members, and/or caregivers are educated about the medication (generic and brand name), rational for use, the prescribed dose, how to take, frequency, duration, schedule, immediate and delayed ADEs, and when to contact a health care professional.</td>
<td>Patient readily disposes of discontinued or unused chemotherapy/biotherapy medications.</td>
</tr>
<tr>
<td>Before the first dose is administered, patients, family members, and/or caregivers are educated about potential reproductive risks and personal safety related to handling, storage, and proper disposal of chemotherapy/biotherapy.</td>
<td>Appropriate PPE is used for a minimum of 48 hours post-administration if handling patient body fluids and excretions.</td>
</tr>
<tr>
<td>Educational information is given both verbally and in written form. Calendars with medication pictures may be provided for complex regimens, and comprehension of information is assessed (e.g., teach-back method).</td>
<td>In Monitoring:</td>
</tr>
<tr>
<td>In Administering:</td>
<td>A standard process to follow up and monitor patients is established according to patient-specific needs (e.g., telephone, e-mail, scheduled clinic visit follow-up).</td>
</tr>
<tr>
<td>In Monitoring:</td>
<td>Patients are informed about which ADEs should prompt them to contact their health care practitioner.</td>
</tr>
<tr>
<td>In Monitoring:</td>
<td>Patients are encouraged to bring in their medication to monitor adherence.</td>
</tr>
</tbody>
</table>

their oncology drugs lack an opportunity to converse directly with a dispensing pharmacist; therefore, interactions with pharmacists at their clinic setting are vital. Even with the education provided by other health care providers, pharmacists can reinforce the information provided and clarify any misconceptions or assumptions.

Storage and Handling
Counseling must include how to safely handle and store chemotherapy. Caregivers should be instructed to wear gloves; patients can handle the drug without gloves. Regardless of who is administering the drug, hands should be washed before and after handling. Medications must be stored away from children and pets. Any special instructions regarding storage should be provided and reinforced with the patient/caregiver. Leftover drugs should be brought back to the clinic for proper disposal. If this is not possible, these drugs should be stored in a safe place until a drug take-back program is offered in the patient’s community. Medications should not be placed in the trash or disposed of in the toilet.

Timing Precautions and Self-Care
Dosing instructions must be clear. Many errors are made in taking drug; therefore, reinforcement is vital. Reports of errors include patients taking the drug continually instead of cycling. For example, some agents are taken daily for 21 of every 28 days. It may be optimal to provide a calendar in these situations to assist patients/caregivers in knowing when to start and stop the drug. Another source of error is taking the wrong dose when many tablets of various doses are required to achieve the prescribed dose. Educating patients and caregivers on how to handle missed doses is also important. Doubling the dosing is never appropriate. Depending on how frequently the drug is to be taken, the patient can usually take the drug as long as no more than one-half the dosing interval has passed (e.g., if a medication is taken every 12 hours and no more than 6 hours have elapsed, the patient can receive the dose). If it has been more than 6 hours, the patient should not try to “make up” the dose but wait to take the dose at the next administration time. Encourage patients to contact a health care team member if any doses are missed. If missed doses continue to be a problem, patient reminders in electronic devices or other cues to increase adherence should be provided.

It is also vital that the patient understands the proper timing of medication administration with food. For example, abiraterone must be taken on an empty stomach; taking it with food results in a 5- to 10-fold increase in absorption and therefore enhanced toxicity. Studies are ongoing to determine the optimal dosing of abiraterone if taken with food. In the treatment of breast cancer, the combination regimen of lapatinib with capecitabine requires that capecitabine be taken twice daily with food and lapatinib to be taken once daily on an empty stomach. Capecitabine is dosed in a cyclic manner for 14 days in 21-day cycles, whereas lapatinib is administered continually. Counseling and ensuring the patient understands directions completely are vital to ensure the safe administration of such a complex regimen. Table 4-1 contains information on counseling points.

Health professionals must review ADEs with patients/caregivers, providing special emphasis on when immediate attention is required. A method for reaching the oncology team during off-hours should be included. Information regarding the self-management of common, less-severe ADEs must be provided. If patients are unable or unwilling to take the drug because of ADEs, they should contact the oncology team. Written instructions are necessary to reinforce the dose, dosing schedule, ADEs, and when to contact the oncology team. Some online sites (e.g., British Columbia Cancer Agency, OncoLink, Chemocare.com) have patient education sheets for oral chemotherapy, or clinics can develop site-specific written instructions. Some example templates of written instructions have been published (Siden 2013).

Adherence
Adherence to oral chemotherapy is important to discuss with patients. Nonadherence rates of up to 38% were seen in patients taking hormone therapy for breast cancer (Partridge 2008). Nonadherence in about 30% of patients who were prescribed imatinib for chronic myelocytic leukemia was correlated with increased development of resistance, poorer outcomes, and increased health care costs. Furthermore, 23.2% of patients identified as nonadherent (defined as an interruption in therapy for more than 1 week) had a suboptimal response compared with only 7.3% in patients identified as adherent. The 5-year event-free survival also correlated with adherence rates (76.7% with adherence vs. 59.8% with nonadherence). The overall nonadherence rate was 29.6% (Ganesan 2011).

The hematology/oncology team, including the pharmacist, should discuss consequences of nonadherence with patients and/or caregivers and identify barriers as well as ways to improve adherence. Causes of nonadherence are multifactorial and include cost and access to drugs, development of ADEs, lack of full comprehension of the dosing regimen, and lack of understanding about the role of the drug in long-term cancer management. Programs that can assist patients with high-cost drug therapy are provided by drug manufacturers, hematology/oncology fundraising groups, and local charitable organizations (e.g., RxAssist, NeedyMeds, Partnership for Prescription Alliance).

Overadherence is also described; in a study of patients with metastatic cancer, overadherence was identified as a common issue. The authors reviewed the literature on adherence to oral chemotherapy and suggested a lack of consistent methods to assess and improve it (Patel 2013). The evidence so far suggests that the best ways to enhance adherence include patient education and close follow-up (Accordino 2013; Patel 2013; Ruddy 2009).
### Table 4-1. Oral Chemotherapy – Dosing, Administration, Counseling, and Drug Interactions

<table>
<thead>
<tr>
<th>Agent (FDA-Labeled Indication)</th>
<th>Usual Dose</th>
<th>Administration</th>
<th>Patient Instructions: When to Contact Health Care Professional</th>
<th>Metabolism/Transport Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Abiraterone</strong> (Advanced prostate cancer) 1000 mg once daily with prednisone 5 mg orally twice daily</td>
<td>Take on an empty stomach 2 hours before or 1 hour after meals. Do not crush or chew</td>
<td>Temperature &gt; 100.4°F (38°C), chills, chest pain or irregular heartbeat, difficulty breathing, inability to urinate for &gt; 8 hours, dizziness/light-headedness, significant headache, diarrhea, unusual bleeding or bruising, black or tarry stools or blood in stool, extreme fatigue, yellow skin or eyes, unusual elevation in BP</td>
<td>Substrate of CYP3A4 (major); inhibits CYP1A2 (weak), CYP2C19, CYP 2D6, CYP 3A4 (moderate), CYP2C8 (strong), Pgp</td>
<td></td>
</tr>
<tr>
<td><strong>Axitinib</strong> (Advanced renal cell cancer) 5 mg twice daily, about every 12 hours</td>
<td>Take with a glass of water with or without food</td>
<td>Severe hypertension: BP &gt; 160 systolic or &gt; 100 diastolic, hypertension, temperature &gt; 100.4°F (38°C), chills, signs of infection, swelling, redness, and/or pain in one leg or arm and not the other (may be symptoms of blood clot), nausea, vomiting, diarrhea, unusual bleeding or bruising, black or tarry stools or blood in stools, blood in urine, pain or burning with urination, extreme fatigue, mouth sores</td>
<td>Substrate of CYP1A2 (minor), CYP2C19 (minor), CYP3A4 (major), UGT1A1</td>
<td></td>
</tr>
<tr>
<td><strong>Bosutinib</strong> (CML) 500 mg daily (200–600 mg daily)</td>
<td>Take with food</td>
<td>Temperature &gt; 100.4°F (38°C), chills, diarrhea, nausea, vomiting, extreme fatigue, unable to eat or drink for 24 hours or signs of dehydration, yellow skin or eyes, urine turns dark or brown (tea color), decreased appetite, pain on the right side of stomach, bleed or bruise more easily than normal, respiratory tract infection, headache, back pain, or joint pain, skin changes (rash, acne, itching, blisters, peeling, redness, or swelling)</td>
<td>Substrate of CYP3A4 (major), Pgp; inhibits Pgp</td>
<td></td>
</tr>
<tr>
<td><strong>Cabozantinib</strong> (Metastatic medullary thyroid cancer) 140 mg once daily</td>
<td>Take on an empty stomach 1 hour before or 2 hours after meals</td>
<td>Chest pain, shortness of breath, temperature &gt; 100.4°F (38°C), chills, unusual bleeding, black or tarry stools or blood in stools, severe headache, light-headedness or other neurologic symptoms (numbness, tingling, difficulty speaking, change in thinking clearly), diarrhea, nausea, vomiting, unable to eat or drink for 24 hours or signs of dehydration, yellow skin or eyes, urine turns dark or brown (tea color), decreased appetite, pain on the right side of stomach, bleed or bruise more easily, itching, cough with or without mucus, mouth sores, pain or burning with urination, extreme fatigue</td>
<td>Substrate of CYP2C9 (minor), CYP3A4 (major); inhibits Pgp</td>
<td></td>
</tr>
<tr>
<td><strong>Crizotinib</strong> (Non–small cell lung cancer) 250 mg twice daily</td>
<td>Take with or without food</td>
<td>Temperature &gt; 100.4°F (38°C), chills, sudden onset of shortness of breath, accompanied by cough and/or fever, diarrhea, nausea, vomiting, unable to eat or drink for 24 hours or signs of dehydration, eye irritation, yellow skin or eyes, urine turns dark or brown (tea color), decreased appetite, pain on the right side of stomach, bleed or bruise more easily than normal, itching, cough with or without mucus</td>
<td>Substrate of CYP3A4 (major), Pgp; inhibits CYP2B6 (moderate), CYP3A4 (moderate), Pgp</td>
<td></td>
</tr>
<tr>
<td>Agent</td>
<td>(FDA-Labeled Indication) Usual Dose</td>
<td>Administration</td>
<td>Patient Instructions: When to Contact Health Care Professional</td>
<td>Metabolism/Transport Effects</td>
</tr>
<tr>
<td>-------</td>
<td>-----------------------------------</td>
<td>----------------</td>
<td>---------------------------------------------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>Dasatinib (CML, ALL) 100–140 mg once daily</td>
<td>Take with or without food</td>
<td>Temperature &gt; 100.5°F (38°C), chills, bleeding or easy bruising, swelling, weight gain, or increasing shortness of breath, nausea, vomiting, diarrhea, unusual bleeding or bruising, black or tarry stools or blood in stools, blood in the urine, pain or burning on urination, extreme fatigue, mouth sores</td>
<td>Substrate of CYP3A4 (major); inhibits CYP3A4 (weak)</td>
<td></td>
</tr>
<tr>
<td>Enzalutamide (Advanced prostate cancer) 160 mg once daily</td>
<td>Take with or without food</td>
<td>Temperature &gt; 100.4°F (38°C), chills, diarrhea, unusual bleeding or bruising, extreme fatigue, swelling of the legs, feet, arms, or hands, difficulty thinking, confusion, falls, dizziness, signs of infection, pink tinge or blood in urine</td>
<td>Substrate of CYP2C8 and CYP3A4 (major); induces CYP2C19 and CYP2C9 (weak/moderate), CYP3A4 (strong)</td>
<td></td>
</tr>
<tr>
<td>Erlotinib (Non–small cell lung cancer) 150 mg once daily</td>
<td>Take on an empty stomach 1 hour before or 2 hours after a meal</td>
<td>Onset or worsening of unexplained shortness of breath or cough, nausea, vomiting, diarrhea, extreme fatigue, mouth sores, eye irritation, unable to eat or drink for 24 hours or signs of dehydration</td>
<td>Substrate of CYP1A2 (minor), CYP3A4 (major).</td>
<td></td>
</tr>
<tr>
<td>Erlotinib (Pancreatic cancer) 100 mg once daily</td>
<td>Take with a glass of water with or without food</td>
<td>Temperature &gt; 100.4°F (38°C), chills, nausea, vomiting, diarrhea, unusual bleeding or bruising, black or tarry stools or blood in stools, blood in the urine, pain or burning with urination, extreme fatigue, mouth sores</td>
<td>Substrate of CYP3A4 (major), Pgp</td>
<td></td>
</tr>
<tr>
<td>Everolimus (Advanced breast cancer, PNET Renal, angio-myolipoma; Advanced renal cell SEGA) 10 mg once daily</td>
<td>May dissolve Disperz tablets in 5–25 mL of water</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imatinib (CML, GIST) 400–800 mg/day</td>
<td>Take with food and a large glass of water Separate 800-mg doses May dissolve tablet in water or apple juice</td>
<td>Temperature &gt; 100.4°F (38°C), chills, shortness of breath, difficulty breathing, significant bleeding from nose, mouth, vagina, rectum that will not stop within 15 minutes, nausea, vomiting, diarrhea, unusual bleeding or bruising, black or tarry stools or blood in your stools, blood in the urine, extreme fatigue, swelling, redness, and/or pain in one leg or arm and not the other, yellow skin or eyes, swelling of the feet or ankles, sudden weight gain</td>
<td>Substrate of CYP1A2, CYP2C19, CYP2C8, CYP2C9, and CYP2D6 (minor), CYP3A4 (major), Pgp; inhibits BCRP, CYP2C9 (weak), CYP2D6, CYP3A4 (moderate), Pgp</td>
<td></td>
</tr>
</tbody>
</table>
Table 4-1. Oral Chemotherapy – Dosing, Administration, Counseling, and Drug Interactions (continued)

<table>
<thead>
<tr>
<th>Agentáf (FDA-Labeled Indication)</th>
<th>Usual Dose</th>
<th>Administration</th>
<th>Patient Instructions: When to Contact Health Care Professional</th>
<th>Metabolism/Transport Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lapatinib (Metastatic breast cancer) 1250 mg once daily in combination with capecitabine or 1500 mg daily with letrozole</td>
<td>1250 mg once daily in combination with capecitabine or 1500 mg daily with letrozole</td>
<td>Take on an empty stomach 1 hour before or 2 hours after meals</td>
<td>Temperature &gt; 100.4°F (38°C), chills, palpitations or shortness of breath, diarrhea, nausea, vomiting, tingling or burning, redness, swelling of the palms of the hands or soles of the feet, unusual bleeding or bruising, black or tarry stools or blood in stools, blood in the urine, extreme fatigue, mouth sores, unable to eat or drink for 24 hours or signs of dehydration</td>
<td>Substrate of CYP3A4 (major), Pgp; inhibits BCRP, CYP2C8 (moderate), CYP3A4 (weak), Pgp</td>
</tr>
<tr>
<td>Lenalidomide (Multiple myeloma Mantle cell lymphoma) 25 mg once daily for 21 days of a 28-day cycle Myelodysplastic syndrome) 10 mg once daily</td>
<td>25 mg once daily for 21 days of a 28-day cycle Myelodysplastic syndrome) 10 mg once daily</td>
<td>Take with or without food</td>
<td>Sudden chest pain and shortness of breath, temperature &gt; 100.4°F (38°C), chills, unusual bleeding or bruising, black or tarry stools or blood in stool, blood in the urine, diarrhea, nausea, extreme fatigue, leg or arm swelling, redness, pain, and/or warm to touch</td>
<td>Substrate of Pgp</td>
</tr>
<tr>
<td>Nilotinib (CML) 300–400 mg twice daily</td>
<td>300–400 mg twice daily</td>
<td>Take on an empty stomach 2 hours before or 1 hour after a meal</td>
<td>Temperature &gt; 100.4°F (38°C), chills, shortness of breath, difficulty breathing, nausea, vomiting, diarrhea, unusual bleeding or bruising, black or tarry stools or blood in stool, blood in the urine, extreme fatigue, swelling of feet or ankles, sudden weight gain, unusual cough, yellow skin or eyes</td>
<td>Substrate of CYP1A2, CYP2C19, CYP2C8, CYP2C9, and CYP2D6 (minor), CYP3A4 (major), Pgp; inhibits BCRP, CYP2C9 (weak), CYP2D6 and CYP3A4 (moderate), Pgp</td>
</tr>
<tr>
<td>PAZOPanib (Renal cell carcinoma Soft tissue sarcoma) 800 mg once daily</td>
<td>800 mg once daily</td>
<td>Take on an empty stomach 1 hour before or 2 hours after a meal</td>
<td>Temperature &gt; 100.4°F (38°C), chills, yellow skin or eyes, hypertension, diarrhea, nausea, vomiting, unusual bleeding or bruising, black or tarry stools or blood in stool, blood in the urine, extreme fatigue, swelling of feet or ankles, sudden weight gain, unusual cough, yellow skin or eyes</td>
<td>Substrate of CYP1A2 and CYP2C8 (minor), CYP3A4 (major), Pgp; inhibits CYP2C8, CYP2D6 and CYP3A4 (weak), SLC01B1, UGT1A1</td>
</tr>
<tr>
<td>Pomalidomide (Multiple myeloma) 4 mg once daily on days 1–21 of repeated 28-day cycle</td>
<td>4 mg once daily on days 1–21 of repeated 28-day cycle</td>
<td>Take on an empty stomach at least 2 hours before or 2 hours after meals</td>
<td>Temperature &gt; 100.4°F (38°C), chills, wheezing, difficulty breathing, closing up of the throat, swelling of facial features, hives (possible allergic reaction), shortness of breath, chest pain, arm or leg swelling (possible blood clot), extreme fatigue, constipation, new rashes, neuropathy, edema, sudden weight gain, infection, severe dehydration, failure in contraception</td>
<td>Substrate of CYP1A2, CYP2C19, and CYP2D6 (minor), CYP3A4 (major), Pgp</td>
</tr>
</tbody>
</table>
Table 4-1. Oral Chemotherapy – Dosing, Administration, Counseling, and Drug Interactions (continued)

<table>
<thead>
<tr>
<th>Agent (FDA-Labeled Indication)</th>
<th>Usual Dose</th>
<th>Administration</th>
<th>Patient Instructions: When to Contact Health Care Professional</th>
<th>Metabolism/Transport Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ponatinib (ALL CML)</td>
<td>45 mg once daily</td>
<td>Take with or without food</td>
<td>Temperature &gt; 100.4°F (38°C), chills, unusual bleeding, black or tarry stools or blood in stools, hypertension, nausea, vomiting, diarrhea, unable to eat or drink for 24 hours or signs of dehydration, yellow skin or eyes, urine turns dark or brown (tea color), decreased appetite, pain on the right side of stomach, bleed or bruise more easily, itching, cough with or without mucus, mouth sores, pain or burning with urination, extreme fatigue</td>
<td>Substrate of BCRP, CYP2C8 (minor), CYP2D6 (minor), CYP3A4 (minor), Pgp; inhibits BCRP, Pgp</td>
</tr>
<tr>
<td>Regorafenib (Metastatic colorectal cancer GIST)</td>
<td>160 mg once daily for the first 21 days of each 28-day cycle</td>
<td>Take at the same time each day with a low-fat breakfast (&lt; 30% fat)</td>
<td>Temperature &gt; 100.4°F (38°C), chills, signs of a severe reaction, sudden change in eyesight, fast heartbeat, severe headache, severe dizziness or passing out, diarrhea, nausea, vomiting, unable to eat or drink for 24 hours or have signs of dehydration, yellow skin or eyes, urine turns dark or brown (tea color), decreased appetite, pain on the right side of stomach, bleed or bruise more easily, skin changes (rash, acne, itching, blisters, peeling, redness, or swelling), increase in BP, extreme fatigue, big weight gain or loss, black or tarry stools or blood in stool, blood in the urine, signs of infection</td>
<td>Substrate of CYP3A4 (major), UGT1A9; inhibits BCRP, Pgp, UGT1A1, UGT1A9</td>
</tr>
<tr>
<td>Sorafenib (Advanced renal cell cancer Hepato-cellular cancer)</td>
<td>400 mg twice daily</td>
<td>Take on an empty stomach 1 hour before or 2 hours after meals</td>
<td>Temperature &gt; 100.4°F (38°C), chills, tingling or burning, redness, swelling of the palms of the hands or soles of the feet, nausea, vomiting, diarrhea, unusual bleeding or bruising, black or tarry stools or blood in stool, blood in the urine, extreme fatigue, constipation unrelieved by laxatives, signs of infection such as redness or swelling, pain on swallowing, coughing up mucus, painful urination</td>
<td>Substrate of CYP3A4 (major); inhibits BCRP, Pgp</td>
</tr>
<tr>
<td>Sunitinib (GIST)</td>
<td>50 mg once daily for first 4 weeks of a 6-week cycle</td>
<td>Take with or without food</td>
<td>Temperature &gt; 100.4°F (38°C), chills, nausea, vomiting, diarrhea, unable to eat or drink for 24 hours or signs of dehydration, unusual bleeding or bruising, black or tarry stools or blood in stool, blood in the urine, pain or burning with urination, extreme fatigue, mouth sores, swelling, redness, and/or pain in one leg or arm and not the other (may be symptoms of blood clot)</td>
<td>Substrate of CYP3A4 (major); inhibits CRP, Pgp</td>
</tr>
<tr>
<td>Sunitinib (PNET)</td>
<td>37.5 mg once daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sunitinib (renal cell cancer)</td>
<td>50 mg daily for first 4 weeks of 6-week cycle</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Oral Chemotherapy Monitoring

Adverse Drug Events

Adverse drug events associated with newer oral chemotherapy agents are discussed here by body system. Several factors associated with oral chemotherapy may contribute to enhanced ADEs. Instead of being administered periodically, oral agents often require continuous administration, resulting in cumulative toxicities. Routine monitoring by the oncology team is not always as frequent with oral administration compared with clinic-administered parenteral chemotherapy; therefore, patients may continue therapy at the same dose while ADEs worsen. Some patients may be hesitant to admit to ADEs because they wish to treat the cancer. A delay in identifying ADEs can limit opportunities to provide supportive care to limit

| Table 4-1. Oral Chemotherapy – Dosing, Administration, Counseling, and Drug Interactions (continued) |
|---|---|---|---|
| **Agent** (FDA-Labeled Indication) | **Usual Dose** | **Administration** | **Temperature** |
| Vandetanib (Thyroid cancer) 300 mg once daily | Take with or without food | Temperature > 100.4°F (38°C), chills, irregular heartbeat, light-headedness or feeling faint, trouble breathing or shortness of breath, headaches, seizures, confusion, changes in vision or thinking, diarrhea, nausea, vomiting, unable to eat or drink for 24 hours or signs of dehydration, yellow skin or eyes, urine turns dark or brown (tea color), decreased appetite, pain on the right side of stomach, bleed or bruise more easily, skin changes (rash, acne, itching, blisters, peeling, redness, or swelling), hypertension | Substrate of CYP3A4 (major); inhibits BCRP, Pgp |
| Vemurafenib (Metastatic or unresectable melanoma) 960 mg twice daily; about every 12 hours in the morning and evening | Take with a glass of water with or without food | Temperature > 100.4°F (38°C), chills, diarrhea, nausea, vomiting, unable to eat or drink for 24 hours or signs of dehydration, sudden change in eyesight, sudden onset of shortness of breath accompanied by cough and/or fever, yellow skin or eyes, urine turns dark or brown, decreased appetite, pain on the right side of stomach, bleed or bruise more easily, fast heartbeat, cough with or without mucus, swelling or pain in hands or feet, change in color or size of a mole, any skin change, irritation, itching, or rash | Substrate of BCRP, CYP3A4 (major), Pgp; inhibits BCRP, CYP1A2 (moderate), CYP2D6 (weak), Pgp; induces CYP3A4 (weak/moderate) |
| Vismodegib (Basil cell carcinoma) 150 mg once daily | Take with or without food | Temperature > 100.4°F (38°C), chills, signs of a reaction, diarrhea, nausea, vomiting, unable to eat or drink for 24 hours or signs of dehydration | Substrate of CYP2C9 and CYP3A4 (minor), Pgp; inhibits BCRP, CYP2C19, CYP2C8 and CYP2C9 (weak) |

ALL = acute lymphoblastic leukemia; BCRP = breast cancer resistance protein; BP = blood pressure; CML = chronic myelogenous leukemia; FDA = U.S. Food and Drug Administration; GIST = gastrointestinal stromal tumor; Pgp = P-glycoprotein; PNET = primitive neuroectodermal tumor; SEGA = subependymal giant cell astrocytoma.

1 Diarrhea: four to six episodes in a 24-hour period.
2 Extreme fatigue: unable to carry on self-care activities.
3 Hypertension: systolic BP > 150 mm Hg or diastolic BP > 90 mm Hg.
4 Signs of infection: very bad sore throat, ear or sinus pain, cough, more sputum or change in color of sputum, pain with passing urine, mouth sores, wound that will not heal, or anal itching or pain.
5 Nausea: interferes with ability to eat and unrelieved with prescribed medication.
6 Vomiting: vomiting more than four or five times in a 24-hour period.
7 Mouth sores: painful redness, swelling, or ulcers.
8 Signs of dehydration: tiredness, thirst, dry mouth, dark and decrease amount of urine, or dizziness
9 Signs of a reaction: wheezing, chest tightness, fever, itching, bad cough, blue or gray skin, seizures, or swelling or the face, lips, tongue, or throat.

**Monitoring**

**Adverse Drug Events**

Adverse drug events associated with newer oral chemotherapy agents are discussed here by body system. Several factors associated with oral chemotherapy may contribute to enhanced ADEs. Instead of being administered periodically, oral agents often require continuous monitoring, resulting in cumulative toxicities. Routine monitoring by the oncology team is not always as frequent with oral administration compared with clinic-administered parenteral chemotherapy; therefore, patients may continue therapy at the same dose while ADEs worsen. Some patients may be hesitant to admit to ADEs because they wish to treat the cancer. A delay in identifying ADEs can limit opportunities to provide supportive care to limit...
or adequately manage ADEs. Patient education regarding toxicities, when to contact the team, and options for management are vital to optimizing treatment.

All the newer oral agents are considered targeted therapies; these have ADEs related to “on-target” and “off-target” mechanisms. On-target effects (e.g., skin reactions from epidermal growth factor receptor [EGFR] agents) are more difficult to prevent than off-target effects; for example, QT prolongation from the c-kit inhibitors can be reduced by changing to another agent within the class. **Figure 4-1 identifies targets and their associated toxicities.**

Table 4-2 lists specific agents by class and ADEs; a version of this table with additional data is available online.

### Hematologic Toxicities

Neutropenia commonly occurs with traditional chemotherapy and is associated with oral chemotherapy agents, including targeted agents. Because many oral targeted therapies are combined with traditional chemotherapy, neutropenia remains a concern. Counseling regarding neutropenia includes recommending that patients obtain a thermometer to monitor for a fever and remain vigilant

(Continued on page 185)
Table 4-2. Selected ADEs Reported in Oral Chemotherapy Registration Studies

<table>
<thead>
<tr>
<th>Drug Class/Target (Medications)</th>
<th>Management*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dermatologic: Rash</strong></td>
<td></td>
</tr>
<tr>
<td>EGFR inhibitors (vandetanib &gt; erlotinib) HER2 inhibitors (lapatinib) BRAF inhibitors (vemurafenib, dabrafenib) Multikinase angiogenesis inhibitors (axitinib, cabozantinib, pazopanib, sunitinib &lt; regorafenib, sorafenib, ponatinib) mTOR inhibitors (everolimus) ALK/c-met inhibitors (crizotinib) Multikinase Abl inhibitors (dasatinib &lt; imatinib &lt; nilotinib, ponatinib, bosutinib) RXR agonist (bexarotene dose-dependent risk) Immunomodulatory agents (thalidomide, lenalidomide, pomalidomide)</td>
<td>Prophylactic treatment with oral minocycline or doxycycline should be considered, particularly for EGFR/BRAF/MEK inhibitors. Apply broad-spectrum sunscreen. Avoid alcohol-containing skin products. Emollients and mild topical steroids (e.g., 1% hydrocortisone cream) can be applied on dry skin 2–3 x daily. Topical antibiotics can be applied on papulopustular eruptions. For rash with moderate pruritus or tenderness, use 0.1% triamcinolone or 2.5% hydrocortisone cream. Withhold treatment for ≥ grade 3 rash, and initiate oral corticosteroids if rash remains severe, despite intake of oral antibiotics. May resume when ≤ grade 1 at reduced dose. Continue prophylactic treatment. Avoid lansoprazole use with imatinib because of potential increased risk of dermatologic toxicity. Withhold treatment for ≥ 2 grade rash. Reduce dose by 100 mg/m²/day on resumption of treatment when ≤ grade 1. Permanently discontinue for severe exfoliative/bullous rash. Withhold treatment for ≥ 2 grade rash. May resume at 50% dose on resolution to baseline or ≤ grade 1 toxicity. Permanently discontinue for severe exfoliative/bullous rash.</td>
</tr>
<tr>
<td><strong>Dermatologic: Rash Hand-foot skin reaction</strong></td>
<td>Preventive measures should be initiated early (callus removal; minimize friction and direct trauma by wearing well-fitted shoes, gloves, thick socks, well-padded footwear, gel pad inserts). Application 2–3 x daily of moisturizers containing salicylic acid, urea, or ammonium lactate recommended on treatment initiation. For painful blisters, topical corticosteroids should be considered. Interrupt treatment for painful or intolerable grade &gt; 2 toxicities. Dose reduction to be considered as clinically indicated on resumption of treatment when toxicity improves to grade &lt; 2.</td>
</tr>
<tr>
<td><strong>Dermatologic: Cutaneous squamous cell cancer/keratoacanthoma</strong></td>
<td>Baseline skin examination and regular dermatologic evaluation. Local excision treatment as indicated.</td>
</tr>
<tr>
<td><strong>Cardiovascular: Decreased LVEF/congestive heart failure</strong></td>
<td>Before initiating treatment, risk factors should be evaluated and treated. Close collaboration with a cardiologist is recommended, especially in high-risk patients. Baseline and periodic evaluation (e.g., every 3 months) of LVEF is recommended for patients with known risk factors. If symptomatic, LVEF declines to &lt; 50% or ≥ 10% from baseline, withhold treatment, initiate heart failure medications, and repeat LVEF measurement. May re-treat if LVEF improves to 50% or if &lt; 10% change from baseline Discontinue treatment for ≥ grade 3 heart failure, LVEF decline &gt; 20% from baseline, recurrent LVEF decline on rechallenge.</td>
</tr>
</tbody>
</table>
Table 4-2. Selected ADEs Reported in Oral Chemotherapy Registration Studies (continued)

<table>
<thead>
<tr>
<th>Drug Class/Target (Medications)</th>
<th>Managementa</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular: Hypertension</strong></td>
<td></td>
</tr>
<tr>
<td>Multikinase angiogenesis inhibitors (sorafenib, &lt; axitinib &lt; sunitinib, pazopanib, regorafenib, cabozantinib, vandetanib &lt; ponatinib) CYP17 inhibitor (abiraterone)</td>
<td>BP should be controlled before initiating treatment. BP should be monitored within first week of treatment, standard antihypertensive therapy should be initiated promptly; target BP is &lt; 140/90 mm Hg. Treatment should be interrupted for severe hypertension &gt; 200 mm Hg or &gt; 110 mm Hg diastolic, hypertensive urgency or persistent hypertension despite antihypertensive medications. Dose reduction should be implemented on improvement in BP control. Treatment should be permanently discontinued in patients with life-threatening symptoms (e.g., reversible posterior leukoencephalopathy syndrome) or if persistently uncontrolled despite treatment</td>
</tr>
<tr>
<td><strong>Cardiovascular: QT prolongation</strong></td>
<td></td>
</tr>
<tr>
<td>Multikinase angiogenesis inhibitors (cabozantinib, ponatinib &lt;&lt; pazopanib, sunitinib &lt;&lt; vandetanib) ALK/c-met inhibitors (crizotinib) Multikinase Abl inhibitors (ponatinib, bosutinib &lt; dasatinib &lt; nilotinib) CYP17 inhibitor (abiraterone)</td>
<td>Use with caution in preexisting cardiac disease or concomitant medications that may prolong the QT interval. Baseline and periodic monitoring of ECG, as well as maintenance of adequate electrolyte balance, is recommended. Because these agents can cause diarrhea, associated electrolyte disturbances can elevate the risk of toxicity. A REMS program has been created for vandetanib and nilotinib. Vandetanib can be prescribed only through the REMS program.</td>
</tr>
<tr>
<td><strong>Venous thromboembolic events</strong></td>
<td></td>
</tr>
<tr>
<td>Multikinase angiogenesis inhibitors (sorafenib, axitinib, pazopanib, sunitinib, ponatinib &lt; cabozantinib) Immunomodulatory agents (pomalidomide, lenalidomide &lt; thalidomide)</td>
<td>Withhold treatment and initiate standard anticoagulant treatment; may resume at original dose after stabilization of patient, resolution of acute symptoms, and achievement of therapeutic levels of anticoagulation. Prophylaxis with low-molecular-weight heparin or full-dose warfarin (INR target 2–3) should be considered in all patients who receive multiagent regimen (e.g., in combination with high-dose dexamethasone or in combination with chemotherapy). Use of aspirin alone should be limited to patients with ≥ 1 risk factor</td>
</tr>
<tr>
<td><strong>Arterial thromboembolic events</strong></td>
<td></td>
</tr>
<tr>
<td>Multikinase angiogenesis inhibitors (axitinib, sorafenib, pazopanib, sunitinib, regorafenib, cabozantinib, vandetanib &lt; ponatinib) Multikinase Abl ( imatinib &lt; nilotinib, bosutinib &lt; dasatinib &lt;&lt; ponatinib)</td>
<td>Treatment should be used with caution in patients at risk of these complications and avoided in patients with events in the preceding 6–12 months. Withhold treatment on occurrence and consider permanent discontinuation for treatment-related life-threatening manifestations. If resumption of therapy is strongly indicated, may resume at original dose after stabilization of patient, resolution of acute symptoms, and achievement of therapeutic levels of anticoagulation</td>
</tr>
</tbody>
</table>
**Table 4-2. Selected ADEs Reported in Oral Chemotherapy Registration Studies (continued)**

<table>
<thead>
<tr>
<th>Drug Class/Target (Medications)</th>
<th>Management*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiratory: Noninfectious pneumonitis/diffuse alveolar damage/pulmonary fibrosis</strong></td>
<td></td>
</tr>
<tr>
<td>Multikinase angiogenesis inhibitors (Sorafenib, sunitinib)</td>
<td>No dose adjustment necessary in patients who are asymptomatic or who have mild symptoms. Follow up with a high-resolution CT scan every 6–8 weeks. Consider treatment interruption or dose reduction with corticosteroids for moderate symptoms once other etiologies have been excluded. Withhold treatment for rapidly developing symptoms, worsening symptoms despite dose reduction on corticosteroids or with severe symptoms on initial presentation. Initiate high-dose corticosteroids. Continue corticosteroids at the same dose until symptoms improve before starting taper. Switching therapy to a different agent in the same drug class has documented success in case reports (e.g., nilotinib in imatinib-induced interstitial lung disease). When using mTOR inhibitors, treatment with the same agent may be reintroduced at 50% reduction when symptoms improve to ≤ grade 1. A management algorithm for inhibitors of PI3K/mTOR/AKT pathway can be found online.</td>
</tr>
<tr>
<td>mTOR inhibitors (everolimus)</td>
<td></td>
</tr>
<tr>
<td>EGFR inhibitors (erlotinib&lt;sup&gt;a&lt;/sup&gt;)</td>
<td></td>
</tr>
<tr>
<td>ALK/c-met inhibitor (crizotinib)</td>
<td></td>
</tr>
<tr>
<td>Multikinase Abl inhibitors (dasatinib, imatinib)</td>
<td></td>
</tr>
<tr>
<td>Immunomodulatory agents (thalidomide, lenalidomide)</td>
<td></td>
</tr>
<tr>
<td><strong>Pulmonary arterial hypertension</strong></td>
<td></td>
</tr>
<tr>
<td>Multikinase Abl inhibitors (dasatinib)</td>
<td>Periodic assessment of pulmonary arterial pressure or development of suggestive symptoms (dyspnea, cough, fluid retention). Withhold therapy if grade ≥ 2. Treatment may be resumed on improvement as clinically indicated. Permanently discontinue for grade ≥ 3</td>
</tr>
<tr>
<td><strong>Gastrointestinal: Mucositis/stomatitis</strong></td>
<td></td>
</tr>
<tr>
<td>Multikinase angiogenesis inhibitors (Cabozantinib, ponatinib, sorafenib, pazopanib, axitinib &lt;&lt; regorafenib &lt; sunitinib)</td>
<td>Avoid alcohol- or peroxide-based mouthwashes. Antifungal agents should be used if infection confirmed. Anesthetic mouthwashes (typically containing equal parts of lidocaine, diphenhydramine or dimethicone, and magnesium hydroxide) may provide brief symptomatic relief, if mild. Initiate topical dexamethasone rinses (0.1 mg/mL) or topical corticosteroids. Persistent grade 2 symptoms or worsening symptoms require withholding treatment and intralesional corticosteroid therapy for severe mucositis. Initiate systemic corticosteroids (prednisone 1 mg/kg or its equivalent) if inadequate relief or for ≥ grade 3 presentation. Treatment may be resumed with dose reduction when symptoms improve to &lt; grade 1. Consider treatment discontinuation in patients with life-threatening presentations (e.g., concomitant esophagitis, diarrhea, or vaginal ulcers)</td>
</tr>
<tr>
<td>mTOR inhibitors (everolimus)</td>
<td></td>
</tr>
<tr>
<td>EGFR inhibitors (erlotinib&lt;sup&gt;a&lt;/sup&gt;)</td>
<td></td>
</tr>
<tr>
<td>HER2 inhibitors (lapatinib)</td>
<td></td>
</tr>
<tr>
<td>Multikinase Abl inhibitors (imatinib &lt; ponatinib)</td>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal: Diarrhea/colitis</strong></td>
<td></td>
</tr>
<tr>
<td>Multikinase angiogenesis inhibitors (Ponatinib &lt; sorafenib, axitinib, pazopanib, regorafenib, sunitinib, vandetanib, cabozantinib)</td>
<td>While investigating the cause of diarrhea, antimotility agents (e.g., loperamide, diphenoxylate/atropine) should be initiated on appearance of mild symptoms, particularly in patients receiving combination with chemotherapy agents known for causing diarrhea and in patients receiving EGFR/-RAF/-MEK pathway inhibitors. Withhold treatment for persistent grade 2 symptoms despite use of antimotility agents and resume on improvement to baseline or CTC grade 1. May consider adding octreotide. Withhold treatment for &gt; grade 3 diarrhea and resume at a lower dose on improvement to baseline or grade 1</td>
</tr>
<tr>
<td>EGFR inhibitors (erlotinib,a vandetanib)</td>
<td></td>
</tr>
<tr>
<td>HER2 inhibitors (lapatinib)</td>
<td></td>
</tr>
<tr>
<td>BRAF inhibitors (vemurafenib)</td>
<td></td>
</tr>
<tr>
<td>BTK inhibitor (ibrutinib)</td>
<td></td>
</tr>
<tr>
<td>Multikinase Abl inhibitors (nilotinib, ponatinib, dasatinib, imatinib, &lt; bosutinib CYP17 inhibitor (abirateroned)</td>
<td></td>
</tr>
<tr>
<td>Pure androgen receptor signaling inhibitor (Enzalutamide)</td>
<td></td>
</tr>
<tr>
<td>Drug Class/Target (Medications)</td>
<td>Managementa</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Neuronal: Neuropathy</td>
<td>Continue treatment but consider dose reduction if grade 1 symptoms develop. Withhold treatment for &gt; grade 2 symptoms. Initiate empiric supportive medications as appropriate. On improvement to &lt; grade 1, may resume treatment at 50% dose reduction. Consider lower dose for chronic maintenance regimen. If recurrent using lower dose or if grade 3, discontinue treatment. Administer 1–2 mg/kg/day of prednisone or its equivalent. IV immunoglobulin or other immunosuppressants may be considered.</td>
</tr>
<tr>
<td>Endocrine/metabolic: Hypothyroidism</td>
<td>Monitor TSH and free T4 at baseline, every 2–3 months, and on developing relevant symptoms. Initiate hormone replacement as indicated.</td>
</tr>
<tr>
<td>Endocrine/metabolic: Hypogonadism/hypopituitarism</td>
<td>Monitor symptoms (e.g., erectile dysfunction, fatigue, loss of muscle mass), and check testosterone level with consideration of testosterone replacement therapy as indicated.</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>No dosage adjustment for grade 1 or 2 changes. Initiate appropriate lifestyle (exercise, diet, limiting alcohol consumption) and pharmacologic interventions. Withhold treatment for grade 3 toxicity. Reinitiate at a lower dose when baseline or grade 2</td>
</tr>
<tr>
<td>Hypertriglyceridermia</td>
<td>No dosage adjustment for grade 1 or 2 changes. Initiate appropriate lifestyle changes and pharmacologic interventions. Correct concomitant hypothyroidism. Withhold treatment if &gt; 800 mg/dL because of the risk of pancreatitis. Fenofibrate or rosuvastatin should be initiated, regardless of baseline lipid profile, 1 week before starting treatment. Increase monitoring with the use of alternative statins metabolized by CYP3A4. Correct for concomitant hypothyroidism. Dose reductions may be needed.</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>Monitor fasting blood glucose and A1C closely. No dosage adjustment for grade 1 or 2 changes. Initiate lifestyle changes. Initiate or adjust antidiabetic medications. Withhold treatment for grade 3 toxicity. Resume at a lower dose on improvement to grade 2. Consider permanent discontinuation for a grade 4 event.</td>
</tr>
<tr>
<td>Drug Class/Target (Medications)</td>
<td>Managementa</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td><strong>Hypoglycemia</strong></td>
<td></td>
</tr>
<tr>
<td>Multikinase angiogenesis inhibitors (axitinib, sorafenib, pazopanib, sunitinib, vandetanib, ponatinib)</td>
<td>Fasting blood glucose levels of patients on antidiabetic medications should be closely monitored. Dose reduction or discontinuation of antidiabetic agents may be required. No dosage adjustment for grade 1 or 2 changes. Withhold treatment for grade 3 or symptomatic grade 2 toxicity and discontinue antidiabetic agents. Resume at same dose when fasting glucose ≤ grade 1. For recurrent toxicity or if toxicity occurred in the absence of antidiabetic agents, reinitiate at a lower dose when fasting glucose &lt; grade 1. Discontinue for persistent grade 3 or symptomatic grade 2 toxicity.</td>
</tr>
<tr>
<td>Multikinase Abl inhibitors (imatinib, dasatinib, ponatinib)</td>
<td></td>
</tr>
<tr>
<td>RXR agonist (bexarotene)</td>
<td>Fasting blood glucose levels of patients on insulin should be closely monitored and the insulin dose adjusted as necessary.</td>
</tr>
<tr>
<td>Multikinase angiogenesis inhibitors (regorafenib, sorafenib, axitinib, vandetanib, cabozantinib, pazopanib, cabozantinib, ponatinib)</td>
<td>Withhold for ANC &lt; 5000 cells/mm³ until ANC 1000 cells/mm³ and platelet count 100,000/mm³. Resume treatment at same dose in general if recovery occurs within 1–2 weeks. Risk of toxicity with vandetanib, lenalidomide, and ruxolitinib is increased in patients with impaired renal function. For lenalidomide and pomalidomide, dose reduction is implemented on resumption of treatment if cytopenia occurs within the first 4 weeks of initial therapy. For prolonged cytopenia, reduce dose on count recovery. If cytopenia recurs, further reduce dose. See specific product labeling instructions for lenalidomide, pomalidomide, and ruxolitinib.</td>
</tr>
<tr>
<td>mTOR inhibitors (everolimus)</td>
<td></td>
</tr>
<tr>
<td>Multikinase Abl inhibitors (imatinib, nilotinib, bosutinib, dasatinib, ponatinib)</td>
<td></td>
</tr>
<tr>
<td>BTK inhibitor (ibrutinib)</td>
<td></td>
</tr>
<tr>
<td>JAK inhibitors (ruxolitinib)</td>
<td></td>
</tr>
<tr>
<td>RXR agonist (bexarotene dose-dependent effect)</td>
<td></td>
</tr>
<tr>
<td>Immunomodulatory agents (thalidomide, lenalidomide, pomalidomide)</td>
<td></td>
</tr>
<tr>
<td>Pure androgen receptor inhibitor (enzalutamide)</td>
<td></td>
</tr>
</tbody>
</table>

| **Thrombocytopenia** | | |
| Multikinase angiogenesis inhibitors (sorafenib, axitinib, vandetanib, regorafenib, pazopanib, cabozantinib, pazopanib, ponatinib) | Withhold until ANC > 1000 cells/mm³ and platelet count ≥ 500,000/mm³. Resume treatment at same dose in general if recovery occurs within 1–2 weeks. Risk of toxicity with vandetanib, lenalidomide, and ruxolitinib is increased in patients with impaired renal function. For lenalidomide, dose reduction is implemented on resumption of treatment if cytopenia occurs within the first 4 weeks of initial therapy. For prolonged cytopenia, reduce dose on count recovery. If cytopenia recurs, further reduce dose. See specific product labeling for platelet count–based dosing of ruxolitinib. |
| mTOR inhibitors (everolimus) | | |
| Multikinase Abl inhibitors (imatinib, nilotinib, bosutinib, dasatinib, ponatinib) | | |
| BTK inhibitor (ibrutinib) | | |
| JAK inhibitors (ruxolitinib) | | |
| Immunomodulatory agents (thalidomide, lenalidomide, pomalidomide) | | |

aProposed are general management approaches. See each individual product label for more specific guidelines.
bData for erlotinib applicable to gefitinib as well.
cData partly from retrospective series for hypoglycemia from multikinase Abl inhibitors.
dAbiraterone in combination with prednisone.

Abl = Abelson; AE = adverse effect; ALK = anaplastic lymphoma kinase; BP = blood pressure; BRAF = B-rapidly accelerated fibrosarcoma; BTK = Bruton tyrosine kinase; CTC = common toxicity criteria; EGFR = epidermal growth factor receptor; HER2 = human epidermal growth factor receptor 2; HZV = herpes zoster virus; IV = intravenous(ly); JAK = Janus kinase; mTOR = mammalian target of rapamycin; PI3K = phosphoinositide 3-kinase; RAF = rapidly accelerated fibrosarcoma; RET = rearranged during transfection; RVO = retinal vein occlusion; RXR = retinoid X receptor; SMO = smoothened; T4 = thyroxine; TSH = thyroid-stimulating hormone; ULN = upper limit of normal; VEGF = vascular epidermal growth factor receptor.

Adapted with permission from: Dy GK, Adjei AA. Understanding, recognizing and managing toxicities of targeted anticancer therapies. CA Cancer J Clin 2013;63:249-79.
for signs of infection. Patients should be instructed that a fever or signs of infection will require them to contact the health care team immediately for evaluation. Fever is defined as a body temperature above 38.3°C (101°F) or a temperature above 38°C (100.4°F) for more than 1 hour. The patient with a fever and/or signs of infection should be evaluated by a health care professional, receive a complete physical examination, and undergo laboratory tests. Cultures can be obtained.

With oral chemotherapy, the nadir may be delayed because dosing is not “bolus” but continuous; a low WBC may go undetected if a complete blood cell count (CBC) is not closely monitored. For example, recommendations for lenalidomide therapy are to monitor CBC weekly for the first 8 weeks in patients with myelodysplasia; and monitor every other week for the first 12 weeks, then monthly thereafter, in patients with multiple myeloma.

Anemia and thrombocytopenia are rare with oral chemotherapy alone but more common when it is combined with traditional chemotherapy. Patients at risk should be counseled on anemia and bleeding, as well as when to contact the health care team. For example, when nilotinib is prescribed, patients should undergo CBC monitoring every 2 weeks for the first 2 months and monthly thereafter.

Cardiovascular Effects

The targeted agents that affect vascular epidermal growth factor receptor (VEGFR) can increase blood pressure, resulting in hypertension and, rarely, reversible posterior leukoencephalopathy syndrome. Stimulation of VEGFR2 regulates vasodilation through nitric oxide activation; inhibition of this target is believed to be responsible for hypertension. Typically, hypertension develops during the first 18 weeks. Close monitoring of blood pressure before initiating therapy is warranted, as is following current standards for hypertension (e.g., lifestyle and dietary modifications, tailored drug therapy for comorbid conditions) during therapy (Hedhli 2011).

Human epidermal growth factor receptor 2 (HER2) modification by the oral agent lapatinib can cause decreased left ventricular ejection fraction (LVEF); however, this effect is much less common than with the monoclonal antibodies affecting HER2. This may partly be secondary to a cardioprotective effect from kinase 5’-adenosine monophosphate–activated protein (AMPK) activation with lapatinib. Left ventricular dysfunction is associated with the VEGF and Abelson (Abl) kinase drugs. Sunitinib is associated with an off-target AMPK inhibition, which may contribute to its cardiotoxicity because restoring AMPK results in less cardiomyocyte toxicity (Dy 2013; Dasanu 2012).

The targeted agents that affect Abl kinase are associated with significant edema. Although edema was originally proposed to be the cause of decreased LVEF in patients receiving imatinib, newer data suggest that a decline in cardiomyocyte contractility results in decreased LVEF. Close monitoring of patients who have preexisting cardiac disease or who develop significant edema is recommended. Imatinib edema is typically periorbital, especially in the morning; later in the day, edema is more likely in dependent areas. Agents affecting the mitogen extracellular signal regulated kinase (MEK) and mesenchymal-epidermal transition (MET) pathways are also commonly associated with edema and weight gain. Edema may be secondary to the changes in LVEF that can occur with these agents (Dy 2013).

Crizotinib causes sinus bradycardia in about 19% of patients, which may be a marker for higher response rate, as presented in an abstract of a retrospective review evaluating a single center’s experience (Ou 2013). Reports of QT prolongation with several of the oral chemotherapy agents warrant baseline assessment when initiating therapy. In addition, electrolyte abnormalities (particularly hypokalemia and hypomagnesemia) can occur with several agents, especially those that cause significant diarrhea. When using agents that may exacerbate the effects on the QT interval, baseline electrocardiogram (ECG), with careful monitoring of ECG and electrolytes, is necessary. Attempts should be made to minimize other agents that affect the QT interval (e.g., certain antibiotics and antiarrhythmic agents) (Dy 2013; Dasanu 2012). For example, the recommendation for nilotinib is to obtain a baseline ECG, monitor for hypokalemia and hypomagnesemia, and correct any electrolyte disturbances before initiating therapy. The nilotinib recommendations include rechecking the ECG 7 days after initiating therapy and periodically as clinically indicated or with dosage adjustments.

An increased risk of thrombophlebitis and deep venous thrombosis (DVT) is associated with the hormonal therapies and antiangiogenesis agents. Although routine prophylaxis for DVT is not recommended in patients with cancer receiving chemotherapy or hormonal therapy, prophylaxis for DVT is recommended when using thalidomide and lenalidomide, low-molecular-weight heparin (e.g., enoxaparin 40 mg subcutaneously daily), or aspirin 81–325 mg daily (Lyman 2013). Patients must be counseled to assess for signs and symptoms of a DVT.
and to contact the health care team immediately for an evaluation.

Arterial thrombosis and arterial ischemia are reported with VEGF inhibitors in less than 2% of patients. Of note, the risk of serious hemorrhage is at least as high as the risk of thrombosis. Vascular epidermal growth factor inhibitors should be avoided in patients with active bleeding, or at higher risk of bleeding, and should temporarily be held before major surgery and immediately afterward.

**Pulmonary Effects**

Pneumonitis is often reported with mammalian target of rapamycin (mTOR) inhibitors, which may correlate with treatment response or stable disease in clear cell renal cancer. Patients should be monitored every 12 weeks with a computed tomography (CT) scan and spirometry testing. Presenting symptoms include cough and dyspnea; these typically occur in the first 6 months of therapy, although lung changes can be detected in 2 months by radiography. Ruling out infectious causes is important, particularly in patients receiving mTOR agents, which are highly immunosuppressive. Because this toxicity has been associated with response in some reports of metastatic renal cell carcinoma, the current recommendation is to continue therapy and closely monitor the patient with mild symptoms. However, if moderate symptoms develop, reducing the dosage and perhaps adding steroids may be necessary. Severe symptoms are managed with drug discontinuation, corticosteroids, and supportive therapy (Mendez-Vidal 2012).

Dasatinib commonly causes pleural effusions. The incidence of effusions is related to the dose and the frequency of dasatinib administration. This toxicity should be managed with corticosteroids and dose interruption. Dasatinib is rarely associated with pulmonary hypertension, in which drug discontinuation is recommended. For other agents associated with pulmonary toxicity, see Table 4-2.

**Metabolic/Endocrine Effects**

Hypothyroidism is the most common endocrine abnormality seen with multikinase inhibitors. Patients taking thyroid supplements upon initiation of axitinib, sorafenib, imatinib, sunitinib, or bexarotene should be monitored early because altered thyroid-stimulating hormone levels are reported with only 2 weeks of therapy. With bexarotene, newly developed hypothyroidism is expected in each patient; therefore, levothyroxine supplementation should be initiated with therapy, together with close monitoring.

Hypophosphatemia from the mTOR inhibitors is hypothesized to arise from renal tubular phosphate losses, without alterations in parathyroid hormone levels. Monitoring is suggested, together with phosphate supplementation when hypophosphatemia occurs (Mendez-Vidal 2012).

In men receiving crizotinib, central hypogonadism is reported early in therapy (typically 2–3 weeks). The effects are reversible upon discontinuation; however, other management strategies have not been studied. In a retrospective report, 10 of 19 patients with crizotinib-induced low testosterone were treated with topical gel testosterone and saw levels return to the normal range (Weickhardt 2012).

Adrenal insufficiency is a concern with abiraterone; therefore, this agent is always administered with prednisone. Patients should be closely monitored. Infection, stress, or nonadherence to prednisone may precipitate adrenal insufficiency.

Hyperglycemia is reported with the mTOR inhibitors, pazopanib, and dabrafenib. It is believed that hyperglycemia, a common ADE, is caused by prevention of beta-cell adaptation to hyperglycemia. Treatment is not yet standardized, although diet, exercise, and oral antidiabetic agents are considered first line. An ASCO guideline states how to manage hyperglycemia and hyperlipidemia related to the mTOR inhibitors; it suggests daily monitoring of fasting glucose, diet, and exercise for grade 1 or 2 toxicity, and adding oral antidiabetic agents or insulin for symptomatic or serious elevations in blood glucose (Busaidy 2012). Abiraterone with prednisone also causes a high incidence of hyperglycemia. Of interest, improvements in glucose level have been reported with multikinase inhibitors such as dasatinib, imatinib, sorafenib, and sunitinib. Close monitoring of blood glucose is warranted in patients with diabetes.

Hypercholesterolemia and hypertriglyceridemia are associated with mTOR inhibitors, retinoids, pazopanib, and abiraterone and can be managed with statins, nico-tinic acid, and fibrates.

**Gastrointestinal Effects**

Nausea and vomiting are obvious concerns in patients taking oral chemotherapy. Although more common with parenteral bolus-administered chemotherapy, nausea can still occur with oral therapy. Paying attention to the recommended times of administration can minimize nausea. When this strategy is inadequate, pretreating with antiemetics should be tried.

Lapatinib, particularly in combination with capecitabine, mTOR inhibitors, EGFR inhibitors, and multikinase Abl inhibitors, has been associated with mucositis. This ADE, which is managed with supportive care, can greatly affect patient quality of life. Withholding therapy until resolution may be required.

Diarrhea is common with targeted therapy; it is important to recognize symptoms early, rule out infection, and manage this condition with antidiarrheals. Grade 3 diarrhea, defined as seven or more bowel movements per day above normal, requires evaluation by a health care provider. In addition, persistent diarrhea warrants monitoring and treatment. Monitoring and managing
electrolyte disturbances is important, especially with agents that prolong the QT interval.

Elevations in liver function tests are common with almost all TKIs; therefore, a baseline evaluation of liver function, as well as screening for viral hepatitis and periodic monitoring, is required.

### Skin and Subcutaneous Tissue Effects

Skin manifestations are among the most common ADEs of targeted and traditional oral chemotherapy; they can be troubling to patients, adversely affect quality of life, and even be life threatening when severe alterations to the skin barrier occur. Most notable are the on-target effects of the EGFR inhibitors, which result in papulopustular exanthemas in up to 90% of patients. These reactions typically appear on the head and upper trunk during the first 1–3 weeks of therapy. The acneiform rash is believed to be inflammatory. Orally administered tetracyclines can prevent rash, probably through anti-inflammatory properties. Treatment includes good face hygiene, avoidance of sun exposure, and the use of topical corticosteroids, topical antibiotics (for bacterial overgrowth), and tetracyclines; these have been evaluated in clinical trials to substantiate their efficacy. With prolonged EGFR use of, the rash often decreases (Robert 2012; Gutzmer 2011).

With longer EGFR inhibitor treatment (1–3 months), dry skin develops, often accompanied by pruritus and photosensitivity. Xerosis can particularly affect the fingertips and heels, where painful fissures may develop. These are treated with vitamin A– or urea-based ointments (Robert 2012).

Agents that affect rapidly accelerated fibrosarcoma (RAF), particularly B-rapidly accelerated fibrosarcoma (BRAF), are noted to cause a downstream up-regulation of mitogen-activated protein kinase, which enhances hyperkeratosis, and cutaneous squamous cell carcinoma. Close monitoring upon therapy initiation is needed because these effects manifest early during treatment. Treatment with RAF can continue if the patient is monitored and cutaneous lesions are promptly treated (e.g., resection).

Rare but serious skin reactions such as toxic epidermal necrolysis and Stevens-Johnson syndrome have been reported with oral chemotherapy and targeted

---

**Table 4-3. Recommendations for Contraception with Oral Chemotherapy**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Contraception Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abiraterone</td>
<td>Pregnant women handling medication should wear gloves; men having intercourse with women of childbearing potential should use barrier protection (condoms) for the duration of therapy and at least 1 week after the last dose</td>
</tr>
<tr>
<td>Crizotinib</td>
<td>Men and women should use contraception during and for 90 days after the last dose</td>
</tr>
<tr>
<td>Dabrafenib</td>
<td>Use nonhormonal contraception during and at least 4 weeks after the last dose (dabrafenib interferes with plasma levels of hormonal contraceptives, rendering them ineffective)</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>Men and women should use contraception during use</td>
</tr>
<tr>
<td>Enzalutamide</td>
<td>Use condoms with reliable contraception during therapy and for 3 months after the last dose</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>Use highly effective contraception during therapy and for at least 2 weeks after the last dose</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>REMS program. Use two effective contraceptives. Men taking lenalidomide must wear a condom during intercourse with women of childbearing potential. Report any suspected fetal exposure to lenalidomide to the FDA MedWatch program</td>
</tr>
<tr>
<td>Pomalidomide</td>
<td>REMS program. Pregnancy must be excluded before therapy. Use two effective contraceptives during and for 4 weeks after the last dose</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>Men and women must use effective contraception during and for at least 2 weeks after the last dose</td>
</tr>
<tr>
<td>Vandetanib</td>
<td>Women must use adequate contraception before and during use and at least 4 months after the last dose</td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>Women must use adequate contraception during use and for at least 2 months after the last dose</td>
</tr>
<tr>
<td>Vismodegib</td>
<td>Pregnancy status must be verified within 7 days before initiating therapy. A highly effective form of contraception must be initiated before the first dose and be continued during therapy and for 7 months after the last dose. Men must wear a condom and use spermicide during therapy and for at least 2 months after the last dose</td>
</tr>
</tbody>
</table>

FDA = U.S. Food and Drug Administration; REMS = Risk Evaluation and Mitigation Strategies.
agents. Serious rashes must be reported to the oncology team immediately, and therapy must be discontinued.

Multikinase inhibitors (particularly sorafenib, sunitinib, and pazopanib) are responsible for palmar-plantar erythrodysesthesia. The reaction differs from traditional chemotherapy-related reactions, typically manifesting as more localized blisters and early development of hyperkeratosis. Self-care strategies include avoiding hot water to shower or wash hands, wearing loose-fitting shoes, and using emollients to keep skin moist. There is no proven effective therapy to manage reactions; however, supportive care options for prevention are also recommended for treatment. Use of urea-based emollients and salicylate-based creams may assist with hyperkeratosis (Robert 2012). Patients should be referred to podiatry services familiar with therapy-related toxicity.

The targeted therapies associated with hair loss include vismodegib and agents affecting BRAF and VEGF. The EGFR inhibitors are often overlooked as causing changes in hair (e.g., alopecia) or hair texture (e.g., straw-like fine hair), which typically appear after 2–3 months of therapy. Texture changes (e.g., drier, curlier hair) occur with the VEGF inhibitors. Agents affecting c-kit (e.g., sunitinib, pazopanib) can cause depigmentation of the hair and the skin that is reversible on discontinuation (Dy 2013).

Ophthalmic Effects

Ocular toxicities from chemotherapy are usually not well described or reported. Imatinib and nilotinib are associated with conjunctivitis, periorbital edema, and dry eye. Vemurafenib causes uveitis, iritis, and retinal vein occlusion. Crizotinib can cause delayed light adaptation, typically within 2 weeks of beginning therapy; however, this does not require treatment alteration or discontinuation (Camidge 2012; Renouf 2012; Singh 2012).

Fetal Risk

All chemotherapy agents are associated with fetal harm; most of the new agents are FDA pregnancy category D. Enzalutamide, lenalidomide, pomalidomide, and thalidomide are pregnancy category X. Lenalidomide and pomalidomide, similar to thalidomide, have Risk Evaluation and Mitigation Strategies programs. Particular concerns are associated with the VEGF inhibitors because angiogenesis is critical during fetal development. Likewise, the hedgehog pathway is critical during embryonic development. Specific recommendations with respect to contraception are provided in Table 4-3.

Conclusion

Changes to practice in community and ambulatory pharmacy have not kept pace with the increased prescribing of oral chemotherapy. Safe-practice standards in the medication use process for oral chemotherapy are available but have not been fully implemented. Newer practice guidelines also show that a substantial change is needed to ensure the safety of health care workers, patients, and caregivers who are exposed to oral chemotherapy.

Although evidence is still emerging regarding adherence to oral therapy, much work remains to ensure that patients are taking drugs correctly and safely. Counseling is vital to ensure that patients understand the proper timing, as well as the expected adverse events, together with how to self-manage any untoward effects, and when to contact the oncology team. Contacting with the patient around the usual times that ADEs emerge is recommended to enhance adherence and management (Huynh 2012). Pharmacists play a vital role in ensuring that patients understand their

**Practice Points**

When dispensing and counseling on oral chemotherapy, the optimal practice should include the following considerations to ensure the safety and efficacy of therapy:

- The dispensing process should include the same safety measures that are used with injectable chemotherapy. Verifications of regimen, and dosing, together with a double check of all aspects of the dispensing, must be conducted.
- To ensure the protection of health care staff members who handle oral chemotherapy, safety measures using PPE are recommended, similar to the practices used with injectable agents.
- Discussions on the safety of oral chemotherapy in the home should include proper handling and disposal of chemotherapy to prevent unnecessary exposure by caregivers and family members.
- Counseling is an integral aspect of oral chemotherapy. Counseling must include when and how to contact the oncology team. Counseling must review common adverse events, together with serious events. A review of when to start and stop therapy, as well as the timing of administration with respect to meals, is also important.
- Counseling should include the teach-back method to ensure that patients and caregivers understand instructions.
- Because oral chemotherapy relies on the patient and caregiver to administer it properly, adherence is an important aspect to assess and encourage throughout treatment.
treatment plan, safely handle and administer their chemotherapy drugs, and collaborate with the health care team to prevent chemotherapy-associated toxicity.

**References**


BC Cancer Agency [www.bccancer.bc.ca/]. *Drug Index (patient)*.


Chemocare.com. *Care During Chemotherapy and Beyond* [www.chemocare.com/]. Drug Information.


Siden R, Kem R, Ostrenga A, et al. *Templates of patient brochures for the preparation, administration and safe-handling of...


SELF-ASSESSMENT QUESTIONS

61. Which one of the following best exemplifies safe oral chemotherapy prescription instructions?
   A. Take 300 mg orally on days 1–3 of therapy.
   B. Take 3 capsules orally twice daily for 5 consecutive days.
   C. Take a 50-mg tablet once daily for 21 days.
   D. Take 25 mg orally once daily for 14 consecutive days beginning on day 1.

62. When drafting a policy for nursing administration of oral chemotherapy within the hospital during an inpatient admission, which one of the following is most important to include?
   A. Store the oral chemotherapy separately from the patient’s other home drugs.
   B. Wear personal protective equipment during administration.
   C. Family caregivers are instructed on how to safely handle the drugs.
   D. Generic and brand names are included on the prescription.

63. Which one of the following is most likely to improve oral chemotherapy safety?
   A. The same safety checks completed for parenteral chemotherapy are used for oral chemotherapy processing.
   B. Verbal orders from providers are permitted to clarify a dose adjustment when treating an adverse drug reaction.
   C. Pharmacists dispensing oral chemotherapy use a separate counting tray and use alcohol-based wash on hands to disinfect before and after contact with chemotherapy.
   D. Patients are encouraged to bring their medication to each clinic visit to monitor adherence.

64. A patient with metastatic renal cell carcinoma and a history of hypertension and type 2 diabetes mellitus is prescribed everolimus 10 mg orally once daily. When refilling his prescription, you note that he is purchasing over-the-counter oral mouth care. After further questioning, you suspect he has developed oral candidiasis. Which one of the following is the best next step in managing this patient’s care?
   A. Facilitate effective glucose monitoring, and contact the patient’s oncology provider to recommend prescribing a course of oral clotrimazole and a patient follow-up.
   B. Check the patient’s blood pressure, reinforce effective glucose monitoring, and review proper oral care.
   C. Facilitate effective glucose monitoring, and contact patient’s primary care physician about initiating an azole for treatment of his candidiasis.
   D. Counsel the patient on preventing infection; identify signs and symptoms of infection during treatment; and encourage follow up with his primary care provider to investigate.

65. You are counseling a patient and/or caregiver on a new oral chemotherapy prescription. Which one of the following is best to include in your discussion and in written form?
   A. Indication for medication use (e.g., cancer disease state).
   B. Medication name (generic and brand), dose, and schedule.
   C. Identification of patient’s next follow-up appointment.
   D. Plan for refilling medications.

66. When counseling a 32-year-old woman who is prescribed vismodegib, which one of the following information points regarding safety would be most important to emphasize?
   A. Information regarding contraception.
   B. Proper administration with respect to meals.
   C. Drug interactions with phenytoin.
   D. Discuss the start and stop date for each cycle.

67. You work for a large clinic of several group practices that manages more than 1000 oncology patients each year. You are asked to design a study that identifies medication errors related to oral chemotherapy administration. Which one of the following methods is best to meet the objective?
   A. Create a survey for the clinic staff designed to recall errors that have occurred in their practice.
   B. Design a structured interview questionnaire for staff to administer to patients regarding medication administration.
   C. At one group practice, train staff to counsel patients regarding administration; compare with a control group practice of similar patients and no specialized training.
   D. Survey several clinics in the region to report the administration errors identified.
68. You are asked to design a protocol for a pharmacy connected to the clinic you practice in for dispensing oral chemotherapy. Which one of the following is most important to consider when designing your policy for your clinic practice?

A. Identify the most common cancers treated in the clinic to ensure the correct drugs are stocked within the pharmacy.
B. Ensure that pharmacy staff are educated on oral chemotherapy agents and interested in working with patients with cancer.
C. Review the current standards published by the Institute for Safe Medication Practices, and tailor these to your space, design, and local practice.
D. Review the written materials for patient education (e.g., Chemocare.org, British Columbia Cancer Agency) to determine which source is best for your patient population.

69. Which one of the following most appropriately represents oral chemotherapy medication safety best practice?

A. Patient is instructed to store the medication with other medications at home to ensure proper handling.
B. The patient or caregiver is provided written instructions on how to compound the medication at home.
C. When adverse events occur, changes to dosing are communicated verbally to the pharmacist in person.
D. Licensed independent practitioner obtains informed consent prior to prescribing oral chemotherapy.

70. Which one of the following medications is most likely to be associated with dosing errors in the administration phase of the medication use process?

A. Axitinib.
B. Nilotinib.
C. Regorafenib.
D. Bosutinib.

Questions 71 and 72 pertain to the following case.
J.R. is a 51-year-old man with newly diagnosed metastatic anaplastic lymphoma kinase gene rearrangement adenocarcinoma of the lung. His performance status is 2. He is given a prescription to begin crizotinib 250 mg orally twice daily and attends the pharmacy clinic today to learn more about the medication.

71. Which one of the following is most important to review with J.R. at his first visit?

A. Download the latest patient version of information on crizotinib from chemocare.org; suggest he review the information and call if he has any questions.
B. Provide J.R. with a calendar on when to begin crizotinib, assist him in setting automatic reminders into his smartphone, and arrange to follow up with him in 1 week.
C. Discuss with J.R. the ADEs of crizotinib, and tell him when to contact the oncology team if any problems occur.
D. Discuss with J.R. the role of crizotinib in his cancer; tell him how to take the medication and explain its major ADEs; and give him an information sheet on crizotinib and the clinic telephone number.

72. Two weeks after beginning therapy, J.R. calls you because he is experiencing extreme fatigue. Which one of the following laboratory tests would best determine the most likely cause of J.R.’s symptoms?

A. Serum testosterone.
B. Serum calcium.
C. Liver function tests.
D. Thyroid-stimulating hormone.

Questions 73–75 pertain to the following case.
M.K. is a 75-year-old man undergoing treatment for advanced prostate cancer. He and his daughter visit the oncology clinic today to discuss beginning abiraterone with prednisone for his prostate cancer. M.K. has some mild dementia, and he lives with his daughter’s family, which consists of her husband and two daughters, 4 and 7 years of age. His daughter assists him with his care needs.

73. Which one of the following is the best strategy for administering abiraterone?

A. Contact M.K.’s provider to suggest alternative therapy because he lives with his granddaughters.
B. M.K.’s daughter should wear gloves when touching the medication as well as a protective gown and mask.
C. M.K. and his daughter agree that M.K. will self-administer from a safety cap bottle while she supervises. M.K. will wash his hands after touching the medication.
D. M.K. can place the medication in the pillbox each week, with his daughter supervising. M.K. should wear gloves when handling the medication.

74. Which one of the following is best to emphasize regarding M.K.’s new medication to prevent adverse events?
A. Take capsule once daily. Do not crush or chew. Swallow capsule whole.
B. Take medication on an empty stomach 2 hours before or 1 hour after meals once daily.
C. Take this medication at the same time with prednisone daily.
D. Take this medication in the evening to avoid fatigue.

75. M.K. calls you at the clinic to let you know that when his daughter monitored his blood pressure the past few days, the readings were as follows: 198/70 mm Hg, 190/72 mm Hg, and 204/84 mm Hg. His heart rate is 74 beats/minute, according to his daughter. Which one of the following would be best to assess in M.K.?

A. Fluid status, serum electrolytes.
B. Liver function tests, renal function.
C. Echocardiogram (ECHO), ECG.
D. Head CT scan, renal function.

Questions 76 and 77 pertain to the following case.

P.P. is a 58-year-old woman with advanced lung cancer. She is the CEO of the local bank and actively seeks online information about her disease and treatments. P.P. is prescribed erlotinib 150 mg daily starting on day 1.

76. P.P. comes to the clinic for counseling as she begins her new prescription for erlotinib. Which one of the following would best improve adherence for P.P.?

A. Use the teach-back method.
B. Discuss that rash correlates highly with efficacy.
C. Provide written instructions and useful Web sites.
D. Discuss best methods to prevent rash.

77. Which time intervals would be best for P.P. to contact the clinic regarding how therapy is going and discuss potential ADEs and management?

A. Day 1 of therapy; days 7, 14, and 21; and monthly.
B. Day 1 of therapy, then weekly thereafter.
C. Monthly.
D. During scheduled clinic visits every 12 weeks.

Questions 78–80 pertain to the following case.

B.C. is a 61-year-old man who worked as a car mechanic until 6 months ago. He just received a diagnosis of inoperable advanced hepatocellular carcinoma. He received a diagnosis of cirrhosis 4 years ago. His Child-Pugh score is 6. Vital signs include temperature 36.4°C (97.6°F), heart rate 70 beats/minute, blood pressure 138/86 mm Hg, respiratory rate 16 breaths/minute, and pulse oxygenation 93% on room air. B.C. used to drink alcohol (6 or more drinks per night reported), but he quit 4 years ago. He smokes six cigarettes per day, down from 2 packs/day a year ago, and has an 80 pack-year history. His current drugs include furosemide 20 mg daily, hydrochlorothiazide 25 mg daily, fluticasone/salmeterol inhaler 250/50 1 inhalation twice daily, albuterol inhaler as needed, tiotropium 1 inhalation daily, citalopram 20 mg daily, and pantoprazole 40 mg daily.

78. The oncologist would like to initiate treatment with sorafenib. Which one of the following is best to order before B.C. begins therapy?

A. No tests necessary; blood pressure is controlled.
B. Baseline ECHO.
C. Baseline pulmonary function test.
D. Baseline multigated acquisition scan.

79. B.C. is able to begin taking sorafenib, and he calls you today to discuss the tingling in his hands. He still works with cars when he can, and yesterday, he was rotating the tires on his wife’s car. He wears his leather gloves for most activities. He describes small, red, swollen areas on his hand. He followed the instructions you provided him before beginning therapy. Which one of the following is best to advise B.C.?

A. Reduce the sorafenib dose by 50%.
B. Apply urea cream to hands three times daily.
C. Apply topical hydrocortisone to hands twice daily.
D. Soak hands in warm baths twice daily.

80. B.C. followed your instructions and his symptoms improved. Now 2 months into therapy, he calls today to discuss his diarrhea. He has had 6 loose bowel movements each day for the past 2 days, but he has not taken anything for his symptoms. He says he feels okay, is able to eat well, and is drinking extra water today. His wife checks his blood pressure at home, and it is 138/88 mm Hg today. Which one of the following is best to recommend for B.C.?

A. Instruct him to go to the emergency department for further evaluation of his symptoms.
B. Instruct him to begin loperamide 2 mg every 4 hours, drink a sports drink containing low glucose and electrolytes, and come to the clinic for evaluation.
C. Stop sorafenib and begin intravenous fluids and octreotide 100 mcg subcutaneously every 8 hours.
D. Stop sorafenib and begin loperamide 4 mg now and 2 mg every 2 hours until diarrhea is controlled for 12 hours.
Chronic Illnesses III
**Long-term Management After Kidney Transplantation**

**Authors**

Steven Gabardi, Pharm.D., FCCP, BCPS  
*Abdominal Organ Transplant Clinical Specialist*  
Departments of Transplant Surgery and Pharmacy Services  
Brigham and Women's Hospital  
*Assistant Professor of Medicine*  
Department of Medicine  
Harvard Medical School  
Boston, Massachusetts

Christin Rogers, Pharm.D., FCCP, BCPS  
*Clinical Pharmacy Coordinator, Solid Organ Transplant*  
Beth Israel Deaconess Medical Center  
Boston, Massachusetts

**Reviewers**

Megan S. Pickard, Pharm.D., BCPS  
*Clinical Pharmacist, Solid Organ Transplant*  
Department of Pharmacy  
Baylor University Medical Center  
Dallas, Texas

Jaime A. Foushee, Pharm.D., BCPS  
*Assistant Professor*  
Department of Pharmacy Practice  
Presbyterian College School of Pharmacy  
Clinton, South Carolina  
*Clinical Pharmacy Specialist and Adjunct Faculty Member*  
Family Medicine Residency Program  
Self Regional Healthcare  
Greenwood, South Carolina

---

**Management of Patients on Dialysis**

**Author**

Neeta Bahal O’Mara, Pharm.D., BCPS  
*Clinical Pharmacist*  
Dialysis Clinic, Inc.  
North Brunswick, New Jersey

**Reviewers**

Amy Barton Pai, Pharm.D., FCCP, FASN, BCPS  
*Associate Professor*  
Department of Pharmacy Practice  
Albany College of Pharmacy and Health Sciences  
Albany, New York

Diane M. Erdman, Pharm.D., BCPS, BCACP, CDE, CPPS  
*Clinical Pharmacy Manager – Specialty*  
*PGY1 Managed Care and PGY2 Ambulatory Care Residency Program Director*  
Department of Pharmacy  
Kaiser Permanente - Georgia  
Atlanta, Georgia
Biologic Therapies for Gastrointestinal Diseases

Authors
Rima A. Mohammad, Pharm.D., BCPS
Clinical Assistant Professor
Department of Clinical, Social and Administrative Sciences
University of Michigan College of Pharmacy
Clinical Pharmacist
Department of Pharmacy Services
University of Michigan Health System
Ann Arbor, Michigan

Michael A. Smith, Pharm.D., BCPS
Assistant Professor of Clinical Pharmacy
Department of Pharmacy Practice
and Pharmacy Administration
Philadelphia College of Pharmacy
University of the Sciences
Philadelphia, Pennsylvania

Reviewers
Lisa S. Smith, Pharm.D., BCPS
Assistant Dean of Faculty Development
Associate Professor of Pharmacy
Wingate University School of Pharmacy
Wingate, North Carolina

Abigail M. Yancey, Pharm.D., BCPS
Associate Professor
Department of Pharmacy Practice
St. Louis College of Pharmacy
St. Louis, Missouri

The American College of Clinical Pharmacy and the authors thank the following individuals for their careful review of the Chronic Illnesses III chapters:

Jeffrey T. Sherer, Pharm.D., MPH, BCPS
Clinical Associate Professor
Department of Clinical Sciences and Administration
University of Houston College of Pharmacy
Houston, Texas

Dale Whitby, Pharm.D., BCPS
Managing Editor, Clinical Content
Elsevier/Gold Standard
Midlothian, Virginia

Mary Wun-Len Lee, Pharm.D., FCCP, BCPS
Vice President and Chief Academic Officer
Pharmacy and Health Sciences Education
Midwestern University
Professor of Pharmacy Practice
Midwestern University
Chicago College of Pharmacy
Downers Grove, Illinois
Learner Chapter Evaluation: Management of Patients on Dialysis.

As you take the posttest for this chapter, also evaluate the material’s quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

1. The content of the chapter met my educational needs.
2. The content of the chapter satisfied my expectations.
3. The author presented the chapter content effectively.
4. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
5. The content of the chapter was objective and balanced.
6. The content of the chapter is free of bias, promotion, or advertisement of commercial products.
7. The content of the chapter was useful to me.
8. The teaching and learning methods used in the chapter were effective.
9. The active learning methods used in the chapter were effective.
10. The learning assessment activities used in the chapter were effective.
11. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

12. Design an appropriate anemia treatment plan for a patient receiving dialysis.
13. Develop an appropriate target hemoglobin range in patients receiving dialysis using the most recent literature on chronic kidney disease (CKD).
14. Determine the most appropriate phosphate-binding medication for a patient on dialysis.
15. Evaluate the role of cinacalcet in the treatment of hyperparathyroidism in patients with CKD on dialysis.
16. Demonstrate an understanding of the roles of both native and active vitamin D in patients on dialysis.
17. Distinguish the role of FGF23 (fibroblast growth factor 23) in the pathophysiology of secondary hyperparathyroidism.
18. Please provide any specific comments relating to any perceptions of bias, promotion, or advertisement of commercial products.
19. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter:
Learner Chapter Evaluation: Management After Kidney Transplantation.

As you take the posttest for this chapter, also evaluate the material’s quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

1. The content of the chapter met my educational needs.
2. The content of the chapter satisfied my expectations.
3. The author presented the chapter content effectively.
4. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
5. The content of the chapter is objective and balanced.
6. The content of the chapter is free of bias, promotion, or advertisement of commercial products.
7. The content of the chapter was useful to me.
8. The teaching and learning methods used in the chapter were effective.
9. The active learning methods used in the chapter were effective.
10. The learning assessment activities used in the chapter were effective.
11. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

12. Distinguish the mechanisms of action, adverse reaction and drug-drug interaction profiles, and recommended monitoring principles for maintenance immunosuppressive agents.
13. Assess the risks of acute rejection and antibody-mediated rejection for the individual patient and evaluate treatment strategies.
14. Design appropriate therapeutic regimens for preventing and managing infectious cardiovascular and endocrine complications after transplantation.
15. Evaluate for the risk of malignancies after kidney transplantation, and compose treatment options for one of these complications.
16. Justify the importance of immunosuppressive drug adherence in transplantation, and demonstrate ways to predict and prevent nonadherence.
17. Please provide any specific comments relating to any perceptions of bias, promotion, or advertisement of commercial products.
18. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter:
Learner Chapter Evaluation: Biologic Therapies for Gastrointestinal Diseases.

As you take the posttest for this chapter, also evaluate the material’s quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

1. The content of the chapter met my educational needs.
2. The content of the chapter satisfied my expectations.
3. The author presented the chapter content effectively.
4. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
5. The content of the chapter was objective and balanced.
6. The content of the chapter is free of bias, promotion, or advertisement of commercial products.
7. The content of the chapter was useful to me.
8. The teaching and learning methods used in the chapter were effective.
9. The active learning methods used in the chapter were effective.
10. The learning assessment activities used in the chapter were effective.
11. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

12. Design evidence-based treatment regimens for the management of gastrointestinal disease, especially inflammatory bowel disease.
13. Distinguish the role of biologic therapies, including safety concerns, in the treatment of inflammatory bowel disease.
14. Evaluate appropriate treatment recommendations with health care providers regarding the use of biologic therapies in inflammatory bowel disease.
15. Justify important drug education with patients regarding the use of biologic therapies in the treatment of inflammatory bowel disease.

16. Please provide any specific comments relating to any perceptions of bias, promotion, or advertisement of commercial products.
17. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter:

Questions 18–20 apply to the entire learning module.

18. How long did it take you to read the instructional materials in this module?
19. How long did it take you to read and answer the assessment questions in this module?
20. Please provide any additional comments you may have regarding this module:
LEARNING OBJECTIVES

1. Design an appropriate anemia treatment plan for a patient receiving dialysis.
2. Develop an appropriate target hemoglobin range in patients receiving dialysis using the most recent literature on chronic kidney disease (CKD).
3. Determine the most appropriate phosphate-binding medication for a patient on dialysis.
4. Evaluate the role of cinacalcet in the treatment of hyperparathyroidism in patients with CKD on dialysis.
5. Demonstrate an understanding of the roles of both native and active vitamin D in patients on dialysis.
6. Distinguish the role of FGF23 (fibroblast growth factor 23) in the pathophysiology of secondary hyperparathyroidism.

INTRODUCTION

Stage 5 chronic kidney disease (CKD) is defined as kidney failure and a glomerular filtration rate (GFR) of less than 15 mL/minute/1.73m². At this stage, renal replacement therapy such as hemodialysis, peritoneal dialysis, or renal transplantation is usually needed. Hemodialysis can be performed in a health care setting (e.g., outpatient hemodialysis center) or at home. Most patients receiving hemodialysis do so in a health care setting; however, the number receiving hemodialysis at home is increasing. Peritoneal dialysis is performed by the patient in the home setting. Caring for patients on dialysis presents several challenges, including the management of CKD-associated diseases such as anemia and mineral and bone disorders (MBDs). This chapter reviews the treatment of anemia and MBDs in patients receiving dialysis.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- Basic physiology of red blood cell production
- Basic physiology of calcium-phosphorus homeostasis
- Interpretation of common laboratory values, including those involving anemia, calcium-phosphorus, and diabetes management

ADDITIONAL READINGS

The following free resources are available for readers wishing additional background information on this topic.

Anemia

Anemia is a common complication of CKD; its occurrence and severity vary with the degree of renal dysfunction. Anemia affects many patients early in the disease process and can increase cardiovascular morbidity, hospitalizations, and mortality. Despite the prevalence of anemia with dialysis, many patients do not receive adequate treatment of anemia before starting dialysis. A clear understanding of the causes and therapies used to treat anemia can improve patient care.

Kidney Disease: Improving Global Outcomes (KDIGO) is an independent, international foundation whose goal is to improve the care and outcomes of patients worldwide with kidney disease through the development and implementation of global clinical practice guidelines. In 2012, KDIGO released its first clinical practice guideline for the treatment of anemia in CKD (KDIGO 2012).

The KDIGO guidelines define anemia according to sex and age: a diagnosis of anemia in adults with CKD can be made when the hemoglobin concentration is less than 13 g/dL in men and less than 12 g/dL in women. These hemoglobin concentrations represent the World Health Organization definitions of anemia and serve as a benchmark across all populations. Although these are the thresholds for the diagnosis of anemia, they are not the concentrations at which to begin treatment.

Anemia, which can occur early in the disease process, worsens as kidney function declines. The National Health and Nutrition Examination Survey III (NHANES III) was a cross-sectional observational study of more than 15,000 people in the United States between 1988 and 1994. This survey found a relationship between a GFR of less than 60 mL/minute/1.73m² and the rate of anemia. The rate of anemia, defined as hemoglobin less than 12 g/dL in men or 11 g/dL in women, increased from 1% in patients with a GFR of 60 mL/minute/1.73m² to 9% in patients with a GFR of 30 mL/minute/1.73m². Moreover, the incidence of anemia increased to 33% for men and to 67% for women with a GFR of 15 mL/minute/1.73m².

Etiology

The etiology of anemia in patients with CKD is multifactorial. Although erythropoietin deficiency is most commonly cited, many other causes exist. These include deficiencies in iron, folate, or vitamin B₁₂; blood loss during hemodialysis and routine phlebotomy; gastrointestinal (GI) bleeding caused by uremia-induced platelet dysfunction; shortened red blood cell survival (30%–60% of the normal 120 days); hemolysis secondary to uremic toxin accumulation; and bone marrow suppression caused by secondary hyperparathyroidism, inflammation, or infection.

The commonly known symptoms of shortness of breath, lethargy, dizziness, and chronic anemia can lead to more severe complications, including cardiovascular issues such as worsening heart failure, left ventricular hypertrophy, and angina. However, studies have not clearly shown improved outcomes with increased erythropoiesis-stimulating agent (ESA) use or higher hemoglobin concentrations. In addition, anemia increases the rates of hospitalization and all-cause mortality and reduces exercise capacity and health-related quality of life.

Treatment Goals

The target hemoglobin range in patients receiving dialysis has changed dramatically since the first ESA was approved 25 years ago. When epoetin alfa was initially marketed, a hypothesis emerged that patients with kidney disease would have “normal” hemoglobin concentrations and better clinical outcomes.

Table 1-1 reviews the Normal Hematocrit Trial (Besarab 1998) as well as more recent clinical trials that examined hemoglobin concentrations and clinical outcomes (Inrig 2012; Pfeffer 2009; Drüeke 2006; Singh 2006). Although these trials were of nondialysis patients with CKD, they bring into question the optimal hemoglobin target for patients with CKD. The 2007 National Kidney Foundation (NKF) guidelines list a target hemoglobin concentration of 11–12 g/dL and recommended against routinely maintaining hemoglobin concentrations of 13 g/dL or greater in patients with CKD. Their rationale was that maintaining concentrations at 11–13 g/dL has been associated with many benefits, including a reduced need for blood transfusions, improved cardiac output and left ventricular hypertrophy, and improved cognitive function and exercise capability. However, these recommendations predate publication of the Trial to Reduce Cardiovascular Events with Aranesp Therapy, which led to a call for further revision of hemoglobin target ranges (Berns 2013; Singh 2010; Winkelmayer 2010). For example, some experts recommend a target hemoglobin of 10–11.0 g/dL (Berns 2013; Singh 2008), whereas others recommend a limit of 9 g/dL (Singh 2010).

The question is whether the target hemoglobin or the actual ESA dose is associated with the poor outcomes observed in the recent trials. It has been hypothesized that ESA agents
### Table 1-1. Studies Evaluating Target Hemoglobin Range in Patients with CKD

<table>
<thead>
<tr>
<th>Study</th>
<th>Population Studied</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Hematocrit Trial (Besarab 1998)</td>
<td>1233 patients on hemodialysis with preexisting cardiac disease treated with etopin alfa to achieve either a hematocrit target of 42% (normalization group) or 30% (control group)</td>
<td>Patients in the higher hematocrit goal group had significantly higher rates of vascular access thrombosis (39% vs. 29% in the control group, p=0.001) Trend toward increased mortality or nonfatal myocardial infarction in those assigned to the higher hematocrit target First study to find that normalizing hematocrit in patients on hemodialysis may be associated with poor outcomes</td>
</tr>
<tr>
<td>Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) (Singh 2006)</td>
<td>1432 patients with non-dialysis-dependent CKD were randomized to a target hemoglobin concentration of 13.5 g/dL or a target hemoglobin concentration of 11.3 g/dL</td>
<td>Patients randomized to the higher hemoglobin concentration had an increase in the composite of death, myocardial infarction, hospitalization for congestive heart failure, and stroke (125 events vs. 97 events; HR 1.34; p=0.03) Higher hemoglobin concentration target was not associated with an improvement in quality of life Trial was prematurely terminated by the data and safety monitoring board because of the low likelihood of detecting a true benefit in the high hemoglobin group by the end of the study</td>
</tr>
<tr>
<td>Cardiovascular Risk Reduction by Early Anemia Treatment (CREATE) (Drüeke 2006)</td>
<td>603 patients in Europe, Asia, and Mexico with stage 4 CKD and mild to moderate anemia (hemoglobin 11–12.5 g/dL), randomly assigned to early or late anemia correction All patients received etopin betta. The early group received etopin betta therapy immediately for a target hemoglobin 13–15 g/dL. The late anemia correction group did not receive treatment until their hemoglobin was &lt; 10.5 g/dL; their target hemoglobin was 10.5–11.5 g/dL</td>
<td>No difference in the rates of cardiovascular events or all-cause mortality in patients randomized to the higher hemoglobin target in the 3-year follow-up Progression to dialysis occurred more frequently in patients in the higher than in the lower hemoglobin groups (127 vs. 111; p=0.03) Quality of life, measured using the SF-36, showed a statistically significant improvement in several domains in patients assigned to the higher hemoglobin target group</td>
</tr>
<tr>
<td>Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) (Pfeffer 2009)</td>
<td>4038 patients with type 2 diabetes mellitus and CKD treated with darbepoetin to study the effect of correcting the anemia of CKD. Patients randomly assigned to receive darbepoetin to achieve a target hemoglobin concentration of 13 g/dL or to placebo. Patients receiving placebo who had a hemoglobin less than 9 g/dL were treated with darbepoetin rescue doses until the hemoglobin concentration was 9 g/dL or higher; then they returned to receiving placebo</td>
<td>Similar risk of death or a cardiovascular event (HR 1.05; 95% CI, 0.94–1.17) or of death or end-stage renal disease (HR 1.06; 95% CI, 0.95–1.19) in both groups at a median follow-up of 29 months The mean hemoglobin concentration achieved was 12.5 g/dL and 10.6 g/dL in the darbepoetin and placebo groups Increased risk of fatal or nonfatal stroke with darbepoetin alfa (101 vs. 53 patients with placebo; HR 1.92; 95% CI, 1.38–2.68) Red blood cell transfusions significantly more common in the placebo group (496 vs. 297 patients) Fatigue was only modestly improved with treatment Increased risk of death because of malignancy in the darbepoetin group, primarily in patients with a history of malignancy</td>
</tr>
</tbody>
</table>

CI = confidence interval; CKD = chronic kidney disease; HR = hazard ratio; SF-36 = short-form health survey [36 items].
are either directly or indirectly toxic. This toxicity may or may not be related to the hemoglobin concentration. For example, it will take further research to determine whether ESAs affect platelet count and platelet activation or cause an increase in blood viscosity (Gori 2011).

The most recent boxed warning on ESA agents recommends weighing the benefits in reducing the need for blood transfusions against the potential cardiovascular risks. The manufacturers state that the lowest ESA dose should be used in order to reduce the need for blood transfusions. Therefore, the recommendation is to reduce or interrupt the ESA dose if the hemoglobin concentration approaches 11 g/dL, with the optimal target hemoglobin range to be determined by further outcome studies.

Treatment of anemia of CKD has become more complex, challenging the clinician to find the optimal balance between ESA treatment and clinical symptoms.

**Treatment with ESAs**

**The Reimbursement Environment**

In 2011, a bundled payment reimbursement system for patients with end-stage kidney disease went into effect. The system, created after a congressional mandate to reduce expenditures in the treatment of these patients, established a fixed payment per patient for items such as intravenous medications, laboratory tests, and supplies used to perform dialysis. The goal was to reduce payments to dialysis facilities by 2% and to reduce the overuse of profitable, previously separately billable drugs (e.g., ESAs) because of the potential for harm if these agents are overused. The law required certain quality standards (e.g., percentage of patients with a hemoglobin less than 10 g/dL or greater than 12 g/dL) to avoid a reduction in Medicare payments (Iglehart 2011). This led to a change in the management of anemia, with many facilities shifting target hemoglobin ranges downward, reducing use of ESAs, and increasing use of iron.

**Erythropoiesis-Stimulating Agents**

Erythropoiesis-stimulating agents (epoetin alfa, darbepoetin alfa) are currently the primary agents used to treat anemia associated with CKD (Table 1-2). The KDIGO clinical practice guidelines recommend treating all correctable causes of anemia (e.g., iron, folate, vitamin B₁₂ deficiency, hypothyroidism) before initiating ESA therapy. This is because ESA therapy is unlikely to be fully effective in raising hemoglobin concentrations until correctable causes of anemia are treated.

Current guidelines recommend that in patients with stage 5 CKD, ESA therapy be initiated when the hemoglobin concentration is 9–10 g/dL. (KDIGO 2012). The actual hemoglobin target range should be individualized, depending on the risk of requiring blood transfusions and the presence of symptoms such as angina, fatigue, or dyspnea. There is no evidence that one ESA is superior to another; thus, choice should be based on cost and availability.

Initial dosing should be based on hemoglobin concentration, body weight, and clinical circumstances. In general, the objective of the initial ESA dose is to achieve an increase in hemoglobin of 1–2 g/dL per month (KDIGO 2012). Doses higher than recommended do not achieve target hemoglobin concentrations faster, but often result in excessively high hemoglobin concentrations. Dosage adjustments should be based on the hemoglobin concentration, rate of change in hemoglobin concentration, current ESA dose, and clinical circumstances (Figure 1-1).

According to the KDIGO guidelines, ESAs should not be used to maintain a hemoglobin concentration above 11.5 g/dL or to intentionally maintain the hemoglobin concentration above 13 g/dL. Although patients who experience increased fatigue or angina or reduced ability to concentrate at lower hemoglobin values may benefit from a hemoglobin concentration of 11.5–13.0 g/dL, these target concentrations must be individualized.

When the hemoglobin concentration is higher – or the rate of rise is faster – than desired, the ESA dose should be reduced rather than withheld. Past practice was to withhold therapy, then reinitiated ESAs 1–2 weeks later, usually at a reduced dose or frequency. However, this often led to precipitous declines in the hemoglobin concentration, sometimes below the target range. Today, with the better understanding of ESA mechanisms of action, including the prevention of apoptotic death of colony-forming unit erythroblasts and early erythroblasts, the practice of withholding ESA doses is no longer recommended. Rather, ESA doses should be decreased, either by reducing the dose – typically by no more than 25% – or by reducing the frequency of administration, thus preventing large fluctuations in hemoglobin concentrations.

The KDIGO guidelines indicate that ESAs can be administered either intravenously or subcutaneously to patients receiving hemodialysis; this differs from earlier guidelines. In patients receiving peritoneal dialysis, the subcutaneous route is preferred because ESAs can be self-administered at home. Initial experience with epoetin, but not intravenous therapy, was associated with a small but increased risk of pure red cell aplasia in patients receiving hemodialysis (Boven 2005). Consequently, for a time, all ESAs were to be administered intravenously in patients receiving hemodialysis. However, the rare cases of pure red cell aplasia were found to be caused by a formulation available in Europe. The most recent guidelines suggest that either route is acceptable (KDIGO 2012; Boven 2005).

Many, but not all, trials have shown that subcutaneous administration allows the use of lower epoetin doses (Kaufman 1998). This is likely because the half-life is longer, even though the bioavailability of epoetin is lower with subcutaneous administration. The efficacy of darbepoetin alfa appears to be similar between subcutaneous and intravenous administration (Kaufman 1998).
Biosimilar ESAs

Biotechnological drugs (e.g., cytokines, hormones, clotting factors, monoclonal antibodies, vaccines) are derived from living organisms such as plant and animal cells, viruses, or yeasts. These agents often replace or supplement a protein normally produced in the body to treat disease. The structure and mechanism of biotechnological molecules are much more complex than traditional medications. They can also interact with genes, making the exact mechanism of action difficult to predict.

Biosimilars or follow-on biologics are copies of biotechnological agents made from different cell lines and with a different manufacturing and purification process. Biosimilars are not considered generics and are not an exact copy of the reference drug. It is expected that each product will have a unique safety profile (FDA 2013). For example, in Europe, a biosimilar growth hormone, Valtropin, has precautions and warnings different from those of the reference product Humatrope. This is because yeasts are used to produce Valtropin, whereas Escherichia coli is used to produce Humatrope. Immunogenicity may also differ, and although this usually does not have clinical consequences, rare cases of antibody-related reactions can be potentially life threatening. Because of this, clinical immunogenicity studies are required for biosimilars before regulatory approval.

The biosimilar epoetins, HXX75 (epoetin alfa [Abseamed, Binocrit, and epoetin alfa Hexal]) and SB309 (epoetin zeta [Retacrit, Silapro]) have been available in Europe since 2007. HXX75 has the same amino acid sequence as the reference products (Eprex, Erypo), but HXX75 has more phosphorylated high mannose-6-phosphate glycans and lower levels of N-glycolyneuraminic acid and diacetylated neuraminic acids (Mikhail 2013). In clinical trials, HXX75 appears to have similar hematopoietic profiles, although some pharmacokinetic differences have been noted. For example, after single-dose administrations, the area under the concentration-time curve (AUC) was 18% lower (0–12 hours) than that with comparator epoetin alfa. In addition, at steady state, the AUC (0–36 hours) was 10% lower than the comparator product (Mikhail 2013). Another study evaluating subcutaneous administration was terminated early because two patients developed neutralizing antibodies. It is not known whether this was caused by the biosimilar product, but currently HXX75 is indicated only for intravenous administration in patients receiving hemodialysis.

SB309 has a protein backbone similar to epoetin alfa but contains a slightly higher amount of glycoforms without an O-glycan chain. Epoetin zeta has a higher amount of N-glycolyl and more acetylated forms of neuraminic acid than does SB309. To date, the pharmacokinetics, safety, and efficacy of epoetin zeta appear similar to those of the comparator epoetin alfa.

In 2010, an abbreviated pathway to approval of biologic products was established in the United States. The Biologics Price Competition and Innovation Act allows 12 years of exclusivity for an innovator product plus another 6 months if pediatric studies are conducted. The act created two sets of standards for biosimilarity and interchangeability. A biosimilar product is highly similar to the brand-name product, even though minor differences in the inactive ingredients may exist. However, there should be no clinically meaningful differences in safety, purity, or potency. In the higher category of interchangeable biosimilar products, the newer product must produce the same

<table>
<thead>
<tr>
<th>Table 1-2. Recommended Dosing Guidelines for Currently Available ESAs in the United States</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial Dose in CKD</strong></td>
</tr>
<tr>
<td>Adults</td>
</tr>
<tr>
<td>Children</td>
</tr>
<tr>
<td><strong>Dosage adjustment frequency</strong></td>
</tr>
<tr>
<td><strong>Dosage adjustments</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Availability</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Discard multidose vial 21 days after initial entry.
CKD = chronic kidney disease; ESA = erythropoiesis-stimulating agent; HD = hemodialysis; IV = intravenously; SC = subcutaneously.
Hemoglobin testing in all patients with CKD, regardless of the cause or stage, at least annually

Hemoglobin < 13.5 g/dL, adult men
Hemoglobin < 12 g/dL, adult women

Diagnosis of anemia, further workup

CBC + RBC indices to assess anemia severity, adequacy of nutrients such as vitamin B₁₂, folate, and iron

Normochromic, normocytic
Macrocytic
Vitamin B₁₂ and/or folate deficiency

Macrocytic
Iron deficiency aluminum overload

Start/adjust ESA\(^{a}\) based on hemoglobin
Start renal multivitamin

Adjust ESA no more often than very 4 weeks unless clinically indicated (e.g., unstable hemoglobin, bleeding, surgery, hospitalization)

Inadequate response

Assess for hyporesponse (see Table 1-3)

Transferrin saturation, ferritin

Hemodialysis
Peritoneal dialysis or non-dialysis CKD

Ferritin < 200 ng/mL and transferrin saturation < 20%

IV iron
100 mg × 10 doses (ID or IS)
OR
125 mg × 8 doses (FG)
OR
510 mg × 2 doses (ferumoxytol)

PO iron
200 mg/day elemental iron
OR
IV iron
200–400 mg infusion (IS) for 2–3 doses
OR
125–250 mg infusion (FG) for 4–4 doses
OR
510 mg × 2 doses (ferumoxytol)

Iron monitoring\(^{b}\):
- Monthly during initial ESA
- At least every 3 months during stable ESA therapy
- After blood loss, surgery, hospitalization, or course of IV iron

Figure 1-1. Anemia treatment algorithm.

\(^{a}\)See Table 1-1 for initial dosing and monitoring values.

\(^{b}\)Wait 1–2 weeks to evaluate iron status if IV doses > 200 mg administered.

CBC = complete blood cell count; CKD = chronic kidney disease; ESA = erythropoiesis-stimulating agent; FG = ferric gluconate; HD = hemodialysis; ID = iron dextran; IS = iron sucrose; IV = intravenous(ly); PD = peritoneal dialysis; PO = by mouth; RBC = red blood cell; TSAT = transferrin saturation.

clinical effects as the brand-name product. Many biosimilar epoetin alfa products are currently under study in the United States. The companies developing these products (i.e., Hospira and Sandoz) have approval for biosimilar epoetin alfa products in Europe. However, when these products will reach the U.S. market is not known.

Although generic products of chemical medications are identical, and the risks associated with substitution are minimal, this is not true with biosimilars. It is impossible to create exact duplicates with biosimilars; therefore, there may be differences in potency, efficacy, and adverse effects. Consequently, the reference product and the biosimilar are not considered interchangeable, and regulations are needed to ensure that automatic substitution rules do not apply to biotechnological products (FDA 2013).

Biosimilars present unique opportunities for pharmacists. Pharmacists should take a leadership role in objectively reviewing the evidence of efficacy, safety, and cost and in determining the interchangeability and equivalence of the newer products versus the comparator product. Pharmacists should also play a role in deciding which agents are suitable for formulary inclusion. Finally, pharmacists are in a unique position to educate health care professionals and patients about biosimilars and their role in therapy.

**Iron Therapy**

Adequate iron storage and transport are vital to the successful treatment of anemia in patients with CKD. In addition to physiologic blood loss, patients with CKD are commonly deficient in iron for several reasons (e.g., increased erythropoiesis stimulation by ESAs, occult GI blood loss, platelet dysfunction, interference of iron absorption from gastric acid secretion inhibitors and phosphate binders). Patients on dialysis, especially hemodialysis, have additional reasons for blood and iron loss (e.g., frequent phlebotomy for laboratory testing, vascular access manipulations and surgery, blood retention or clotting in the dialyzer or tubing). Because patients on hemodialysis often receive heparin, prolonged bleeding from the puncture sites after dialysis sometimes occurs. It has been estimated that patients on hemodialysis lose 2 g of iron or more annually compared with less than 500 mg in a patient without CKD.

<p>| <strong>Table 1-3. Currently Available IV Iron Products in the United States</strong> |</p>
<table>
<thead>
<tr>
<th>Drug Name, Concentration (mg/mL)</th>
<th>Indication</th>
<th>Test Dose?</th>
<th>Typical Adult Dose</th>
<th>Maximum Single Dose&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Total Dose Infusion (TDI)&lt;sup&gt;b&lt;/sup&gt;?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron dextran, 50</td>
<td>Iron deficiency</td>
<td>Yes&lt;sup&gt;b&lt;/sup&gt;</td>
<td>100 mg IV over 2 min</td>
<td>100 mg (though higher doses have been used) or IM (INFeD only)</td>
<td>No (but TDI has been used over 4–6 hr)</td>
</tr>
<tr>
<td>Sodium ferric gluconate complex in sucrose, 12.5</td>
<td>Iron deficiency in hemodialysis</td>
<td>No</td>
<td>125 mg IV over 10 min or diluted over 1 hr</td>
<td>125 mg (though doses of up to 250 mg have been used)</td>
<td>No</td>
</tr>
<tr>
<td>Ferric gluconate, 12.5</td>
<td>Iron deficiency in hemodialysis in patients receiving supplemental epoetin therapy</td>
<td>No</td>
<td>125 mg IV over 10 min or diluted over 1 hr</td>
<td>125 mg</td>
<td>No</td>
</tr>
<tr>
<td>Iron sucrose, 20</td>
<td>Iron deficiency in CKD</td>
<td>No</td>
<td>100 mg IV over 2–5 min or diluted over 15 min</td>
<td>400 mg over 2.5 hr</td>
<td>No</td>
</tr>
<tr>
<td>Ferumoxytol, 30</td>
<td>Iron deficiency in CKD</td>
<td>No</td>
<td>510 mg over 17 s</td>
<td>510 mg</td>
<td>No</td>
</tr>
<tr>
<td>Ferric carboxymaltose, 50</td>
<td>Iron deficiency in adults with nondialysis-dependent CKD</td>
<td>No</td>
<td>750 mg over 7.5 min or diluted over 15 min</td>
<td>750 mg</td>
<td>No</td>
</tr>
</tbody>
</table>

<sup>a</sup>Not FDA approved.

<sup>b</sup>Requires a 0.5-mL test dose.

CKD = chronic kidney disease; hr = hours; IM = intramuscularly; INFeD = iron dextran; IV = intravenous(ly); min = minutes, s = seconds.
Because of poor GI absorption, oral replacement of iron is typically inadequate. In patients on dialysis with anemia who are not receiving an ESA or iron, a 1- to 3-month trial of intravenous iron is warranted. This is especially true for patients with a transferrin saturation of 30% or less and a ferritin of 500 ng/mL or less. In these patients, an increase in hemoglobin concentration may be noted without initiation of ESA therapy. More commonly, however, dialysis patients are receiving an ESA. In these patients, a 1- to 3-month trial of iron is warranted if the transferrin saturation is 30% or less and the ferritin is 500 ng/mL or less. Often, a trial of iron will result in an increased hemoglobin concentration and a reduced ESA dose. Subsequent iron therapy should be based on hemoglobin response to recent iron therapy, continuing blood loss, iron status tests, hemoglobin concentrations, and ESA dose. Select intravenous iron products are compared in Table 1-3.

Data are limited on the long-term benefits and risks of iron administration other than hemoglobin increases in the dialysis population. In addition, the optimal iron regimen for patients receiving dialysis is unknown. Although the KDIGO guidelines suggest intravenous iron therapy in all patients with CKD who are receiving an ESA, many clinicians initiate oral iron therapy in patients receiving peritoneal dialysis because it is an easier method of administration in outpatients. Often, intravenous therapy is considered only in patients receiving peritoneal dialysis who become intolerant of oral iron therapy or who remain iron-deficient while receiving oral therapy. Parenteral iron administration in patients receiving peritoneal dialysis is cumbersome and requires placement of intravenous access and several office visits to administer necessary doses. In contrast, intravenous iron administration is preferred in patients receiving hemodialysis because these patients are unlikely to absorb enough iron to replace ongoing losses. In these patients, iron may be administered as a loading dose or as a maintenance dose. In iron loading, intravenous iron is given periodically to replenish iron stores (e.g., 1000 mg given over 8 or 10 consecutive dialysis sessions). Alternatively, patients can be given small intravenous maintenance doses (e.g., 50–125 mg) of iron weekly, every other week, or monthly to maintain iron stores at acceptable concentrations. For patients receiving peritoneal dialysis, accelerated dosing regimens (e.g., 400-mg doses of iron sucrose over 2½ hours) have been safely administered (see Table 1-3).

The ideal method for administering iron is a subject of debate (Besarab 2011). Proponents of loading doses argue that maintenance dosing requires frequent monitoring to avoid iron overload and that frequent dosing increases nursing time and supply costs. Others suggest that continuous exposure to higher concentrations of iron in the blood can lead to adverse effects such as increased risk of infection, oxidative stress, and cardiovascular disease (Brookhart 2013). Critics of loading doses suggest that although large doses over a shorter period lead to significant improvements in erythropoiesis in the short term, the total amount of iron may be insufficient to maintain the concentration of erythropoiesis long term. These experts argue that maintenance iron dosing more closely mimics physiologic processes. In addition, loading doses may lead to periods of functional iron deficiency, which is when there are adequate iron stores but insufficient iron at the site to be incorporated into red blood cells. Another phenomenon caused by iron-loading regimens is a rollercoaster effect in both serum iron and hemoglobin concentrations; this is thought to occur when ESA doses are reduced in response to the initial increase in hemoglobin, leading to lower subsequent concentrations in the future when iron stores are depleted. Finally, proponents of maintenance dosing point to many studies that have shown a reduction in ESA requirements in patients who receive maintenance iron regimens (KDIGO 2012).

**Iron Similarars**

Iron carbohydrates such as iron sucrose are complex macromolecules consisting of an elemental iron core and a carbohydrate shell; their chemical and biological properties vary with the manufacturing process. Subtle structural modifications may affect the stability of the preparation. Unstable iron-carbohydrate complexes could dissociate in the body too quickly, leading to the appearance of free iron and the generation of reactive oxygen species that induce oxidative stress and inflammation (Rottembourg 2011; Toblli 2009). This could have efficacy and safety implications.

Despite the complex structure of iron sucrose, generic versions (also known as iron sucrose similar) have been approved outside the United States. In 2011, a generic version of sodium ferric gluconate (Nulecit) was approved in the United States for use as a bioequivalent and therapeutic equivalent to Ferrlecit (Stein 2012). However, this was before the the U.S. Food and Drug Administration (FDA) released guidance on biosimilar medication approval, and no assessment of free or labile iron or inflammation was conducted.

The introduction of generic intravenous iron preparations has prompted questions about their therapeutic equivalence. In one case series, three patients who previously tolerated the brand-name iron sucrose agent developed urticaria, edema, and headache within 1 hour after infusion of an iron sucrose similar. In an observational crossover study comparing brand-name iron sucrose (Venofer) with an iron similar product (Fer Mylan), 75 hemodialysis patients received intravenous iron during two 27-week periods. During the period of iron similar administration, mean hemoglobin was statistically lower, and patients spent more days outside the target hemoglobin range than in the brand-name administration period (Rottembourg 2011). In addition, despite the use of higher doses of intravenous iron during the iron similar period, mean ferritin and transferrin saturation...
were lower than during the brand-name administration period. The authors concluded that iron similar products may not be therapeutically equivalent to innovator products and that caution should be used when switching iron products. No iron similar products are currently available in the United States. However, the FDA has released a draft guidance on the design of bioequivalence studies to support abbreviated new drug applications for iron sucrose injection (FDA 2013).

Monitoring

Monitoring of ESA and iron therapy is imperative to optimize anemia treatment. Hemoglobin concentrations should be monitored at least monthly to assess that they are within the target range. Many hemodialysis centers monitor hemoglobin concentrations every 2 weeks, especially in patients who are clinically unstable or who have concentrations that are unstable or outside the target range. Other patients requiring more frequent monitoring are those who experience blood loss (e.g., those who are hospitalized or who undergo surgery). Monthly monitoring is usually enough in patients who have a hemoglobin concentration that is stable and within the target range and in patients receiving peritoneal dialysis.

Iron indices including transferrin saturation and ferritin are used to evaluate the etiology of anemia or to monitor iron therapy. The ideal assessment of iron stores involves bone marrow aspiration, but this is rarely done. Alternatively, markers of iron stores, namely transferrin saturation and ferritin, are assessed at baseline, before initiation of ESA therapy, and then monthly during initial treatment with ESAs. Of note, however, ferritin can be a poor marker of iron stores. Ferritin, an acute-phase reactant, is often increased in cases of infection or inflammation, even when patients are iron-deficient. Once the ESA regimen is stable, iron indices can be assessed less frequently, but assessments should occur at least every 3 months. Assessment at least quarterly should be performed in patients receiving hemodialysis but not treated with an ESA.

During ESA therapy initiation, the bone marrow is stimulated to produce red blood cells; the demand for iron is high and can lead to depletion of iron stores and iron deficiency. Other clinical situations that require more frequent iron testing include when there has been recent bleeding, during postoperative periods, and after hospitalization when blood loss has occurred. Similarly, iron indices measurement should be considered after a 1-g loading regimen of intravenous iron to assess whether additional doses are necessary. Although there are no specific guidelines for monitoring reticulocyte hemoglobin content, this marker can be used to assess the ability of the bone marrow to respond to anemia and produce red blood cells.

In addition to routine laboratory monitoring, signs and symptoms of bleeding should be considered when the response to ESA or iron is suboptimal. Patients with CKD are at increased risk of bleeding for several reasons, particularly when platelet dysfunction occurs because of circulating uremic toxins. Although dialysis improves platelet abnormalities, it does not eliminate them, putting patients with CKD at risk of hemorrhage. For example, patients should be asked about nosebleeds or black tarry stools to assess for GI bleeding. Stools should be checked for occult blood using a guaiac test, and women of childbearing age should be instructed to report abnormally heavy menstrual periods.

Treatment of ESA Hyporesponsiveness

Because of the concern that high ESA doses may be responsible for the detrimental effects that occurred in the recent ESA trials, treatment with the lowest effective dose is warranted. To achieve this, hyporesponsiveness must be addressed. Hyporesponse or refractoriness to ESAs is a common problem encountered in patients with CKD. Hyporesponse or resistance to ESA therapy is defined as the inability to achieve target hemoglobin concentrations, despite receiving substantial ESA doses, or a need for high doses of an ESA. The KDIGO guidelines define initial ESA hyporesponsiveness as a lack of hemoglobin increase from baseline after the first month on appropriate weight-based dosing. Initial ESA hyporesponsiveness is rare unless there is an underlying uncorrectable cause (e.g., bone marrow disorder), and the ESA dose should not exceed double the initial weight-based dose in these patients.

Subsequent ESA hyporesponsiveness is defined as a patient’s need for two increases in ESA doses by up to 50% beyond the dose at which the patient had been stable. In patients with ESA hyporesponsiveness, causes should be investigated and treated, if possible (Table 1-4). Often, hyporesponsiveness has more than one cause (Bamgbola 2012). The most common cause of hyporesponsiveness to ESAs is iron deficiency. Other correctable causes include infection or inflammation, drugs, and nutritional deficiencies. Easily correctable causes (e.g., vitamin B₁₂, folate, or iron deficiency) should be addressed as soon as possible. Other causes (e.g., secondary hyperparathyroidism, hematologic malignancy) may require a longer period to correct. Chronic medical conditions (e.g., systemic lupus erythematosus, sickle cell anemia) may not be correctable. For patients who remain poorly responsive to ESA therapy, the maximal ESA dose is recommended not exceed 4 times the initial weight-based dose.

The role of hepcidin in hyporesponsiveness to ESAs is a new area of research. Hepcidin is a protein produced in the liver in response to iron status, hypoxia, and inflammation. Moreover, it is a key regulatory protein involved in controlling intestinal iron absorption and distribution. High circulating hepcidin concentrations reduce iron absorption after oral or intravenous administration. In addition, high hepcidin concentrations impair the release of iron for storage sites and may inhibit red blood cell production and survival. Conversely, low serum iron concentrations
<table>
<thead>
<tr>
<th>Cause</th>
<th>Mechanism of Hyporesponse</th>
<th>Clinical Signs and Symptoms</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminum overload</td>
<td>Inhibition of heme synthesis</td>
<td>MCV &lt; 80 fL</td>
<td>Monitor aluminum serum concentrations, Minimize exogenous aluminum intake, Consider aluminum chelation therapy, Adjust ESA therapy, as necessary</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased serum aluminum concentrations (normal &lt; 10 mcg/L)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased exogenous aluminum intake (e.g., sucralfate, aluminum hydroxide)</td>
<td></td>
</tr>
<tr>
<td>Blood loss</td>
<td>Increased turnover of red blood cells</td>
<td>Positive test for occult blood loss (e.g., in stool)</td>
<td>Assess patient for occult blood loss (e.g., in stool), Minimize phlebotomy, Minimize post-hemodialysis vascular access bleeding, Adjust ESA therapy, as necessary</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Frequent phlebotomy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recent GI bleed or surgery</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Menses or abnormal uterine bleeding</td>
<td></td>
</tr>
<tr>
<td>Cancer/malignancy</td>
<td>Inflammation</td>
<td>Diagnosis of malignancy</td>
<td>Treat cancer/malignancy, as appropriate, Adjust ESA therapy, as necessary</td>
</tr>
<tr>
<td>Chronic illnesses/conditions (i.e., AIDS, pregnancy, sickle cell anemia, others)</td>
<td>Inflammation; bone marrow suppression</td>
<td>Diagnosis of chronic illness</td>
<td>Treat illnesses, as appropriate, Adjust ESA therapy, as necessary</td>
</tr>
<tr>
<td>Hemolysis</td>
<td>Increased turnover of red blood cells</td>
<td>Increased serum haptoglobin, Increased LDH, Increased serum potassium</td>
<td>Monitor laboratory values for hemolysis, Remove causes of hemolysis</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>Blood loss; inflammation</td>
<td>History of recent or frequent hospitalization</td>
<td>Ensure ESA therapy is continued during hospitalization, Adjust ESA therapy, as necessary, to account for blood loss, phlebotomy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>History of recent surgery or procedure such as declotting or revision of hemodialysis arteriovenous access</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Known or suspected missed or inadequate doses of ESA during hospitalization</td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Lack of nutrients necessary for red blood cell production; bone marrow suppression</td>
<td>Symptoms of hypothyroidism such as weight gain, cold intolerance, thinning hair, Increased TSH</td>
<td>Correct hypothyroidism using thyroid replacement therapy</td>
</tr>
<tr>
<td>Cause</td>
<td>Mechanism of Hyporesponse</td>
<td>Clinical Signs and Symptoms</td>
<td>Management</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>----------------------------------------------------------------</td>
<td>-----------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
<td>Lack of nutrients necessary for red blood cell production; bone marrow suppression</td>
<td>Elevated iPTH Diagnosis based on bone biopsy</td>
<td>Treat hyperparathyroidism by controlling phosphorus, calcium, iPTH Adjust ESA therapy, as necessary</td>
</tr>
<tr>
<td>Infections (e.g., access site, hepatitis, osteomyelitis)</td>
<td>Inflammatory cytokines, which reduce erythropoiesis</td>
<td>Diagnosis of infection Increased serum ferritin concentration Increased C-reactive protein or ESR rate</td>
<td>Monitor signs and symptoms of infection Assess for occult infection Treat underlying infection, if possible Adjust ESA therapy, as necessary</td>
</tr>
<tr>
<td>Inadequate dialysis</td>
<td>Uremia</td>
<td>Low dialysis adequacy or kT/V Low urea reduction ratio (URR) History of missed or shortened treatments</td>
<td>Change hemodialysis catheter to arteriovenous fistula or graft Increase length of dialysis treatment</td>
</tr>
<tr>
<td>Inflammation (e.g., presence of dialysis catheter, lupus, surgery, transplant rejection, gangrene)</td>
<td>Inflammatory cytokines, which reduce erythropoiesis</td>
<td>Chronic diseases associated with inflammation Increased serum ferritin concentration Increased C-reactive protein or ESR rate Increased WBC</td>
<td>Monitor signs and symptoms of inflammation Treat inflammation, if possible Remove hemodialysis catheters Adjust ESA therapy, as necessary</td>
</tr>
<tr>
<td>Iron deficiency</td>
<td>Lack of nutrients necessary for red blood cell production</td>
<td>Low serum TSAT Low serum ferritin Low serum MCV Recent rapid rise in hemoglobin</td>
<td>Most common cause of ESA hyporesponse Administer iron replacement. For low TSAT and high ferritin, consider IV iron (to differentiate functional iron deficiency and an inflammatory iron block) If no erythropoietic response occurs, an inflammatory block is most likely, and no further IV iron should be given until the inflammatory condition has resolved</td>
</tr>
<tr>
<td>Medications</td>
<td>Bone marrow suppression; depletion of nutrients necessary for red blood cell production; hemolysis</td>
<td>Taking medications known to exacerbate anemia (e.g., corticosteroids, tacrolimus, amphotericin, fluconazole, valganciclovir)</td>
<td>Assess medication profile for drugs that can affect red blood cell production, life span If possible, discontinue medications Adjust ESA therapy, as necessary</td>
</tr>
</tbody>
</table>
lead to low serum concentrations of hepcidin, which in turn lead to increased intestinal iron absorption and release of iron from storage sites (Coyne 2011). In patients with kidney disease, concentrations of hepcidin and the metabolites are elevated. These high concentrations and elevated metabolites may play a role in the development and severity of anemia as well as the lack of response to anemia treatment in patients with CKD (Atkinson 2012).

The clinical utility of hepcidin as a diagnostic aid and as a potential therapeutic target is under investigation.

**Patient Education**

At a minimum, patients should know the name, dose, frequency, and indication for all drugs. In addition, patients should be instructed about the proper timing of administration. Patients with CKD who are initiating ESA therapy must be instructed regarding proper subcutaneous injection technique, ESA storage, and syringe disposal. Ideally, on initiation of therapy and periodically thereafter, the pharmacist should observe the patient’s administration technique. This direct observation will allow the pharmacist to identify problems (e.g., inability to withdraw correct dose or incorrect injection technique). Patients with anemia should understand the importance of adherence to ESA therapy and be aware of the detrimental effects of non-adherence. Finally, patients should be instructed on what to do if doses are missed, especially for drugs such as ESAs, which are generally administered infrequently.

As part of a Risk Evaluation and Mitigation Strategy program, all ESA prescriptions must be accompanied by a medication guide. Medication guides can be frightening, and pharmacists should carefully review them with patients to place the information in perspective.

**Mineral and Bone Disorder**

The kidney is vital in maintaining homeostasis of calcium, phosphorus, activated vitamin D, and intact parathyroid hormone (iPTH) concentrations. As kidney function declines, mineral metabolism progressively deteriorates. This has many consequences, including abnormalities in bone turnover and mineralization and calcification in areas outside the bones. The abnormalities ultimately increase the risk of bone fractures, vascular calcification, tissue calcification, endothelial dysfunction, arterial stiffness, left ventricular hypertrophy, cardiovascular disease, and death. The KDIGO foundation has developed and published clinical practice guidelines for the diagnosis, evaluation, prevention, and treatment of CKD-MBD (KDIGO 2009).

**Etiology**

The relationship between CKD, hyperplasia of the parathyroid glands, and bone disease is well known. Beginning at around stage 3 CKD, the kidney is unable to excrete an adequate amount of phosphorus, resulting in transient elevations in serum phosphorus. This sets off a cascade of events as the body tries to achieve phosphorus homeostasis. The result is elevated iPTH and reduced activity of 1α-hydroxylase and 24,25-hydroxylase (renal enzymes necessary for the conversion of 1,25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol and non-protein amino acids; TSAT = transferrin saturation; WBC = white blood cell count.

Table 1-4. Common Causes, Clinical Signs and Symptoms, and Management of ESA Hyporesponse (continued)

<table>
<thead>
<tr>
<th>Cause</th>
<th>Mechanism of Hyporesponse</th>
<th>Clinical Signs and Symptoms</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonadherence (e.g., patients receiving peritoneal dialysis or home hemodialysis)</td>
<td>Erythropoietin deficiency</td>
<td>History of frequent missed or shortened treatments Patient interview</td>
<td>Assess adherence by discussing with patient, refill records Educate regarding importance of adherence, negative consequences of anemia</td>
</tr>
<tr>
<td>Protein energy malnutrition</td>
<td>Lack of nutrients necessary for red blood cell production</td>
<td>Low dietary protein intake Low serum albumin or prealbumin Low nPA intake</td>
<td>Increase dietary protein intake Offer protein supplements In extreme cases, initiate intradialytic parenteral nutrition</td>
</tr>
<tr>
<td>Vitamin B12 or folate deficiency</td>
<td>Lack of nutrients necessary for red blood cell production</td>
<td>High serum MCV Recent rapid rise in hemoglobin</td>
<td>Consider in patients with macrocytic anemia Assess vitamin B12 and folate serum concentrations Treat, as necessary</td>
</tr>
</tbody>
</table>

ESA = erythropoiesis-stimulating agent; iPTH = intact parathyroid hormone; nPA = non-protein amino acids; TSAT = transferrin saturation; WBC = white blood cell count.
24,25-dihydroxycholecalciferol). This in turn leads to a reduction in 1,25-D serum levels as well as a reduction in calcium absorption from the GI tract. Hypocalcemia further increases iPTH release from the parathyroid glands.

Fibroblast growth factor 23 (FGF23) is a recently discovered protein primarily secreted by osteocytes in the bone. FGF23 is mainly secreted in response to high dietary phosphate, calcitriol, and hyperphosphatemia. FGF23 concentrations are inversely related to renal function (i.e., as GFR declines, FGF23 increases). Recent studies suggest that increased FGF23 is associated with mortality, left ventricular hypertrophy, endothelial dysfunction, and CKD progression (Damasiewicz 2011). These results are consistently independent of serum phosphate concentrations. It is possible that markedly increased FGF23 concentrations in CKD contribute directly to tissue injury in the heart, vessels, and kidneys.

FGF23 exerts its effect by binding to FGF receptors in the renal tubule and parathyroid gland. However, Klotho protein also appears to be necessary. Klotho is a transmembrane protein that determines the tissue specificity of FGF23. In animal studies, Klotho directly acts with the FGF receptors, allowing FGF23 binding with a higher affinity and greater specificity.

The main effects of FGF23 are its regulation of urinary phosphate excretion and maintenance of normal serum phosphorus concentrations. In addition, FGF23 acts as a counterregulatory mechanism for vitamin D synthesis. As FGF23 concentrations increase, a compensatory reduction in vitamin D concentrations occurs. However, in patients with kidney disease, increasing FGF23 concentrations do not result in increased phosphorus excretion.

Only a few trials have studied the treatment effects of CKD-MBD on FGF23 concentrations. In these small trials, cinacalcet and phosphate binders have lowered FGF23 concentrations, independently of phosphate serum concentrations.

For now, FGF23 is emerging as a novel biomarker that may influence when and how patients with CKD are treated. For example, FGF23 may help identify which patients with CKD will benefit most from aggressive management of disordered phosphorus metabolism. Theoretically, agents that prevent high FGF23 concentrations by either inhibiting secretion or reducing elevated FGF23 concentrations can have benefits. Nevertheless, many questions remain unanswered, such as the exact role of FGF23 in the progression of CKD (and its associated morbidity and mortality), and the normal ranges of FGF23 concentrations.

### Treatment Goals

The treatment goal in patients with CKD and abnormalities of bone metabolism is to normalize mineral metabolism, prevent bone disease, and prevent extrakrystal manifestations. The gold standard test to assess bone disease in CKD is a bone biopsy; however, this is expensive, invasive, and not available in all practice settings. Consequently, the measurement of biochemical abnormalities is the mainstay of assessment. Beginning at stage 3 CKD, serum levels of calcium, phosphorus, iPTH, and alkaline phosphatase should be measured periodically. One or more of these levels should be abnormal for a diagnosis of CKD-MBD.

The frequency of monitoring for patients receiving dialysis is listed in Table 1-5 (KDIGO 2009). When evaluating serum calcium and phosphorus concentrations, it is important to consider postprandial and diurnal variations. For example, phosphorus varies more than serum calcium because it is affected by recent intake and diurnal variation. Consequently, treatment decisions should be made according to trends rather than a single laboratory result.

<table>
<thead>
<tr>
<th>Minerals, Frequency of Measurement (months)</th>
<th>Target Range</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium, 1–3</td>
<td>In the normal range (e.g., 8.5–10.5 mg/dL)</td>
<td>Must be corrected according to serum albumin concentrations</td>
</tr>
<tr>
<td>Phosphorus, 1–3</td>
<td>Toward the normal range (e.g., &lt; 5.0 mg/dL)</td>
<td>In dialysis patients, the positive relationship of hyperphosphatemia with mortality is robust, but the threshold above which risk is increased varies across studies, ranging from 5.0 mg/dL to 7.0 mg/dL.</td>
</tr>
<tr>
<td>iPTH, 3–6</td>
<td>About 2–9 times the upper reference limit for the assay</td>
<td>Corresponds to an iPTH value of around 130–600 pg/mL</td>
</tr>
</tbody>
</table>

CKD-MBD = chronic kidney disease-mineral and bone disorder; iPTH = intact parathyroid hormone.
A newer recommendation is to measure 25-hydroxyvitamin D (25(OH)D) or calcitriol concentrations in patients with stage 3 CKD or higher (KDIGO 2009). This recommendation is based on recent data regarding the role of vitamin D deficiency in several diseases, including secondary hyperparathyroidism. As in the general population, serum 25(OH)D or calcitriol insufficiency is defined as a serum concentration less than 32 ng/mL. There is no consensus on the definition of a normal or therapeutic concentration. Levels should be assessed at baseline and then repeated, depending on therapeutic interventions. In patients who are serum 25(OH)D-deficient, replacement should be initiated using the same treatment as for the general population.

The calcium-phosphorus product has been used to guide treatment decisions, but this is falling out of favor. It was believed that there was benefit in maintaining the calcium-phosphorus product below 70; this was reduced to 55 because of a perceived increased risk of calcification and possibly lower rate of survival (NKF 2003). However, the product is largely influenced by the serum phosphorus concentration, and its labeling provides no additional information. Moreover, because a normal product can lead to poor outcomes in some situations, the calcium-phosphorus product is no longer recommended to guide therapy in clinical practice.

Treatment goals for the various CKD-MBD values are listed in Table 1-5 (KDIGO 2009). The KDIGO guidelines are vague with respect to therapeutic values because high-level evidence is unavailable to make definite recommendations. Although observational data for patients receiving dialysis have shown an association between higher serum phosphorous concentrations and mortality and cardiovascular events, this association has not been studied in randomized controlled trials. No prospective studies have specifically examined the benefits on patient outcomes of targeting different serum phosphorus concentrations. In addition, the actual best upper limit cutoff is unknown but is likely 5.0–7.0 mg/dL. Similarly, the upper threshold of calcium concentrations that increases the relative risk of all-cause mortality is unknown; however, according to observational trials, it appears to be 9.5–11.4 mg/dL (KDIGO 2009).

As with target phosphorus and calcium concentrations, the suggested iPTH level range for patients on dialysis is not supported by high-quality evidence. In general, as CKD progresses, iPTH concentrations must be maintained at higher concentrations because skeletal resistance to iPTH appears to increase. No randomized controlled trials have examined whether treatment to achieve a specific iPTH target improves clinical outcomes. The recommended wide range of iPTH concentrations considers the wide interassay variability that occurs with commercially available assays, which often measure iPTH and PTH fragments.

In observational trials, the iPTH concentrations associated with increased all-cause mortality appear to be 400–600 pg/mL. However, this recommendation is controversial (Qunibi 2011). Opponents of this range point out that in the KDIGO guidelines, the target iPTH range for patients with CKD who are not yet on dialysis involves maintaining the iPTH within the normal range, or up to 65 pg/mL. In addition, the guidelines published before the current KDIGO guidelines recommended an iPTH target range of 150–300 pg/mL. Because of these recommendations and the concerns about adverse effects such as bone fractures and cardiovascular calcification, critics suggest that the new upper limit of iPTH of 600 pg/mL is excessively high (Qunibi 2011). Consequently, in the absence of randomized clinical trials, opponents of the new recommendations propose a narrower target iPTH range of 100–300 pg/mL.

Box 1-1 provides a stepwise approach to treatment for a patient with MBD associated with CKD.

**Treatment**

**Phosphate Binders**

Together with lifestyle modification, phosphate binders are used for the primary treatment of hyperphosphatemia. Serum phosphorus concentrations vary depending on dietary intake, intestinal absorption, bone turnover, and renal phosphorus excretion. Dietary phosphorus is absorbed throughout the small intestine by a nonsaturable passive transport so that the greater the dietary phosphorus intake, the higher the absolute amount absorbed (Malberti 2013). Phosphorus is contained in many foods, including milk and milk products, meat, poultry, fish, grain products, and legumes. These are also high-protein foods, and excessive dietary restriction can result in protein malnutrition. Hence, patients should be encouraged to avoid foods containing phosphorus-containing additives (e.g., meats, baked goods, colas, fast foods) (Calvo 2013).

High serum levels of phosphorus can lead to hyperparathyroidism, renal bone disease, vascular calcification, and mortality. However, because phosphorus is ubiquitous in food and dialysis does not effectively remove it, most patients with CKD will require a phosphate-binding medication. The ideal phosphate binder would be unaffected by gastric pH, be associated with minimal or no systemic absorption, be well tolerated, and be inexpensive. It also would have a high binding capacity for phosphorus, thereby allowing a lower pill burden. Unfortunately, such a binder has not been developed.

Table 1-6 summarizes the characteristics of currently available phosphate binders. The choice of binder is based on concomitant therapies, adverse effect profile, patient preference, and cost. In general, treatment is begun with a calcium-based binder at the lowest dose and titrated to maintain a serum phosphorus concentration within the desired target range. These agents are given with meals and snacks to bind the intestinal phosphorus from dietary intake before it is absorbed. If phosphorus control is not achieved or hypercalcemia occurs, the binder
can be switched to a non–calcium-based binder such as sevelamer. Although aluminum is an effective phosphate binder, it can accumulate in patients with decreased kidney function. Because of serious toxicities (e.g., osteomalacia, central nervous system toxicity, decreased responsiveness to erythropoietic agents), aluminum is seldom used. In current management of hyperphosphatemia, aluminum is typically reserved for short-term use when the phosphorus concentration is very high.

Several studies have compared the currently available phosphate binders. In a meta-analysis, there was no significant decrease in all-cause mortality or hospitalization with sevelamer compared with calcium-based agents. In this analysis, there was a significantly greater reduction in phosphorus and iPTH concentrations with calcium-based phosphate binders (Navaneethan 2009). However, this was at the expense of a significantly increased risk of hypercalcemia. There were significantly more GI adverse events (e.g., abdominal bloating, diarrhea, constipation) with sevelamer than with calcium salts. Moreover, compared with calcium-based agents, lanthanum treatment resulted in significantly lower serum calcium concentrations but similar phosphorus levels. There appeared to be no difference in the effects of calcium acetate and calcium carbonate; the authors concluded that data do not show any important differences in cardiovascular mortality or other patient-level outcomes (Navaneethan 2009).

More recently, in a meta-analysis of 11 randomized trials, patients receiving non–calcium-based binders had a 22% reduction in in all-cause mortality compared with those receiving calcium-based phosphate binders (Jamal 2013). With increasing evidence that hypercalcemia caused by calcium-based binders has serious long-term adverse outcomes including vascular calcification, it is likely that more non–calcium-based phosphate binders will be used in the future (Moe 2006).

Several other agents, including activated charcoal and niacin, have been studied for the treatment of hyperphosphatemia. However, these trials have been small and poorly controlled. The role of these agents remains unclear in the treatment of hyperphosphatemia associated with CKD.

**Vitamin D Analogs**

The term vitamin D is used for both vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). These are considered native forms of vitamin D. Dietary vitamin D comes from ergocalciferol, which is synthesized in plants and yeasts after a UV exposure of the precursor (ergosterol) and cholecalciferol (found in oily fish). More than 90% of human vitamin D comes from sunlight exposure, which converts 7-dehydrocholesterol to previtamin D3, which then undergoes conversion to vitamin D3. Both vitamin D2 and vitamin D3 are hydroxylated in the liver to metabolites known as 25(OH)D. After being hydroxylated in the liver, 25(OH)D is further hydroxylated in the kidney and at other extrarenal sites by 1α-hydroxylase.

### Box 1-1. Example of Treatment Steps in the Management of Bone and Mineral Disorder in Patients Receiving Dialysis

**Step 1:** Measure serum calcium, albumin, phosphorus, iPTH, and vitamin D concentrations.

**Step 2:** Manage hyperphosphatemia.

- Dietary restriction of phosphorus to about 900 mg/day
- Treat with phosphate-binding medications while minimizing hypercalcemia
  - Calcium-based phosphate binder if corrected serum calcium consistently ≤ 10.5 mg/dL
  - Non–calcium-based phosphate binder if corrected serum calcium consistently > 10.5 mg/dL
- Treat vitamin D deficiency

**Step 3:** Assess iPTH after optimal phosphate-binder regimen initiated. Manage hyperparathyroidism.

- If iPTH > 450–600 pg/mL, initiate therapy with a vitamin D analog unless corrected serum calcium consistently > 10.5 mg/dL and/or serum phosphorus consistently > 5.0 mg/dL
- Start with oral calcitriol three times weekly or daily
- If hypercalcemia (serum calcium consistently > 10.5 mg/dL) or hyperphosphatemia (serum phosphorus consistently > 5 mg/dL) occurs with calcitriol, consider changing to paricalcitol or doxercalciferol
- Consider calcimimetic (cinacalcet) if corrected serum > 10.5 mg/dL and/or serum phosphorus consistently > 5.0 mg/dL

**Step 4:** Titrate phosphate binders and vitamin D analog or calcimimetic according to periodic evaluation of serum calcium, albumin, phosphorus, and iPTH.

**iPTH = intact parathyroid hormone.**


Several vitamin D receptor agonists are approved for the treatment of secondary hyperparathyroidism in patients with CKD. Paricalcitol and doxercalciferol, which are synthetic, biologically active vitamin D2 analogs of calcitriol, bind to vitamin D receptors, including those in the parathyroid gland, to reduce PTH production and correct the resultant abnormalities in calcium and phosphorus. Table 1-7 reviews the initial dosing and titration of these agents.

Calcitriol is available generically in both oral and injectable formulations. In general, calcitriol is the least-expensive oral or injectable product available. Calcitriol has affinity for both intestinal and parathyroid gland
<table>
<thead>
<tr>
<th>Drug (dosage form)</th>
<th>Initial Dose</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Approx. Monthly Cost of Initial Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminum hydroxide Suspension, 320 mg/5 mL, others</td>
<td>15–30 mL three times daily with meals; for short-term therapy only</td>
<td>Effective Inexpensive Does not increase serum calcium Efficacy unaffected by gastric pH</td>
<td>Long-term use associated with aluminum accumulation, dementia, encephalopathy, osteomalacia, anemia GI adverse effects – constipation, fecal impaction, nausea, vomiting Poor palatability</td>
<td>Not applicable; for short-term therapy only</td>
</tr>
<tr>
<td>Calcium acetate Capsule, 667 mg (United States only) Tablet, 667 mg (Canada only) Suspension, 667 mg/5 mL</td>
<td>1334 mg three times daily with meals</td>
<td>Less systemic calcium absorption than calcium carbonate</td>
<td>Large tablets/capsules that must be swallowed Has been associated with hypercalcemia Efficacy somewhat affected by gastric pH May require large pill burden Calcium may be associated with vascular calcification GI adverse effects – constipation, nausea, vomiting</td>
<td>$75</td>
</tr>
<tr>
<td>Calcium carbonate Tablets, suspension, various strengths</td>
<td>500 mg three times daily with meals</td>
<td>Many dosage forms Inexpensive</td>
<td>Inexpensive Has been associated with hypercalcemia Efficacy affected by gastric pH May require large pill burden Calcium may be associated with vascular calcification GI adverse effects – constipation, nausea, vomiting</td>
<td>$15</td>
</tr>
<tr>
<td>Lanthanum Chewable tablet, 250 mg (Canada only), 500 mg, 750 mg, 1000 mg</td>
<td>500 mg three times daily with meals</td>
<td>Effective Does not increase serum calcium Efficacy unaffected by gastric pH Low pill burden</td>
<td>Expensive Must be chewed completely GI adverse effects – nausea, vomiting</td>
<td>$775</td>
</tr>
<tr>
<td>Sevelamer carbonate Tablet, 800 mg Powder for oral suspension, 800 mg, 2400 mg</td>
<td>800–1600 mg three times daily with meals</td>
<td>Does not increase serum calcium Available in powder for suspension for patients unable to swallow Lowers TC and LDL-C</td>
<td>Less effective Expensive Efficacy affected by gastric pH May require large pill burden Binds fat-soluble vitamins GI adverse effects – nausea, vomiting</td>
<td>$250</td>
</tr>
<tr>
<td>Sevelamer hydrochloride Tablet 800 mg</td>
<td>800–1600 mg three times daily with meals</td>
<td>Does not increase serum calcium Lowers TC and LDL-C</td>
<td>Less effective Expensive Efficacy affected by gastric pH May require large pill burden Binds fat-soluble vitamins GI adverse effects – nausea, vomiting Causes acidosis in some patients</td>
<td>$300</td>
</tr>
<tr>
<td>Sucroferric oxyhydroxide Tablet, 500 mg</td>
<td>500 mg three times daily with meals</td>
<td>Does not increase serum calcium</td>
<td>Expensive Must be chewed completely</td>
<td>$1000</td>
</tr>
</tbody>
</table>
voltage-sensitive calcium channels and may increase serum calcium concentrations. Paricalcitol and doxercalciferol are available in oral and injectable formulations. Doxercalciferol is a vitamin D2 prohormone, 1α-hydroxyvitamin D2, which requires activation in the liver by 25-hydroxylase; thus, it should only be used in patients with normal hepatic function.

In patients with an elevated iPTH concentration who do not respond to dietary restriction of phosphorus and phosphate-binding medications, additional therapy is warranted. In these cases, a vitamin D receptor agonist (calcitriol, paricalcitol, and doxercalciferol) or the calcimimetic cinacalcet should be added. Agent selection should be based on the trends of calcium, phosphorus, and iPTH concentrations; their degree of abnormality; and concomitant therapy with phosphorus binders. If the serum calcium concentration is low or normal, vitamin D receptor agonists should be initiated.

No data support the clinical superiority of any vitamin D receptor agonist available in the United States. Calcitriol and, to a lesser extent, paricalcitol and doxercalciferol are associated with increased concentrations of serum calcium or phosphorus in some patients. However, data regarding more patient-centered outcomes such as morbidity and mortality are not available. In a meta-analysis of 76 trials (3667 patients; 71 trials used placebo), vitamin D analogs did not reduce the risk of death, bone pain, vascular calcification, or parathyroidectomy compared with placebo. In fact, compared with placebo, vitamin D analogs were associated with an increased risk of hypercalcemia and hyperphosphatemia, but a consistent reduction in iPTH concentrations was not noted. The authors concluded that the value of vitamin D treatment for patients with CKD remains uncertain (Palmer 2007).

Few studies have compared paricalcitol directly with doxercalciferol. Clinically, the choice between agents may be based on patient-specific information, cost, formulary issues, and indication. Because calcitriol is commonly the least-expensive vitamin D drug available, it is an attractive first-line option, provided the calcium concentration is within the target range. If the calcium concentration is not well controlled, a newer vitamin D drug (paricalcitol or doxercalciferol) should be recommended.

Because the vitamin D agents are similar (especially doxercalciferol and paricalcitol), it may be necessary to switch from one agent to another for reasons such as hypercalcemia or formulary restraints. Of note, in the era of a bundled payment from Medicare, intravenous medications are not separately reimbursed to dialysis facilities but are included in the lump sum payment received per patient. This has led to a shift toward the use of oral vitamin D receptor agonists and to increased use of oral calcitriol, the only oral agent available in a generic formulation. There is no set guide for conversion between agents. One study showed that, when converting a patient from paricalcitol to doxercalciferol, the dose should be reduced by 40% (i.e., the doxercalciferol dose should be about 60% of the paricalcitol dose). Other sources have suggested a ratio of 1:4:5 between the agents calcitriol/doxercalciferol/paricalcitol, respectively (Tomasello 2007). A 1:3 ratio of calcitriol/paricalcitol has also been recommended (Mittman 2006). If converting between agents, the iPTH, calcium, and phosphorus concentrations should be monitored monthly until the dose is stable. Adjustments in the vitamin D agent, phosphate binders, and/or calcimimetics may be needed after the conversion.

Vitamin D therapy should be discontinued if the iPTH concentration is below goal because oversuppression may

Table 1-7. Use of Vitamin D in Patients Receiving Dialysis

<table>
<thead>
<tr>
<th>Agent</th>
<th>Availability</th>
<th>Initial Dosing</th>
<th>Titration*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcitriol</td>
<td>Capsules, 0.25 mcg and 0.5 mcg, Injection, 1 mcg/1 mL</td>
<td>0.25 mcg PO daily</td>
<td>Increase by 0.25 mcg/day at 4- to 8-week intervals</td>
</tr>
<tr>
<td>(Rocaltrol, generics)</td>
<td>Injection, 1 mcg/1 mL</td>
<td>1–2 mcg IV TIW</td>
<td>Increase by 0.5–1 mcg at 2- to 4-week intervals</td>
</tr>
<tr>
<td>Doxercalciferol</td>
<td>Capsules, 0.5 mcg, 1 mcg, and 2.5 mcg, Injection 4 mcg/2 mL</td>
<td>10 mcg PO TIW</td>
<td>Increase by 2.5 mcg at 8-week intervals</td>
</tr>
<tr>
<td>(Hectorol)</td>
<td>Injection, 4 mcg/2 mL</td>
<td>4 mcg IV TIW</td>
<td>Increase by 1–2 mcg at 8-week intervals</td>
</tr>
<tr>
<td>Paricalcitol</td>
<td>Capsules, 1 mcg, 2 mcg, and 4 mcg</td>
<td>Based on initial iPTH Dose (mcg) = iPTH (pg/mL)/80</td>
<td>Increase according to iPTH using same formula at 2- to 4-week intervals</td>
</tr>
<tr>
<td>(Zemplar)</td>
<td>Injection 2 mcg/mL, 5 mcg/mL</td>
<td>0.04–0.1 mcg/kg IV</td>
<td>Increase by 2–4 mcg at 2- to 4-week intervals</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TIW (2.8–7 mcg)</td>
<td></td>
</tr>
</tbody>
</table>

*Titration based on serum iPTH, serum calcium, and serum phosphorus concentrations.

iPTH = intact parathyroid hormone; IV = intravenously; PO = by mouth; TIW = three times weekly.
lead to adynamic bone disease. Adynamic bone disease is characterized low-bone turnover with lower rates of both collagen synthesis by osteoblasts and subsequent mineralization of bone collagen. Research has shown that during the altered bone metabolism of adynamic disease, patients are also at a higher risk of vascular calcification.

Calcimimetics

A newer strategy to control secondary hyperparathyroidism is use of the calcimimetic agent cinacalcet. Cinacalcet acts by binding to and allosterically modifying the calcium-sensing receptor on the chief cell of the parathyroid gland. This causes an increased sensitivity of the receptor to extracellular calcium. The calcium-sensing receptor is a G-coupled receptor, and through a series of second messenger pathways, the parathyroid gland down-regulates gene transcription and release of iPTH. Because cinacalcet does not increase serum calcium concentrations, and is in fact associated with hypocalcemia, it is especially useful in patients with hypercalcemia in whom vitamin D therapy cannot be used or optimized. Cinacalcet helps decrease iPTH concentrations and maintain calcium and phosphorus concentrations with or without concomitant vitamin D agents.

The initial dosage of cinacalcet is 30 mg by mouth once daily. The dose is then titrated, in 30-mg increments, every 2–4 weeks until the iPTH is within the target range to a maximum of 180 mg/day. However, in clinical practice, iPTH values are obtained monthly or less frequently, so dosage titration occurs over a longer period. The most common adverse effect of cinacalcet is nausea and vomiting, but this is typically generally self-limiting and can be reduced by administration with food. Cinacalcet should not be initiated in patients if their corrected serum calcium concentration is less than 8.4 mg/dL. Product labeling recommends the monitoring of serum calcium within 1 week of initiation or dose adjustment and monthly once the dose has been stabilized. If serum calcium falls below 8.4 mg/dL but remains above 7.5 mg/dL, or if symptoms of hypocalcemia occur, calcium-containing phosphate binders and/or vitamin D sterols should be used to increase serum calcium concentrations. If the serum calcium concentration is below 7.5 mg/dL, or if symptoms of hypocalcemia persist and the dose of vitamin D or calcium-containing phosphate binder cannot be increased, cinacalcet should be withheld until serum calcium concentrations are 8.0 mg/dL. Treatment should be reinitiated using a lower cinacalcet dose. If the serum iPTH concentration decreases to less than 2 times the upper reference limit for the assay, cinacalcet should be reduced or discontinued.

Cinacalcet’s role in the treatment of hyperparathyroidism in patients with CKD is not known. In a recent randomized controlled trial, 3883 patients with moderate to severe secondary hyperparathyroidism who were undergoing hemodialysis received either cinacalcet or placebo. The patients were followed for up to 64 months. The primary composite end point was the time until death, myocardial infarction, hospitalization for unstable angina, heart failure, or a peripheral vascular event. In an unadjusted intention-to-treat analysis, none of the primary end points showed a statistical difference (EVOLVE 2012).

A recent meta-analysis of 18 evaluable trials (7446 patients) compared cinacalcet plus conventional therapy (phosphate binders, vitamin D analogs) with placebo or no treatment plus conventional therapy (Palmer 2012). Cinacalcet had minimal or no effect on all-cause mortality and minimal effect on cardiovascular mortality. Cinacalcet was effective at preventing the need for parathyroidectomy and for treating hypercalcemia. However, cinacalcet therapy was associated with significant hypocalcemia as well as nausea and vomiting. The authors calculated that, on average, treating 1000 people receiving dialysis with cinacalcet for 1 year had no effect on survival and prevented about three patients from needing parathyroidectomy. However, this was at the risk of a patient’s developing hypocalcemia (60 of 1000 patients) or nausea (150 of 1000 patients).

For an example of managing BMD in patients receiving dialysis, see Box 1-1.

Role of Native Vitamin D

Although patients on dialysis are often treated with vitamin D analogs, the need for native vitamin D has been underrecognized until recently. In the past, the kidneys were thought to be the only sites of 1α-hydroxylation, so administering native vitamin D to patients with CKD was considered unnecessary. More recent evidence suggests a potential role for 25(OH)D in several tissues, apart from renal conversion. In addition, in the general population, vitamin D has widespread extraskeletal benefits, and vitamin D deficiency has been associated with an increased risk of falls, infection, cancer, autoimmune diseases, cardiovascular diseases, and mortality. The effects of low 25(OH)D concentrations in patients with CKD have been less well studied. Preliminary evidence in patients with CKD suggests that vitamin D deficiency is associated with mortality, vascular calcification and stiffness, and kidney disease progression in patients not yet on dialysis. Because cardiovascular disease is so common in patients with CKD, the potential cardiovascular benefits of vitamin D may be even more important in them than in patients without CKD.

Vitamin D deficiency is common in patients with CKD; concentrations are typically measured using a serum 25(OH)D. Although the proper cutoff values for diagnosing insufficiency and deficiency are often debated, deficiency is usually defined as a serum 25(OH)D of less than 10 ng/mL, and concentrations of 10–30 ng/mL are considered indicative of vitamin D insufficiency. Between 80% and 100% of patients in renal dialysis units in North America are thought to have low serum 25(OH)D concentrations. The cause is multifactorial and includes lack
of exposure to sunlight, inadequate vitamin D intake in the diet, and uremic toxins affecting the 25-hydroxylation step in the liver. In addition, higher concentrations of FGF23 may increase vitamin D catabolism.

Regardless of the cause of 25(OH)D insufficiency and deficiency, it is recognized that patients with CKD may require supplementation. The KDIGO treatment guidelines note that although no randomized controlled trials with cholecalciferol or ergocalciferol in patients on dialysis are available, one uncontrolled study evaluating treatment with cholecalciferol for 6 months resulted in improvements of iPTH, calcium, and phosphorus in some patients (KDIGO 2012). Other studies have shown no improvements in iPTH, calcium, and phosphorus serum concentrations (Kandula 2011; Palmer 2007). However, because of the theoretical benefits, relative safety, and low cost of supplements, some experts recommend the use of native vitamin D supplementation, in addition to calcitriol, paricalcitol, or doxercalciferol, to increase 25(OH)D levels in patients with CKD, including those on dialysis.

A variety of dosing regimens have been suggested to treat low vitamin D concentrations in patients with CKD. Typically, ergocalciferol is used in the United States, whereas cholecalciferol is used in Europe. Although animal studies suggest that vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol) are equipotent, evidence in humans suggests that high-dose vitamin D2 is less effective than vitamin D3 in increasing 25(OH)D concentrations. Older NKF guidelines suggest dosing regimens of ergocalciferol 50,000 international units weekly to monthly, depending on the 25(OH)D concentration in patients with stage 3 or 4 CKD. No specific regimens were suggested for patients receiving dialysis. Other guidelines have recommended cholecalciferol 20,000 international units weekly to monthly.

Further research is needed to determine the efficacy of cholecalciferol or ergocalciferol in patients with later stages of CKD, including those on dialysis, and to determine the effects on the prevention or delay of arterial calcification in patients with vitamin D deficiency. The primary end point has been suggested to be cardiovascular and all-cause mortality, with parallel assessments of cardiovascular and aortic calcification in CKD.

### Patient Education

Despite substantial evidence of the risks they carry that are associated with MBD, phosphorus, calcium, and iPTH remain suboptimally controlled in many patients. A recent study showed that, despite the use of phosphate binders, 70% of hemodialysis patients still had hyperphosphatemia. In another study, almost 40% of patients reported nonadherence to their phosphate binders. Effective treatment of hyperphosphatemia and hyperparathyroidism requires multifaceted efforts to educate...
patients on self-management behaviors and appropriate use of phosphate binders (Toussaint 2011).

The pharmacist plays an important role in developing and monitoring a therapeutic regimen to effectively treat disorders of calcium, phosphorus, and iPTH. Factors to consider when selecting a regimen for the treatment of MBD include insurance coverage, pill burden, palatability, comorbid diseases, drug interactions, and adverse effects. Patients who do not maintain biochemical values within the target ranges should be evaluated for potential nonadherence. Directly questioning the patient, doing pill counts, and reviewing patients’ pharmacy prescription profiles and refill histories may all be necessary to determine whether nonadherence is contributing to poor phosphorus control. Patients may not understand that they must take phosphate binders with food, and not too long before or after meals. They may be under a false impression about phosphate binders. For example, patients may believe that calcium carbonate is only for indigestion or that they can take binders only with meals, not with snacks. Consequently, patient education and frequent reinforcement are often necessary.

**Conclusion**

The incidence of CKD is expected to continue to increase. Many patients with CKD will progress to stage 5 CKD and require either peritoneal dialysis or hemodialysis. Pharmacists are key members of the health care team caring for these patients, contributing an understanding of the etiology, treatment, and monitoring of conditions associated with dialysis. Anemia and BMD are universal conditions in patients receiving dialysis, and pharmacists can have a significant impact on the treatment of these conditions.

**References**


Berns JS. Anemia of chronic kidney disease: target hemoglobin/hematocrit for patients treated with erythropoietic agents. Up to Date, November 14, 2013.


Gori T. **Viscosity, platelet activation, and hematocrit: progress in understanding their relationship with clinical and subclinical vascular disease.** *Clin Hemorheol Microcirc* 2011;49:37-42.


Qunibi W, Kalantar-Zadeh K. **Target levels for serum phosphorus and parathyroid hormone.** *Semin Dial* 2011;24:29-33.


Singh AK. **ESAs in dialysis patients: are you a hedgehog or a fox?** *J Am Soc Nephrol* 2010;21:543-6.


Stein J, Dignass A, Chow KU. **Clinical case reports raise doubts about the therapeutic equivalence of an iron sucrose similar preparation compared with iron sucrose originator.** *Curr Med Res Opin* 2012;28:241-43.


Winkelmayer WC. **Confusion about the appropriate use of erythropoiesis-stimulating agents in patients undergoing maintenance dialysis.** *Semin Dial* 2010;23:486-91.
Self-Assessment Questions

Questions 1 and 2 pertain to the following case.
M.G. is a 72-year-old woman (weight 70 kg) with diabetes and hypertension who has been undergoing hemodialysis (HD) for 1 year. She is currently receiving epoetin alfa 4000 units subcutaneously once weekly, and her dose has been the same for the past month. She tells you she is having trouble walking around her apartment. At her last HD session, laboratory tests results were as follows: transferrin saturation 15% and serum ferritin 435 ng/mL. Her hemoglobin concentration is 9.3 g/dL; 2 weeks ago, it was 9.7 g/dL. She is receiving sodium ferric gluconate complex in sucrose 62.5 mg intravenously once weekly.

1. Which one of the following is best to recommend for M.G.?
   A. Discontinue weekly iron sucrose; increase epoetin alfa dose to 5000 units three times weekly.
   B. Continue weekly iron sucrose; increase epoetin alfa dose to 5000 units three times weekly.
   C. Discontinue the weekly iron sucrose; start iron sucrose 100 mg intravenously at every HD session for the next 10 sessions.
   D. Discontinue weekly iron sucrose; start oral ferric gluconate 300 mg three times daily, and increase epoetin alfa to 5000 units three times weekly.

2. The action you recommended was initiated, and it is now 4 weeks later. M.G.’s hemoglobin is 10.2 g/dL. She reports that she has been feeling better the past week. Which one of the following is best to recommend for M.G.?
   A. Increase her epoetin dose by 25%.
   B. Decrease her epoetin dose by 25%.
   C. Continue her current epoetin dose.
   D. Increase her epoetin dosing to twice weekly.

Questions 3–5 pertain to the following case.
G.R. is a 56-year-old man (weight 80 kg) with chronic kidney disease (CKD) who is new to peritoneal dialysis. He has a peritoneal dialysis catheter that was placed “a while ago,” but he did not follow up, and he is not receiving epoetin. He states that he feels tired and short of breath. His complete blood cell count (CBC) reveals hemoglobin 7.5 g/dL and hematocrit 22.2%. His serum creatinine (SCr) is 9.0 mg/dL. Erythropoiesis-stimulating agent (ESA) therapy is initiated, and he undergoes laboratory testing.

3. Which one of the following is the best initial ESA regimen for G.R.?
   A. Epoetin alfa 8000 units subcutaneously three times weekly.
   B. Epoetin alfa 24,000 units subcutaneously three times weekly.
   C. Epoetin alfa 24,000 units subcutaneously once weekly.
   D. Darbepoetin alfa 100 mcg subcutaneously once weekly.

4. Four weeks later, G.R. returns to the clinic. His current drugs are the ESA he was initiated on at his last visit, ferrous sulfate 325 mg twice daily, a multivitamin supplement, calcium acetate 667 mg three times daily, and insulin. He admits forgetting to go for his laboratory tests and missing “a few” of his ESA doses. You check his hemoglobin concentration in the clinic using a point-of-care hemoglobin concentration analyzer, which reveals his hemoglobin concentration as 7.7 g/dL. His blood pressure is 130/85 mm Hg, heart rate 80 beats/minute, and respiratory rate 18 breaths/minute. His symptoms have not changed since his last visit 2 weeks ago. You have none of his other laboratory values. Which one of the following is the best to recommend for G.R.?
   A. Increase his ESA dose by 25%.
   B. Administer iron sucrose 200 mg intravenously today and schedule him to return for four additional doses.
   C. Observe self-administration of the ESA and discuss adherence.
   D. Monitor G.R. for another 4 weeks to allow maximal effect of ESA therapy.

5. G.R. goes to the laboratory for tests after his visit. Laboratory results show that hemoglobin 8.5 g/dL, transferrin saturation 5%, ferritin 25 mg/dL, glucose 252 mg/dL, intact parathyroid hormone (iPTH) 846 pg/mL, and ferritin 25 mg/dL. He takes ferrous sulfate 325 mg three times daily and a multivitamin supplement. Which one of the following is the most appropriate change to G.R.’s regimen today?
   A. Increase ESA by 50%.
   B. Administer ferumoxytol 510 mg intravenously today, and schedule him to return for one additional dose.
   C. Increase ferrous sulfate to 650 mg three times daily and add a stool softener.
   D. Administer ferrous gluconate 125 mg today, and schedule him to return for seven additional doses.
6. A 78-year-old woman is hospitalized for 4 days for a cardiac catheterization. Her medical history includes type 2 diabetes mellitus, coronary artery disease and a previous myocardial infarction, hypertension, and arthritis. During her hospitalization, she is empirically treated with epoetin alfa 20,000 units intravenously three times weekly at each HD session. She is discharged and reports for her first post-hospitalization HD session the next day. Her hemoglobin is 8.5 g/dL (before hospitalization, it was 10.0 g/dL, and she was receiving epoetin 5000 units intravenously three times weekly at dialysis). Her new outpatient dialysis orders are to continue the hospital’s epoetin order of 20,000 units intravenously three times weekly. Which one of the following is the best intravenous epoetin dose to give this patient today?
A. 20,000 units.
B. 25,000 units.
C. 5000 units.
D. 10,000 units.

Questions 7–9 pertain to the following case.
S.W. is a 68-year-old woman (weight 80 kg) who presents to the emergency department with nausea and vomiting, fatigue, and “pain in her bones.” She states that food does not taste good and that she has a metallic taste in her mouth. She has not seen a health care professional in 10 years. In the emergency department, her SCr is 9.2 mg/dL, and her estimated GFR is 6 mL/minute/1.73m². Her laboratory values are as follows: sodium 135 mEq/L, potassium 7.0 mEq/L, bicarbonate 14 mEq/L, glucose 464 mg/dL, hemoglobin 8.4 g/dL, hematocrit 27%, albumin 2.8 g/dL, calcium 8.0 mg/dL, phosphorus 8.9 mg/dL, and PTH 986 pg/mL. In addition, her blood pressure is 192/98 mm Hg. S.W. is given a diagnosis of stage 5 CKD, likely caused by long-standing hypertension and diabetes mellitus, and HD is initiated. An HD catheter is placed.

7. Which one of the following is the most appropriate treatment for S.W.?
A. Transfuse packed red blood cells to achieve a hemoglobin concentration of 11 g/dL.
B. Start epoetin alfa 20,000 units intravenously three times weekly at each HD session.
C. Start darbepoetin alfa 25 mcg intravenously once weekly at the first HD session of the week.
D. Start darbepoetin alfa 40 mcg intravenously once weekly at the first HD session of the week.

8. Three months later, while rounding in the outpatient HD unit, you see S.W. She tells you that she is feeling better but still has muscle weakness and joint pain. After reviewing her laboratory values, you note that her hemoglobin concentration has not increased as expected and that today, her concentration is 8.7 g/dL, despite progressive increases in her ESA dose. Her most recent iron studies show a transferrin saturation of 35% and a serum ferritin concentration of 1154 mg/dL. Her serum PTH concentration is 1400 mcg/mL, and serum calcium and phosphorus are within the target range. She has not made an appointment with the vascular surgeon to have an arteriovenous fistula inserted; instead, she continues to be dialyzed through an HD catheter. Her dialysis adequacy is low. Which one of the following actions is most likely to improve S.W.’s response to darbepoetin alfa?
A. Start paricalcitol 5 mcg by intravenous push three times weekly at each HD session.
B. Start ferric gluconate 125 mg intravenously for the next eight dialysis sessions.
C. Increase ESA by 50%.
D. Transfuse with packed red blood cells to achieve a hemoglobin of 11 g/dL.

9. Which one of the following actions would most greatly affect S.W.’s response to ESAs?
A. Placing an arteriovenous fistula.
B. Increasing the length of dialysis to improve dialysis adequacy.
C. Placing an arteriovenous fistula and initiating oral iron.
D. Increasing the length of dialysis to improve dialysis adequacy and initiating intravenous levocarnitine.

Questions 10 and 11 pertain to the following case.
E.O. presents to the emergency department with concerns about shortness of breath and dyspnea on exertion. His only other known medical problem is a history of heart failure. E.O. is given a diagnosis of stage 5 CKD, and HD is initiated immediately. Other pertinent laboratory values include hemoglobin A1C 7.9%, blood glucose 315 mg/dL, calcium 9.0 mg/dL, phosphorus 9.8 mg/dL, albumin 2.4 g/dL, and serum 25-hydroxyvitamin D (25(OH)D) 9 ng/mL. E.O. is currently taking no medications.

10. In addition to dietary phosphorus restriction, which one of the following phosphate-binding agents is most appropriate for E.O.?
A. Calcium acetate 667 mg by mouth three times daily with meals.
B. Sevelamer 800 mg by mouth three times daily with meals.
C. Aluminum hydroxide 30 mL by mouth three times daily with meals.
D. Calcium carbonate 1250 mg by mouth twice daily spaced between meals.
11. Which one of the following is best to recommend for E.O.?
   A. Ergocalciferol 5000 international units once daily for 6 months.
   B. Cholecalciferol 50,000 international units once daily for 6 months.
   C. Ergocalciferol 50,000 international units once weekly for 6 months.
   D. Cholecalciferol 25,000 international units twice weekly for 6 months.

Questions 12–14 pertain to the following case.
F.F. is a 32-year-old woman with kidney failure secondary to systemic lupus erythematosus. She has been on peritoneal dialysis for 2 years. At her monthly clinic visit, she is concerned about her “upset stomach.” Her laboratory values are as follows: calcium 8.8 mg/dL, albumin 2.8 g/L, and phosphorus 5.1 mg/dL. Her most recent iPTH level was 702 pg/mL. Her drugs include prednisone 10 mg by mouth once daily, hydroxychloroquine 200 mg by mouth once daily, sevelamer 800 mg by mouth three times daily with meals, and paricalcitol 5 mcg by mouth every other day.

12. Which one of the following is best to recommend for F.F.’s CKD–bone and mineral disorder (BMD)?
   A. Increase paricalcitol to 10 mcg by mouth once daily.
   B. Discontinue paricalcitol. Start doxercalciferol 0.5 mcg by mouth every other day.
   C. Discontinue paricalcitol. Start calcitriol 1 mcg by mouth once daily.
   D. Start cinacalcet 30 mg by mouth once daily.

13. Which one of the following laboratory monitoring recommendations is best to recommend for F.F.?
   A. Check serum calcium in 1 week.
   B. Check iPTH value in 1 week.
   C. Check serum calcium and phosphorus values in 2 weeks.
   D. Check iPTH value in 2 weeks.

14. Three months later, F.F. returns to the clinic. Her laboratory values include calcium 8.8 mg/dL, phosphorus 7.6 mg/dL, albumin 2.6 g/dL, and iPTH 289 pg/mL. She does not like sevelamer therapy because it bothers her stomach, and she has not been taking it regularly. Which one of the following is best to recommend for F.F.?
   A. Discontinue sevelamer; start aluminum hydroxide 30 mL three times daily with meals.
   B. Discontinue sevelamer; start calcium carbonate 500 mg by mouth three times daily and at bedtime.
   C. Increase sevelamer to 1600 mg three times daily with meals.
   D. Discontinue sevelamer; start lanthanum 500 mg by mouth three times daily with meals.

Questions 15–19 pertain to the following case.
G.R. is a 55-year-old man (weight 85 kg) who was given a diagnosis of diabetes 25 years ago. He admits that he dislikes taking his medications and that his fasting blood glucose is often greater than 200 mg/dL. His other medical problems include arthritis, hypothyroidism, and glaucoma. He comes to the clinic today with concerns of shortness of breath, lack of appetite, and fatigue. He has noticed that these symptoms have progressively worsened during the past year. His home drugs include glipizide 10 mg daily, ibuprofen 400 mg once or twice weekly as needed for pain, timolol 0.25% eyedrops twice daily, and latanoprost 0.005% eyedrops at bedtime. His laboratory values include the following: sodium 144 mEq/L, potassium 5.4 mEq/L, SCR 4.5 mg/dL, BUN 115 mg/dL, estimated GFR 11 mL/minute/1.73m², random glucose 353 mg/dL, serum phosphorus 7.2 mg/dL, calcium 8.8 mg/dL, albumin 3.7 g/dL, hemoglobin 8.9 g/dL, hematocrit 27%, white blood cell count 7.3 x 10³ cells/mm³, PTH 651 pg/mL, and serum 25(OH)D 8 ng/mL. G.R.’s red blood cell indices are within normal limits. Hemodialysis is initiated.

15. Which one of the following would best treat G.R.’s vitamin D deficiency?
   A. Ergocalciferol 50,000 international units by mouth weekly.
   B. Calcitriol 0.25 mcg by mouth three times weekly.
   C. Doxercalciferol 4 mcg intravenously three times weekly.
   D. No treatment necessary.

16. Which one of the following is the most likely cause of G.R.’s anemia?
   A. Elevated concentrations of FGF23 (fibroblast growth factor 23).
   B. GI bleed because of nonsteroidal anti-inflammatory use.
   C. Deficiency of erythropoietin.
   D. Deficiency of vitamin D.

17. Which one of the following is the most appropriate target hemoglobin range for G.R.?
   A. 7.5–8 g/dL.
   B. 9.5–10 g/dL.
   C. 11–12 g/dL.
   D. 10–12 g/dL.
18. Which one of the following is the most appropriate target iPTH range for G.R.?
   A. 10–55 pg/mL.
   B. 55–100 pg/mL.
   C. 100–300 pg/mL.
   D. Greater than 600 pg/mL.

19. Which one of the following would best treat G.R.’s BMD?
   A. Dietary phosphorus restriction and phosphate-binding therapy.
   B. Oral calcitriol 0.5 mcg three times weekly.
   C. Oral doxercalciferol 2.5 mg three times weekly.
   D. Oral cinacalcet 30 mg once daily.

20. Which one of the following would be best to treat G.R.’s anemia?
   A. Epoetin alfa 8500 units intravenously three times weekly.
   B. Epoetin alfa 8000 units intravenously three times weekly.
   C. Epoetin alfa 20,000 units intravenously three times weekly.
   D. Epoetin alfa 40,000 units intravenously three times weekly.
LONG-TERM MANAGEMENT AFTER KIDNEY TRANSPLANTATION

BY STEVEN GABARDI, PHARM.D., FCCP, BCPS; AND CHRISTIN ROGERS, PHARM.D., FCCP, BCPS

Reviewed by Megan S. Pickard, Pharm.D., BCPS; and Jaime A. Foushee, Pharm.D., BCPS

LEARNING OBJECTIVES

1. Distinguish the mechanisms of action, adverse reaction and drug-drug interaction profiles, and recommended monitoring principles for maintenance immunosuppressive agents.
2. Assess the risks of acute rejection and antibody-mediated rejection for the individual patient and evaluate treatment strategies.
3. Design appropriate therapeutic regimens for preventing and managing infectious cardiovascular and endocrine complications after transplantation.
4. Evaluate for the risk of malignancies after kidney transplantation, and compose treatment options for one of these complications.
5. Justify the importance of immunosuppressive drug adherence in transplantation, and demonstrate ways to predict and prevent nonadherence.

INTRODUCTION

Since the first successful one in 1954, almost 350,000 kidney transplants have been done in the United States. Optimal pharmacologic management of renal transplant recipients (RTRs) is vital to achieving long-term patient and allograft survival. Late allograft loss and complications of long-term immunosuppression remain of utmost concern, especially because long-term allograft survival has shown minimal improvement during the past 10 years (Schaefer 2012).

The primary objective of immunosuppression is to prevent acute allograft rejection while limiting allograft dysfunction and improving survival. However, medical immunosuppression is imprecise because satisfactory in vivo monitoring techniques are lacking. There is a fine balance between over- and under-immunosuppression; therefore, use of immunosuppressants necessitates intense...
Induction Therapy

Induction therapy helps prevent acute rejection during the critical early posttransplant period by providing a high degree of immunosuppression at the time of transplantation. Therapy is initiated intraoperatively or immediately postoperatively and ends shortly after transplantation. A complete discussion on induction therapy is outside the scope of this chapter. However, the choice of induction agent affects the long-term management of RTRs. For example, use of T cell–depleting antibodies (i.e., antithymocyte globulin, alemtuzumab) allows minimization of maintenance immunosuppression but may increase the long-term risk of infection and malignancy.

Maintenance Immunosuppression

An immunosuppressive regimen requires careful dosage adjustment to balance the risks of rejection with the toxicities. The degree and net exposure to immunosuppression strongly correlate with the occurrence of infection and malignancy; therefore, it is vital that immunosuppression be reduced whenever appropriate.

Modern regimens have made it possible to attain T cell–mediated rejection rates less than 10% and 1-year graft survival rates greater than 97% (Matas 2013). The five classes of maintenance immunosuppressants are calcineurin inhibitors (CNIs), target of rapamycin (ToR) inhibitors, antiproliferatives, costimulation blockade, and corticosteroids. Table 2-1 describes the maintenance immunosuppressive agents. Most regimens include a CNI and an adjuvant agent (i.e., antiproliferative, ToR inhibitor), with or without corticosteroids. More than 80% of renal transplant centers use tacrolimus and mycophenolic acid (MPA) as their maintenance immunosuppressive backbone (Matas 2013). However, determining appropriate dosing or whether to continue the immunosuppressive agents chosen at the time of transplantation or to convert to another agent should be patient-specific with consideration of the agent’s pharmacologic properties, adverse event profile, and potential for drug–drug interactions, as well as patient comorbidities.

Calcineurin Inhibitors

The CNIs reduce cytokine synthesis with a resultant decline in T-lymphocyte proliferation. In 2009, almost 94% of all RTRs in the United States received a CNI as their primary immunosuppressant (Matas 2013). These agents have proved most effective in preventing allograft rejection and promoting good, but not excellent, long-term graft function. More than 87% of transplant centers use tacrolimus as their principal CNI, mainly because of its proven benefits in clinical trials. A meta-analysis (almost 4200 patients; more than 30 randomized controlled trials) examined the relative efficacy and safety of the CNIs in RTRs (Webster 2005). Tacrolimus was associated with significantly less allograft loss than cyclosporine (graft loss reduced by 44%; relative risk [RR] 0.56; 95% confidence interval [CI], 0.36–0.86). This benefit persisted at 3 years posttransplantation but was diminished in patients with

<table>
<thead>
<tr>
<th>Abbreviations in This Chapter</th>
</tr>
</thead>
<tbody>
<tr>
<td>aHUS</td>
</tr>
<tr>
<td>AMR</td>
</tr>
<tr>
<td>CCB</td>
</tr>
<tr>
<td>CMV</td>
</tr>
<tr>
<td>CNI</td>
</tr>
<tr>
<td>CVD</td>
</tr>
<tr>
<td>DSA</td>
</tr>
<tr>
<td>EBV</td>
</tr>
<tr>
<td>FSGS</td>
</tr>
<tr>
<td>Ig</td>
</tr>
<tr>
<td>IVlg</td>
</tr>
<tr>
<td>MPA</td>
</tr>
<tr>
<td>NODAT</td>
</tr>
<tr>
<td>PCP</td>
</tr>
<tr>
<td>PTLD</td>
</tr>
<tr>
<td>REMS</td>
</tr>
<tr>
<td>RTR</td>
</tr>
<tr>
<td>TDM</td>
</tr>
<tr>
<td>ToR</td>
</tr>
</tbody>
</table>

patient monitoring. Although experience has helped streamline management strategies, immunosuppressive regimens must be individualized and continually evaluated.

Immunosuppressive regimens are based on the premise that the immune response is most robust immediately after transplantation, requiring maximal suppression. Host-graft adaptation leads to a reduced immune response over time, enabling lessened immunosuppression. Most protocols begin with induction therapy and/or high-dose maintenance immunosuppression in the early posttransplant period. The degree of immunosuppression can be reduced over time to a level appropriate for the given patient. To maximize allograft outcomes and reduce untoward complications, it is imperative that clinicians understand the advantages and disadvantages of immune suppression agents. There are no universally accepted guidelines on managing immunosuppressants in RTRs. Center-specific transplantation protocols are available, but therapy must be individualized, and a one-size-fits-all model is not appropriate. This chapter focuses on the long-term management of RTRs who receive maintenance immunosuppression at least 3 months after transplantation.
<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of Action</th>
<th>General Dosing Recommendation</th>
<th>Key Information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Calcineurin Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Inhibits expression of key cytokine genes such as IL-2, IL-4, and TNF</td>
<td>Concentration controlled dosing generally given in two divided doses General TDM recommendations (12-hour trough concentrations): • First 6 months posttransplantation: 200–300 ng/mL • After 6 months: 100–200 ng/mL</td>
<td>Selected adverse events • Cardiovascular (hypertension, hyperlipidemia) • Cosmetic (gingival hyperplasia, hirsutism, alopecia) • Electrolyte abnormalities (hyperkalemia, hypomagnesemia) • Endocrine (hyperglycemia) • GI (nausea, vomiting, diarrhea) • Hematologic (leukopenia, thrombocytopenia) • Neurologic (hand tremor, headache, insomnia) • Renal (nephrotoxicity, long-term allograft dysfunction) Clinical pearls • CYP3A4/Pgp substrate (many DDIs)</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Concentration-controlled dosing generally given in two divided doses or once daily with the extended-release formulation General TDM recommendations (12- and 24-hour [extended release only] trough concentrations): • First 6 months posttransplantation: 8–12 ng/mL • After 6 months: 4–8 ng/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antiproliferatives</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Antagonizes purine metabolism and inhibits synthesis of DNA, RNA, and proteins</td>
<td>Recommended dosing is 2–5 mg/kg given once daily Most patients develop hematologic adverse events with higher doses and generally tolerate only 1–3 mg/kg/day TDM not recommended</td>
<td>Selected adverse events • Hematologic (leukopenia, thrombocytopenia) Clinical pearls • Significant dose reductions required in the presence of xanthine oxidase inhibitors or with TPMT deficiency</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>Inhibitor of inosine monophosphate dehydrogenase, thereby preventing the de novo pathway of purine synthesis</td>
<td>1000 mg twice daily starting dose Doses may be divided and given three or four times daily to help manage GI intolerance Doses may be lowered to help manage GI intolerance or hematologic adverse events TDM not recommended</td>
<td>Selected adverse events • Hematologic (leukopenia, thrombocytopenia) • GI (nausea, vomiting, diarrhea, abdominal pain, dyspepsia, gastritis) Clinical pearls • Equimolar doses of the two mycophenolate products: 1000 mg of mycophenolate mofetil = 720 mg of enteric-coated MPA</td>
</tr>
<tr>
<td>Enteric-coated MPA</td>
<td></td>
<td>720 mg twice daily starting dose Doses may be divided and given three or four times daily to help manage GI intolerance TDM not recommended</td>
<td></td>
</tr>
<tr>
<td><strong>Proliferation Signal Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sirolimus</td>
<td>Inhibits ToR, resulting in a reduction in IL-2–driven lymphocyte proliferation</td>
<td>Concentration-controlled dosing generally given once daily General TDM recommendations (24-hour trough concentrations): • Combined with mycophenolate: 6–10 ng/mL • Combined with CNI: 4–8 ng/mL</td>
<td>Selected adverse events • Cardiovascular (hypertriglyceridemia, hyperlipidemia) • Endocrine (hyperglycemia) • GI (nausea, vomiting, diarrhea) • Hematologic (leukopenia, thrombocytopenia) • Miscellaneous (prolonged DGF, impaired wound healing, lymphocele, mucositis) • Neurologic (hand tremor, headache, insomnia) • Pulmonary (aseptic pneumonitis) • Renal (proteinuria) • Skin (rash) Clinical pearls • CYP3A4/Pgp substrate (many DDIs) • It should strongly be considered to hold ToR inhibitor therapy (e.g., convert to a CNI) in patients undergoing surgical procedures because of the risk of impaired wound healing</td>
</tr>
<tr>
<td>Everolimus</td>
<td>Concentration-controlled dosing generally given in two divided doses General TDM recommendations (12-hour trough concentrations): 3–8 ng/mL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
higher tacrolimus trough concentrations (not defined by authors). Tacrolimus was also associated with less biopsy-proven acute rejection (RR 0.69; 95% CI, 0.60–0.79) and steroid-resistant rejection (55% reduction; RR 0.49; 95% CI, 0.37–0.64) at 12 months. New-onset diabetes after transplantation (NODAT), neurologic adverse events, and gastrointestinal (GI) toxicities were more prevalent with tacrolimus, whereas cyclosporine was associated with more cosmetic-related adverse events and cardiovascular disease (CVD).

Both CNI agents are generally given twice daily; however, to improve adherence, tacrolimus has been reformulated as a once-daily preparation. A systematic review found similar rejection rates for extended-release versus conventional-release tacrolimus (RR 1.24; 95% CI, 0.93–1.65; p=0.15) (Ho 2013). Moreover, both preparations had similar rates of patient survival (RR 0.99; 95% CI, 0.97–1.02; p=0.55) and allograft survival (RR 0.99; 95% CI, 0.97–1.02; p=0.67). The safety analysis revealed no differences between the formulations. If a dose is missed, the once-daily formulation can be administered any time within 14 hours of the missed dose. This formulation may improve adherence, but this has yet to be shown in clinical trials.

### Therapeutic Drug Monitoring

Whole-blood cyclosporine and tacrolimus therapeutic drug monitoring (TDM) is essential, especially given the wide inter- and intra-patient variability in these agents. Trough concentration (C0) monitoring has been the standard for both agents. However, data suggest that the
cyclosporine area under the concentration-time curve (AUC) best correlates with concentrations drawn 2 hours postdose (C2) (Knight 2007). The long-term benefits of C2 monitoring remain unclear, yet short-term data suggest it improves renal function and reduces cyclosporine-induced hypertension. One main limitation of C2 monitoring is that concentrations must be drawn 2 hours plus or minus 15 minutes after administration; this is why most centers continue using C0. All tacrolimus formulations, including those that are extended release, use TDM and recommend similar trough goals. Of note, CNI concentrations are not accurate unless steady state has been reached, which generally occurs 2–3 days after dose titration. Target CNI TDM recommendations are institution-specific and vary significantly. They are also patient-specific and depend on the degree of immunologic risk, concomitant immunosuppressants, and time since transplantation. In general, 6 months or more after transplantation, the goal C0 values for cyclosporine and tacrolimus are 100–200 ng/mL and 3–8 ng/dL, respectively. However, goals may be significantly lower when these agents are coadministered with a ToR inhibitor.

Management of Adverse Events

After its introduction in the 1980s, cyclosporine revolutionized transplantation by significantly decreasing rejection rates and improving short- and long-term patient survival. The widespread use of CNIs led to the recognition of multiple clinically relevant adverse events with immediate and long-term implications. Although some adverse events with cyclosporine and tacrolimus are idiosyncratic, most CNI-related adverse events are concentration-dependent and can be managed with dose reductions. However, dose reduction or conversion between immunosuppressants may increase the risk of adverse immunologic events such as rejection. Managing CNI-related adverse events is an important role for the transplant pharmacist. Recognized long-term adverse events of CNIs include CVD and cosmetic, endocrine, renal, and neurologic effects (Table 2-2).

Cardiovascular Disease

Hypertension

Almost 90% of RTRs have hypertension. Cyclosporine is the most likely CNI to cause hypertension because of its ability to activate the renin-angiotensin-aldosterone and sympathetic nervous systems, suppress atrial natriuretic factor and nitric oxide production, and induce sodium retention. Management of posttransplant hypertension generally involves the initiation or optimization of antihypertensive pharmacotherapy. Antihypertensive agents are reviewed later in this chapter. However, antihypertensive pharmacotherapy may not be sufficient to manage resistant hypertension in RTRs; therefore, other interventions may be considered, such as angioplasty for renal artery stenosis or removal of one or both native kidneys.

Hyperlipidemia

Almost 50% of RTRs have lipid abnormalities. Cyclosporine is the most likely causative agent among the CNIs and has been associated with alterations in low-density lipoprotein metabolism and distribution, as well as altered bile acid synthesis. Posttransplant hyperlipidemia generally does not respond to therapeutic lifestyle changes and requires lipid-lowering therapy. Lipid-lowering agents are reviewed later in this chapter. Patients with hyperlipidemia who are receiving cyclosporine should be strongly considered for cyclosporine dose reductions or conversion to tacrolimus or a non–CNI-containing regimen, although ToR inhibitors are not appropriate for patients with significant hypertriglyceridemia.

Cosmetic

Cosmetic adverse events should be treated seriously, especially in women and adolescents, because of their potential to result in nonadherence. The most common CNI-induced cosmetic adverse events are alopecia, gingival hyperplasia, and hirsutism.

Alopecia

Tacrolimus has been associated with alopecia in almost 20% of RTRs (Chan 2003). The mechanism of tacrolimus-induced hair loss has not been elucidated. Resolution of alopecia appears to coincide with lower tacrolimus concentrations; therefore, initial therapy should be dose reduction. If dose reduction is not possible or ineffective, the use of topical minoxidil or oral finasteride, in male patients only, is appropriate. Some clinicians recommend the use of thiamine, folic acid, and/or biotin. If these options are unsuccessful, conversion of tacrolimus to either cyclosporine or a non–CNI-containing regimen is indicated.

Gingival Hyperplasia

In 20% of patients cyclosporine is associated with gingival hypertrophy; this is believed to be secondary to increased interleukin (IL)-6 and transforming growth factor β-1 concentrations (Hood 2002). This condition is worsened in patients with poor dental hygiene and those receiving other agents known to induce gum hyperplasia (e.g., nifedipine, phenytoin). Gingival hyperplasia often responds to reduced cyclosporine concentrations; however, some patients may require gingivectomy. Conversion from cyclosporine to tacrolimus or a non–CNI-containing regimen may also be effective in managing gingival hyperplasia. Although some case reports show the efficacy of azithromycin and metronidazole in treating cyclosporine-induced gum hypertrophy, no clinical trials have evaluated these methods.
<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Most Likely Offending CNI</th>
<th>Monitoring Values</th>
<th>Therapeutic Management Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephrotoxicity</td>
<td>Either</td>
<td>SCr, BUN, Urine output, Biopsy-proven CNI-induced nephrotoxicity</td>
<td>Reduce CNI dose (if possible), Use of CCBs for hypertension control, Modify regimen (change to non–CNI-containing regimen [ToR inhibitor or belatacept])¹</td>
</tr>
<tr>
<td>Hypertensionb</td>
<td>Cyclosporine</td>
<td>Blood pressure, Heart rate</td>
<td>Initiate patient-specific antihypertensive therapy, Reduce cyclosporine dose (if possible), Modify regimen (change to tacrolimus or non–CNI-containing regimen)¹</td>
</tr>
<tr>
<td>Hyperlipidemiab</td>
<td>Cyclosporine</td>
<td>Fasting lipid panel</td>
<td>Initiate patient-specific cholesterol-lowering therapy, Reduce cyclosporine dose (if possible), Modify regimen (change to tacrolimus or non–CNI-containing regimen)¹</td>
</tr>
<tr>
<td>Hyperglycemiac</td>
<td>Tacrolimus</td>
<td>Blood glucose (fasting and nonfasting), A1C</td>
<td>Lifestyle modifications, Reduce tacrolimus dose (if possible), Reduce steroids (if patient is taking them and if possible), Initiate patient-specific glucose-lowering therapy (insulin or oral therapy), Modify regimen (change to cyclosporine or non–CNI-containing regimen)¹</td>
</tr>
<tr>
<td>Neurotoxicitiesc</td>
<td>Tacrolimus</td>
<td>Fine hand tremor, Headache, Mental status changes</td>
<td>Reduce tacrolimus dose (if possible), Modify regimen (change from tacrolimus to cyclosporine or non–CNI-containing regimen)¹</td>
</tr>
<tr>
<td>Hirsutism</td>
<td>Cyclosporine</td>
<td>Patient has excessive hair growth or male-pattern hair growth</td>
<td>Reduce cyclosporine dose (if possible), Cosmetic hair removal, Modify regimen (change to tacrolimus or non–CNI-containing regimen)¹</td>
</tr>
<tr>
<td>Alopecia</td>
<td>Tacrolimus</td>
<td>Patient has excessive hair loss</td>
<td>Reduce tacrolimus dose (if possible), Hair growth treatments (i.e., minoxidil, finasteride – males only), Consider using a multivitamin with thiamine and folic acid and/or biotin 5000 mcg daily, Modify regimen (change to cyclosporine or non–CNI-containing regimen)¹</td>
</tr>
<tr>
<td>Gingival hyperplasia</td>
<td>Cyclosporine</td>
<td>Patient has excessive gum growth, Discuss options for therapy with the patient’s dentist</td>
<td>Reduce cyclosporine dose (if possible), Review regimen for other offending medications, Oral surgery (gum resection), Modify regimen (change to tacrolimus or non–CNI-containing regimen)¹</td>
</tr>
</tbody>
</table>

¹Modifying the immunosuppressive regimen increases the risk of rejection, even in patients who are stable. This option should be chosen cautiously and implemented with proper monitoring and follow-up.

bTacrolimus is also associated with hypertension and hyperlipidemia, but to a lesser extent than cyclosporine.

cCyclosporine is also associated with hyperglycemia and neurotoxicities, but to a lesser extent than tacrolimus.

CCB = calcium channel blocker; CNI = calcineurin inhibitor; ToR = target of rapamycin.
Hirsutism
Hirsutism occurs in almost 60% of patients treated with cyclosporine (Walker 2007). This is partly caused by cyclosporine’s growth-promoting influence on hair epithelial cells and is most pronounced in children and young adults. Cyclosporine-induced hirsutism often responds well to dose reductions; however, in some patients this may be impossible. Cosmetic hair removal (e.g., waxing, laser hair removal) may be temporary solutions until doses can be reduced. In severe cases, conversion from cyclosporine to tacrolimus or a non-CNI-containing regimen may be appropriate.

Endocrine
Alterations in blood glucose levels are common after renal transplant, most likely secondary to CNI and corticosteroids. Both CNIs are toxic to pancreatic islet cells; however, tacrolimus appears to have a greater impact on beta-cell function, likely secondary to increased tacrolimus concentrations within islet cells. Other risk factors for hyperglycemia include obesity, African or Hispanic race, family history of diabetes, and history of hepatitis C infection.

Overall, NODAT occurs in almost 20% of patients receiving tacrolimus. The effect of NODAT is less pronounced in patients receiving an early steroid withdrawal immunosuppressive regimen. Tacrolimus-induced hyperglycemia is often related to concentrations, and tacrolimus dose reductions may improve glucose handling. In patients with persistent hyperglycemia or established NODAT, conversion from tacrolimus to cyclosporine or belatacept may provide benefit. However, in most cases, the management of NODAT will require glucose-lowering therapies. Hypoglycemic agents appropriate for RTRs are discussed later in this chapter.

Nephrotoxicity
Calcineurin inhibitor–induced renal dysfunction is a concentration-related, often reversible, renal vasoconstriction that primarily affects the afferent arterioles (Issa 2013). Some literature suggests that the vasoconstriction is more pronounced with cyclosporine than with tacrolimus, but both agents are considered major nephrotoxins.

The primary management for CNI-induced renal dysfunction is to lower the dose, if appropriate. Even small reductions in concentrations can significantly affect renal function. Calcium channel blockers (CCBs), particularly the dihydropyridines, may reduce the incidence and severity of CNI-related nephrotoxicity. Some data show that amlodipine use, even in normotensive RTRs, significantly improves renal function (Cross 2009). When dose reduction and CCBs are ineffective, conversion to a non–CNI-based regimen may be beneficial. However, conversion to a ToR inhibitor must precede significant renal dysfunction (i.e., glomerular filtration rate [GFR] greater than 40 mL/minute/1.73m² and proteinuria less than 500 mg).

Neurologic
Several neurologic toxicities have been observed with CNIs and are generally more pronounced with tacrolimus (Webster 2005). Hand tremor, dysesthesias, headache, and insomnia are common and are generally concentration-related. However, some patients develop neurotoxicities despite therapeutic or subtherapeutic concentrations. Dose reduction is considered first line, if appropriate. For patients in whom dose reduction is unwarranted or ineffective, converting from tacrolimus to cyclosporine or a non–CNI-based regimen is appropriate.

CNI Minimization Strategies
Although CNIs decrease rejection rates and improve short-term outcomes in RTRs, focus has shifted toward preventing CNI-related toxicities by CNI minimization, avoidance, or withdrawal. A randomized controlled trial studied the efficacy and safety of de novo CNI avoidance (Ekberg 2007b). Patients(n=1645) were randomized to one of four treatment groups: (1) standard-dose cyclosporine (C0 150–300 ng/mL x 3 months; then 100–200 ng/mL); (2) MPA and prednisone versus a regimen that included daclizumab induction; (3) MPA and prednisone in addition to low-dose tacrolimus (C0 3–7 ng/mL); (4) low-dose sirolimus (C0 4–8 ng/mL), and (5) low-dose cyclosporine (C0 50–100 ng/mL). The tacrolimus group, compared with other patient groups, had the highest mean calculated GFR at 12 months (65.4 mL/minute vs. 56.7–59.4 mL/minute; p<0.001) and lowest rejection (12.3% vs. 24%–37.2%; p<0.001). Allograft survival rate was also significantly higher with tacrolimus than with the other groups (94.2% vs. 89.3%–93.1%; p=0.02). Serious adverse events, which were not well defined, were most common with sirolimus. At 36 months, the low-dose tacrolimus group continued to have the highest mean GFR compared with the other groups (68.6 mL/minute vs. 65.3–68.6 mL/minute; p=0.17), but this was no longer statistically different (Ekberg 2009). The tacrolimus group continued to have the lowest rejection rate and the highest graft survival rate, although differences among the groups were less over time. The authors concluded that low-dose tacrolimus is the most beneficial and efficacious regimen.

A different trial investigated the efficacy and safety of de novo reduction and delayed withdrawal of cyclosporine (Ekberg 2007a). This prospective multicenter trial randomized 536 patients into three groups: standard-dose cyclosporine, MPA, and prednisone; daclizumab, low-dose cyclosporine (C0 50–100 ng/mL), MPA, and prednisone; and daclizumab, low-dose cyclosporine (withdrawn at 6 months), MPA, and prednisone. There was no difference between the three groups in 12-month mean GFR; however, the rate of rejection at 12 months was significantly higher in the cyclosporine withdrawal group (p<0.05). This study showed that complete CNI withdrawal, without the addition of another immunosuppressant, was associated with poor short-term results.
Given the need to balance the increased rejection rate with improved renal function, CNI minimization requires careful identification and selection of patients with low immunologic risk. De novo CNI minimization may spare renal function and maintain acceptable rejection rates; however, long-term data are needed to confirm the short-term benefits shown in current trials.

ToR Inhibitors

The ToR inhibitors are a potent class of immunosuppressants that block IL-2–driven T-cell proliferation. The ToR inhibitors may be used in CNI avoidance, minimization, or conversion regimens. In 2009, ToR inhibitors were used in only 3%–6% of RTRs overall (Matas 2013). Although not considered nephrotoxic, these agents have a large adverse event profile and must be monitored appropriately.

Therapeutic Drug Monitoring

There is excellent correlation between whole-blood C0 and the AUC for the ToR inhibitors. Some transplant centers use the ToR inhibitors in CNI withdrawal regimens and aim for C0 concentrations lower than those recommended by the manufacturers, especially with sirolimus. Like the CNI, ToR inhibitor TDM recommendations are institution and patient-specific. In general, for patients greater than 6 months posttransplantation, sirolimus goal C0 values are 5–10 ng/mL when coadministered with MPA and 3–8 ng/mL when coadministered with CNI. Everolimus goal C0 values are 3–8 ng/mL. Of note, sirolimus has a lengthy half-life; therefore, a loading dose is warranted to achieve steady state quicker. However, in maintenance patients requiring dose adjustments, steady-state will not be achieved for several days. In this situation, C0 should be monitored 7–8 days after dose adjustment. Everolimus has a significantly shorter half-life (28 hours) than sirolimus (62 hours).

Special Considerations

Complications such as prolonged delayed graft function, delayed wound healing, and lymphocyte formation limit the de novo use of ToR inhibitors. Proteinuria and glomerulonephropathy have been reported, especially after conversion from a CNI. It has been suggested not to use these agents in patients with preexisting proteinuria or a GFR of less than 40 mL/minute/1.73m² (Schena 2009).

Antimetabolites

The antiproliferatives, which inhibit purine synthesis, are used as adjuvant agents and are coadministered with a CNI, a ToR inhibitor, or belatacept. This class consists of azathioprine and the MPA derivatives. The MPA derivatives have largely replaced azathioprine as the antiproliferative drug of choice and are used in almost 90% of RTRs (Matas 2013).

Special Considerations

The MPA derivatives are associated with GI adverse events and myelosuppression. Enteric-coated MPA was developed to reduce upper GI adverse events but in two studies had comparable efficacy and safety outcomes (Budde 2004; Salvadori 2004). However, in an open-label study of RTRs with mycophenolate mofetil–induced GI distress, conversion to enteric-coated MPA reduced GI symptoms and improved quality of life (Chan 2006). A change from twice-daily to three- or four-times-daily dosing at the same daily dosage, or decreasing the total daily dosage, may also help manage GI intolerance. Efforts to convert to enteric-coated MPA and/or divide doses are likely warranted first because dose reductions may lead to unwanted immunologic effects. Azathioprine can be considered in patients intolerant of the GI adverse effects of both MPA formulations.

Costimulation Blockade

Belatacept is a fusion protein that prevents costimulation, resulting in T-cell anergy. Compared with cyclosporine, belatacept improved GFR despite a higher incidence of rejection (Rostaing 2013). Cardiovascular and metabolic outcomes were also better with belatacept than with cyclosporine. This agent has not proven more effective than tacrolimus (Ferguson 2011).

Special Considerations

Belatacept carries a boxed warning for an increased risk of posttransplant lymphoproliferative disorders (PTLDs), especially in the central nervous system. Its use is contraindicated in patients who are Epstein-Barr virus (EBV) seronegative and in those with an unknown EBV status. Cases of progressive multifocal leukoencephalopathy have also been reported.

Belatacept is the first intravenous maintenance immunosuppressant, and all doses are based on actual body weight at the time of initiation. Doses should not be modified unless there is a greater than 10% change in body weight. In addition, all doses should be rounded to the nearest 12.5-mg increment.

Corticosteroids

Their immunosuppressive mechanism is poorly understood, but large doses of corticosteroids are believed to be lymphotoxic, and small doses (i.e., less than 100 mg of prednisone equivalent) are associated with a reduction in various cytokines. The substantial metabolic adverse event profile necessitates a long-term goal of minimizing steroid exposure. This can be accomplished with low maintenance dosages (5 mg/day or less) or steroid withdrawal–based regimens.

Corticosteroid Minimization Strategies

In a long-term analysis of more than 18,000 RTRs, death with a functioning allograft accounted for 40% of
all graft loss; CVD was the leading cause of death (Ojo 2000). These results provide impetus to prevent corticosteroid-induced CVD. In a 2008 open-label trial (n=337), patients received basiliximab induction, modified cyclosporine, and enteric-coated MPA. The three treatment arms included no intravenous or oral steroids at any time (steroid avoidance), withdrawal from steroids at postoperative day 7 (early steroid withdrawal), and long-term maintenance corticosteroids (standard). Several patients in the steroid-avoidance group required add-on steroid therapy at some point to maintain appropriate graft function. However, the early steroid withdrawal group had rejection rates similar to the standard steroid maintenance group and a better metabolic profile (Vincenti 2008).

A similar analysis comparing steroid withdrawal with a standard maintenance steroid protocol showed a higher risk of rejection in the withdrawal group (p=0.058) but improved metabolic outcomes. Both groups had similar 1-year allograft survival and patient outcomes (Woodle 2008). In two large meta-analyses, RTRs considered at low immunologic risk experienced similar rates of rejection and allograft survival with corticosteroid withdrawal versus maintenance corticosteroids (Knight 2010; Pascual 2005). However, rates of rejection and graft loss increased when corticosteroids were withdrawn 3 months after transplantation (Pascual 2004). The consensus is that corticosteroids should be withdrawn rapidly before 3 months posttransplantation.

**Drug-Drug Interactions**

As the number of agents a patient receives increases, so does the potential for drug interactions. Other risk factors include disease severity, age, and organ dysfunction. Therefore, RTRs are at a high risk of significant interactions. Often, drug interactions with the immunosuppressants are unavoidable but acceptable with proper dose adjustments and monitoring.

**Pharmacokinetic Interactions**

Pharmacokinetic drug interactions pose a major dilemma with maintenance immunosuppressants. These interactions can occur during drug absorption, distribution, metabolism, and elimination.

**Interactions of Absorption**

Gut metabolism, modifications in active transport, and changes in intestinal motility and chelation interactions alter the absorption of the immunosuppressants. P-glycoprotein (Pgp) affects the absorption of the CNI and ToR inhibitors; therefore, drugs that inhibit or induce Pgp affect the bioavailability of these agents. For example, Pgp inhibitors such as verapamil or quinidine increase the concentrations of cyclosporine, tacrolimus, sirolimus, and everolimus because of reduced Pgp-dependent drug elimination.

Prokinetic agents interact with the CNIs through changes in intestinal motility. Metoclopramide increases the absorption of cyclosporine and tacrolimus by enhancing gastric motility and emptying, resulting in increased CNI concentrations.

Most interactions with the MPA products result in reduced intestinal absorption. Proton pump inhibitors decrease the oral absorption of mycophenolate mofetil but not enteric-coated MPA. Divalent and trivalent cations (e.g., aluminum, magnesium, calcium) decrease MPA absorption through chelation. These agents should be administered at least 1 hour before or 2 hours after MPA. The clinical implications of these interactions are unknown, but reductions in MPA exposure can theoretically increase rejection risk.

**Interactions of Distribution**

Interactions of distribution occur most often with highly protein-bound drugs. Mycophenolic acid is the only highly protein-bound (97%) maintenance immunosuppressant with an interaction of distribution. Concomitant administration of MPA with salicylates increases MPA-free concentrations. The adverse sequelae of this interaction are unknown. Drug interaction studies have not been conducted with MPA derivatives and other highly protein-bound drugs.

**Interactions of Metabolism**

Oxidative metabolism by cytochrome P450 (CYP) isozymes is the primary method of xenobiotic metabolism. The CNI and ToR inhibitors are substrates of the CYP3A isozyme system and interact with known substrates, inhibitors, and inducers of CYP3A. Empiric dose changes are necessary when coadministration with an interacting drug cannot be avoided. For example, it is recommended to reduce tacrolimus doses by one-third in patients initiating voriconazole. Some clinicians use interactions of metabolism to reduce the dose of an immunosuppressant, such as using diltiazem to treat hypertension, which also helps reduce tacrolimus doses and decrease pill burden.

Not all metabolic drug interactions occur through the CYP system. Azathioprine has a considerable interaction with allopurinol and febuxostat that is mediated through the inhibition of xanthine oxidase, the enzyme responsible for metabolizing 6-mercaptopurine to 6-thiouricarboxylic. Combining these agents can result in 6-mercaptopurine accumulation and severe myelosuppression. Concomitant therapy with azathioprine and allopurinol or febuxostat should be avoided, but if necessary, azathioprine doses should be empirically reduced by 75%.

**Interactions of Elimination**

Mycophenolate is metabolized to MPA glucuronide by hepatic glucuronosyltransferase and then excreted in the bile for gut elimination. Deconjugation of MPA...
pharmacodynamic interactions are common and can be troublesome, such as when drugs with similar adverse events are used concomitantly. For example, nephrotoxic agents (e.g., amphotericin B, aminoglycosides, nonsteroidal anti-inflammatory drugs) may potentiate CNI-induced renal dysfunction, whereas myelosuppressive agents (e.g., sulfamethoxazole/trimethoprim, valganciclovir) can enhance the myelosuppressive potential of antiproliferatives.

In addition to reviewing prescription drugs, it is essential to ask patients about nonprescription agents and dietary supplements, which also have the potential for significant interactions (e.g., St. John’s wort induces metabolism of CNIs and ToR inhibitors; willow bark can worsen CNI-induced nephrotoxicity).

IMMUNOLOGIC COMPLICATIONS

Despite advances in surgical techniques, histocompatibility testing, and immunosuppression, immunologic complications are common and include hyperacute rejection, T cell–mediated rejection, antibody-mediated rejection (AMR), and chronic rejection. Onset generally depends on the time since transplantation. Times of allograft injury are classified as immediate (less than 1 week), early (1–12 weeks), and late (more than 3 months) posttransplantation. This chapter discusses long-term management but not immediate and early immunologic complications.

T cell–Mediated Rejection

Defined as an acute deterioration in renal function associated with specific pathologic changes in the allograft, T cell–mediated rejection can occur any time posttransplantation but usually occurs early. Induction immunosuppression has decreased rejection, which now occurs in only about 12% of RTRs (Matas 2013). Acute rejection is rare after the first 6 months; its occurrence may signal insufficient immunosuppression or medication nonadherence. Rejection should be suspected when signs of renal dysfunction are present, including elevated SCr, decreased urine output, and fluid retention. Fever and graft tenderness, historically symptoms of rejection, are less common in the era of modern immunosuppression. Table 2-3 summarizes antirejection agents.

Treatment Strategies

Corticosteroids

Pulse corticosteroids are considered first-line treatment of cellular rejection because high-dose corticosteroids are lymphotoxic. Intravenous methylprednisolone is the treatment of choice for low-grade T cell–mediated rejection; after completing intravenous therapy, patients may resume oral steroids tapered to their pre-pulse daily dose. For patients previously withdrawn from corticosteroids, it may be reasonable to reinitiate a low daily dose.

Special Precautions

Any increase in immunosuppression may increase susceptibility to the opportunistic infections, most notably Pneumocystis jiroveci pneumonia (PCP), cytomegalovirus (CMV), and oral candidiasis. Clinicians may consider reinitiating targeted antimicrobial prophylaxis during and/or after pulse corticosteroid therapy.

Clinical Efficacy

Success rates for courses of pulse corticosteroids are 60%–76% with intravenous methylprednisolone and 56%–72% with oral therapy (Park 1984). If successful, increased urine output and decreased SCr are usually noted within 5 days of therapy. Studies randomizing high-dose (methylprednisolone 1000 mg) and low-dose (methylprednisolone 250–500 mg) corticosteroids have noted no significant differences in success rates but have noted a dose-related increase in toxicity. If renal function continues to decline despite an adequate steroid pulse, escalated therapy using a T cell–depleting antibody may be warranted.

Antithymocyte Globulin

Two antithymocyte globulin products are available for the treatment of rejection – equine antilymphocyte globulin and antithymocyte globulin rabbit. Head-to-head studies strongly favor antithymocyte globulin rabbit, the focus of this discussion.

Pharmacology

Antithymocyte globulin rabbit is a pasteurized, purified immunoglobulin (Ig) preparation produced by immunizing rabbits with human thymocytes. This agent binds to lymphocytes, promoting T-cell depletion through complement-mediated cytotoxicity. The agent also promotes B-cell apoptosis, opsonization, and phagocytosis. After T-cell depletion with antithymocyte globulin rabbit, immune reconstitution may take several months. During therapy, patients require daily complete blood cell count (CBC) monitoring; significant decreases warrant reducing or holding a dose.

Special Precautions

Cytokine release and serum sickness are adverse events requiring special monitoring. Antithymocyte globulin administration destroys monocytes and lymphocytes,
### Table 2-3. Selected Characteristics of Agents Used for TCMR and AMR

<table>
<thead>
<tr>
<th>Agent</th>
<th>TCMR or AMR</th>
<th>Dosing Guidelines and General Recommendations</th>
<th>Common Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids(^a)</td>
<td>TCMR</td>
<td>250–500 mg IV methylprednisolone x 3–5 doses</td>
<td>Endocrine (insulin resistance, osteoporosis)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Considered first-line therapy for low-severity TCMR</td>
<td>Miscellaneous (impaired wound healing, water retention)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Considered second-line therapy for low-severity TCMR</td>
<td>Neurologic (hand tremor, mood disturbances, psychosis, muscle weakness)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Considered first-line therapy for moderate- and high-severity TCMR</td>
<td></td>
</tr>
<tr>
<td>Antithymocyte globulin rabbit</td>
<td>TCMR</td>
<td>1.5 mg/kg IV x 4–14 doses</td>
<td>Hematologic (leukopenia, thrombocytopenia)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Considered second-line therapy for low-severity TCMR</td>
<td>Infusion-related (cytokine-release syndrome(^b))</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Considered first-line therapy for moderate- and high-severity TCMR</td>
<td>Miscellaneous (serum sickness)</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>Both</td>
<td>15–30 mg IV or SC x 1–2 doses</td>
<td>Hematologic (leukopenia, thrombocytopenia)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infusion-related (nausea, vomiting, diarrhea, headache, dysesthesias, and dizziness)</td>
<td></td>
</tr>
<tr>
<td>Intravenous Ig AMR</td>
<td>AMR</td>
<td>10–100 g after each plasmapheresis session; or 2 g/kg IV x 1 dose</td>
<td>Hematologic (thrombosis)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Together with plasmapheresis, IVIg is often considered first-line therapy for AMR</td>
<td>Infusion-related (hypotension, shaking, chills, wheezing, flushing, nausea, anxiety, chest tightness, back pain, hypertension)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neurologic (septic meningitis)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Renal (renal dysfunction)</td>
<td></td>
</tr>
<tr>
<td>Rituximab</td>
<td>AMR</td>
<td>375 mg/m(^2) – 1000 mg IV x 1 dose</td>
<td>Hematologic (leukopenia, thrombocytopenia)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Should not be administered as monotherapy for AMR</td>
<td>Infusion related (urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, anaphylactoid events(^c))</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Should not be administered with eculizumab because needs complement for rituximab to be effective</td>
<td>Miscellaneous (infectious complications including PML)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Skin (severe mucocutaneous reactions)</td>
<td></td>
</tr>
<tr>
<td>Bortezomib AMR</td>
<td>AMR</td>
<td>1.3 mg/m(^2) IV on days 1, 4, 8, and 11(^d)</td>
<td>Hematologic (leukopenia, thrombocytopenia)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Often given with plasmapheresis and IVIg in cases of refractory AMR or AMR reoccurrence</td>
<td>Infusion related (nausea, vomiting, diarrhea, fever, headache, insomnia, dizziness, hypotension, peripheral edema, dyspnea)</td>
</tr>
<tr>
<td>Eculizumab AMR</td>
<td>AMR</td>
<td>1200 mg IV x 1 dose, followed 1 week later by four weekly doses of 900 mg, with a final dose of 1200 mg at week 5(^e)</td>
<td>Miscellaneous (infectious complications including meningococcal infection)</td>
</tr>
</tbody>
</table>

\(^a\)Short-term complications of corticosteroids listed; long-term complications can be found in Table 2-1.

\(^b\)Cytokine-release syndrome symptoms include fever, chills, headache, nausea, diarrhea, myalgias, hypotension, tachycardia, and (rarely) cardiorespiratory events.

\(^c\)Infusion-related reactions occur within 30–120 minutes after infusion.

\(^d\)Bortezomib doses should be separated by 72 hours to allow proteasomes time to restore function.

\(^e\)Supplemental dose of 600 mg should be administered after plasmapheresis (if patient is currently receiving plasmapheresis).

AMR = antibody-mediated rejection; IV = intravenous(ly); PML = progressive multifocal leukoencephalopathy; SC = subcutaneous; TCMR = T cell–mediated rejection.
which release cytokines that cause severe, acute infusion-associated reactions. These reactions occur shortly after therapy initiation and can present as fever, chills, headache, nausea, diarrhea, myalgias, hypotension, and tachycardia. Severe acute cytokine release can cause serious cardiopulmonary events and significant morbidity and mortality. The incidence and severity of reactions are reduced by premedicating with antihistamines and acetaminophen and reducing infusion rates. In the patient with cytokine release syndrome, routine medical management of symptoms is warranted, and therapy may be delayed or aborted.

Serum sickness is a self-limiting allergic reaction: an immune complex consisting of the patient’s antibodies and antithymocyte globulin rabbit is deposited in small blood vessels, and an inflammatory response ensues. The classic presentation is a triad of fever, rash, and joint stiffness/pain occurring 5–15 days after therapy is completed. Serum sickness generally resolves on its own, but corticosteroids and plasmapheresis may hasten resolution. The reported incidence of serum sickness secondary to antithymocyte globulin rabbit is 2%–20%.

Comparative Efficacy and Safety
Many trials have compared antithymocyte globulin rabbit with both oral and intravenous corticosteroids. Although trial regimens have had significant heterogeneity, pooled analyses suggest that antithymocyte globulin rabbit is superior to corticosteroids alone in reversing rejection episodes (failure to reverse rejection; RR 0.50; 95% CI, 0.26–0.96) (Webster 2006). Compared with corticosteroids alone, antithymocyte globulin rabbit decreased graft loss and reduced time to reversal of rejection and recurrent rejection episodes. However, antithymocyte globulin rabbit is associated with more short-term adverse events and long-term infectious complications and malignancy, and therefore is generally reserved for severe or steroid-resistant rejection. As stated earlier, reinitiating antimicrobial prophylaxis is prudent when treating rejection.

Alemtuzumab
Pharmacology
Alemtuzumab is a monoclonal antibody directed against CD52 that causes complement-mediated lysis. CD52 is present on almost all B and T lymphocytes and on several other immune-modulating cells. Alemtuzumab-induced lymphocyte depletion is rapid and extensive, with cellular reconstitution taking several months to years. Alemtuzumab is not indicated for transplantation but has a role as a T-cell–depleting antibody. There are few data on its use for rejection and no consensus on the appropriate dose.

Comparative Efficacy and Safety
Steroid-resistant rejection episodes are generally treated with antithymocyte globulin rabbit, but one study compared alemtuzumab (n=11; 15–30 mg subcutaneously on 2 subsequent days) with antithymocyte globulin rabbit (n=20; 2.5–4.0 mg/kg intravenously for 10–14 days) for steroid-resistant rejection. Patients had similar rates of treatment failures and infectious complications, but alemtuzumab caused fewer infusion-related reactions (p=0.013). The authors concluded that alemtuzumab might be effective for steroid-resistant rejection but called for further analysis (van den Hoogen 2013).

Antibody-Mediated Rejection
Occurring any time posttransplantation, AMR generates histologic findings similar to those of hyperacute rejection but the severity of rejection is usually less. Studies report an AMR incidence of 5%–8% in RTRs. Almost 50% of all rejection episodes after renal transplantation are caused by AMR; these episodes have a worse prognosis than T cell–mediated rejection. Although AMR has few signs and symptoms, it should be suspected with a steady, but often slow, rise in SCr.

Treatment Strategies
No drugs are indicated for AMR, but given the mechanism of injury, several agents may mitigate the antibody response. The high cost, off-label use, and lack of data on the efficacy and safety of these agents make it difficult to recommend a single treatment strategy for all patients. Moreover, an individualized treatment strategy depends on the level of kidney dysfunction, the histology, and the presence of donor-specific antibodies (DSAs). In general, for patients without a history of sensitization, plasmapheresis and intravenous Ig (IVIg) can be considered first-line treatment. In patients with DSAs or those with significant renal dysfunction (e.g., GFR decreases greater than 50%), initial treatment with plasmapheresis and IVIg, together with bortezomib and corticosteroids, may be considered. Some centers choose to add rituximab to this regimen.

Intravenous Immunoglobulin
Pharmacology
The most common strategy for managing AMR is to neutralize or remove DSAs with either high-dose (2 g/kg) IVIg or plasmapheresis with low-dose (10–100 g) IVIg. Intravenous Ig, which has immunomodulatory effects, is often used for autoimmune diseases or in desensitizing protocols. The role of IVIg in the treatment of AMR is 2-fold: it replenishes the Ig removed during plasmapheresis and has an inhibitory effect on B lymphocytes and plasma cells. High-dose IVIg affects B lymphocytes through B-cell apoptosis and modulated B-cell signaling.

Special Precautions
Acute kidney injury occurs with IVIg but is usually associated with sucrose-containing preparations.
Thrombosis, another serious adverse event, is associated with high-osmolality preparations. Most new-generation IVIg products are sucrose free and iso-osmotic. One report describes aseptic meningitis in a patient requiring IVIg for AMR.

Clinical Efficacy
Retrospective studies have evaluated IVIg for AMR in renal transplantation (Fehr 2012; Terasaki 2004). The IVIg doses varied from 100 mg/kg every other day until response to 2 g/kg as a single dose. The reported AMR reversal rates with IVIg are 50%–90%. Allograft survival appears to be about 80% in IVIg–treated AMR. In many of these cases, IVIg was used after a series of plasmapheresis with or without corticosteroids.

**Rituximab**
Pharmacology
Rituximab is a chimeric monoclonal antibody that binds to CD20 on pre, mature and memory B cells. Rituximab induces B-cell lysis through complement-dependent and antibody-mediated cytotoxicity, thus blocking B-cell activation and maturation to plasma cells. Unfortunately, because CD20 is not present on pro-B cells or plasma cells, rituximab does not affect existing plasma cells. Therefore this agent has little impact on an ongoing AMR episode but may assist in long-term management or prevention of further AMR episodes.

Special Precautions
Rituximab is associated with infectious complications in up to 50% of patients. The most common causative organisms include CMV, varicella, polyomavirus, hepatitis, and fungus. Fatal infections have been reported, especially after concurrent use of antithymocyte globulin rabbit. Rituximab carries boxed warnings for an increased incidence of JC (John Cunningham) virus–induced progressive multifocal leukoencephalopathy, hepatitis B reactivation, and severe, fatal mucocutaneous and infusion-related reactions. Acetaminophen and antihistamines are often used as premedications before infusion. Mild reactions such as chills, fever, and rigors can be managed by slowing infusion rates by 50%.

Clinical Efficacy
Some studies have reported 75%–100% graft survival when using rituximab together with plasmapheresis and corticosteroids, with or without IVIg (Mulley 2009; Faguer 2007). Two studies comparing rituximab with historic controls reported improved graft survival (Kaposztas 2009; Lefaucheur 2009). Conversely, one retrospective study comparing bortezomib with rituximab reported worse outcomes in the rituximab group, with only 10% graft survival (Waiser 2012). The role of rituximab in AMR treatment is currently unclear.

**Alemtuzumab**
Pharmacology
Alemtuzumab’s mechanism of action was discussed earlier. Given its ability to deplete B lymphocytes, it may be beneficial in managing AMR.

Clinical Efficacy
Alemtuzumab has been used to treat AMR with plasmapheresis and IVIg, with or without rituximab (Jirasiritham 2010; Csapo 2005; Thomas 2004). In all reports, allograft function initially improved. However, in one case, AMR recurrence was noted 3 months posttherapy.

**Bortezomib**
Pharmacology
Plasma cells are one possible target when treating AMR. Bortezomib is a proteasome inhibitor that interrupts normal intracellular protein degradation, which disturbs cell cycling regulation and mitosis. An in vitro study confirmed that bortezomib induces plasma cell apoptosis and blocks anti–human leukocyte antigen (HLA) antibody production. The optimal dose and therapy duration for managing AMR are not established; however, most centers use at least one course of 1.3 mg/m² administered on days 1, 4, 8, and 11.

Special Precautions
Acute hepatic dysfunction is seldom reported; thus, bortezomib should be used cautiously in patients with moderate to severe hepatic impairment. Bortezomib has also been associated with significant myelosuppression and peripheral neuropathy.

Clinical Efficacy
Bortezomib has been used together with plasmapheresis and IVIg or rituximab. The reported outcomes of these cases show graft survival rates of 85%–100%. Anti-HLA antibodies decrease by 50% within 2 weeks of therapy and remain suppressed for up to 5 months (Walsh 2011; Everly 2008). The efficacy of bortezomib in AMR may be more pronounced in patients with SCr less than 3 mg/dL or proteinuria less than 1 g/day. Patients who develop early AMR (less than 6 months posttransplantation) have a greater reduction in DSAs and reversal of rejection. Bortezomib also seems effective in AMR refractory to plasmapheresis and IVIg.

**Eculizumab**
Pharmacology
Eculizumab, a humanized anti-C5 monoclonal antibody, inhibits the membrane attack complex formation. The complement cascade plays a vital role in AMR, and eculizumab directly inhibits this mechanism of injury. Eculizumab has minimal effect on DSAs.
Special Precautions
Eculizumab carries a U.S. Food and Drug Administration (FDA) boxed warning of meningococcal infection. Meningococcal vaccination is recommended 14 days before eculizumab, but infections have been reported even in vaccinated patients. It may be beneficial to vaccinate all patients at high risk of developing AMR pretransplantation. In patients who do not receive vaccine within 2 weeks, prophylactic antibiotics are warranted. However, the risk-benefit of antibiotic prophylaxis has not been studied.

Clinical Efficacy
There is limited but convincing evidence that eculizumab is safe and effective in preventing AMR and managing atypical hemolytic uremic syndrome (aHUS) after transplantation. However, only a few case reports show its efficacy in treating AMR (Kocak 2013; González-Roncero 2012; Stewart 2012; Locke 2009). In these reports, eculizumab was used only when other agents failed but produced rapid improvement of renal function within 1 week. The benefit of eculizumab is that it works on the exact step of allograft damage. Introducing eculizumab early (i.e., at AMR diagnosis) is worth considering, given the rapidly progressing nature of AMR.

Chronic Rejection
The mechanism of allograft failure in the first year after transplantation is not fully understood. Late allograft failure is usually called chronic rejection. A poorly understood process, it is defined as renal allograft dysfunction occurring at least 3 months posttransplantation in the absence of active acute rejection, drug toxicity, or other diseases. Risk factors for chronic rejection include previous acute rejection, infection, use of high-dose CNIs, inflammation, delayed graft function, and CVD. Around 3% of allografts are lost annually because of chronic rejection.

Prevention and Treatment Strategies
Chronic rejection remains one of the main obstacles in improving long-term allograft survival. Prevention and treatment strategies are based, in part, on the time since transplantation. In the first year, attention may be directed at preventing rejection and AMR. In subsequent years, the focus may be on limiting CNI exposure through withdrawal or minimization protocols. In a 2011 meta-analysis (17 studies; 4131 patients), CNI minimization was associated with an overall reduction in graft loss (OR 0.73; 95% CI, 0.58–0.92; p=0.009) (Sharif 2011).

Nonimmunologic interventions for chronic rejection focus primarily on aggressive control of blood pressure, particularly with the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blocker (ARB) agents, and managing hyperlipidemia. This is discussed later in this chapter. There is no known directed therapy useful for the treatment of chronic rejection, so prevention by appropriately managing immunosuppression and its associated complications, as well as by improving adherence, is advisable.

LONG-TERM MANAGEMENT ISSUES
Reoccurrence of Primary Disease
In 2011, the most common indications for renal transplantation were diabetes (25.7%), hypertension (23.5%), glomerulonephritis (19.2%), and cystic kidney disease (12.8%) (Matas 2013). Five-year graft survival is superior in living donor transplants, regardless of the primary cause of renal disease. Overall, in living and deceased donor RTRs, 5-year graft survival is highest in those receiving transplants for cystic disease, followed by glomerulonephritis, hypertension, and diabetes (Matas 2013).

Recurrence of disease secondary to diabetes and hypertension is prevented by appropriate disease state management and medication adherence. These disease states are not curable with renal transplantation and can affect long-term allograft function if not managed appropriately. Management strategies for posttransplant diabetes and hypertension are reviewed later in this chapter.

Recurrence of glomerulonephritis has been reported in 6.0%–19.4% of renal allograft recipients, with increased prevalence on extended follow-up. Recurrence is reported as the cause of graft loss in 1.1%–4.4% of transplant recipients. In a large registry trial, recurrent glomerulonephritis was the third most common cause of graft failure 10 years after transplantation. Mesangiocapillary (membranoproliferative) glomerulonephritis type 1 was the most common cause of graft loss, followed by focal segmental glomerulosclerosis (FSGS), membranous nephropathy, and IgA nephropathy (Canaud 2009; Briganti 2002).

Focal Segmental Glomerulosclerosis
Focal segmental glomerulosclerosis has a global annual incidence of 8 cases per 1 million people and is the most common primary glomerular disease in dialysis patients. The five forms of FSGS are genetic, adaptive, virus associated, drug induced, and primary (idiopathic). Only primary FSGS recurs after transplantation. Primary FSGS recurs in 20%–50% of RTRs and in up to 80% if it has recurred in a prior kidney transplant (Canaud 2009). Most cases of FSGS recurrence present within hours to days of transplantation and are associated with gross proteinuria resulting in rapid allograft loss when left untreated. For this reason, the 2009 KDIGO guidelines recommend screening RTRs with primary FSGS for proteinuria at least daily for the first week, weekly for 4 weeks, every 3 months for the first year, and yearly thereafter (KDIGO 2009). Known risk factors for recurrent FSGS include
younger age (especially children younger than 6 years at onset of FSGS), non–African American race, rapid progression to end-stage renal disease in the native kidneys (less than 3 years), heavy proteinuria before transplantation, and loss of a previous transplant to recurrence.

Management of recurrent FSGS is challenging because no therapeutic option has shown consistent efficacy. The most widely used intervention is plasmapheresis, but the optimal time for initiation and duration of therapy are unknown. Several single-center case series have shown rituximab to have efficacy of in the treatment and prevention of recurrent FSGS (Araya 2011). Abatacept may play a role: it induced partial or complete remission of proteinuria in four RTRs (Yu 2013). The role of belatacept-based regimens in patients with FSGS is unknown.

**IgA Nephropathy**

The most common form of glomerulonephritis necessitating transplantation is IgA nephropathy. Like other causes of nephropathy, IgA nephropathy can recur in 30%–50% of patients, with recurrence leading to graft loss in 5%–10% of cases. To date, no specific therapy to prevent or treat recurrent IgA nephropathy has been identified. The risk of recurrence is higher if a previous transplant was lost because of recurrent IgA nephropathy. Posttransplantation screening for proteinuria and microhematuria should occur in the first month, every 3 months in the first year, then annually. The ACE inhibitors and ARBs may be used to control hypertension and reverse proteinuria. Data suggest that use of antithymocyte globulin rabbit and avoidance of corticosteroid withdrawal protect against recurrent disease (Clayton 2011; Berthoux 2008).

**Atypical Hemolytic Uremic Syndrome**

Historically, aHUS was thought to be a contraindication to transplantation because of the high rate of graft loss with recurrent disease. Recent breakthroughs have been made in the understanding and treatment of aHUS. The risk of recurrent disease depends on genetic variants and mutations. Additional risk factors are donation after brain death; delayed graft function, rejection, and infection; and specific immunosuppressants. The CNI and ToR inhibitors are associated with the development of de novo aHUS. Choice of one agent over the other does not affect the risk of recurrence. Belatacept, which has not been associated with the development of de novo aHUS, has been used successfully in patients with a history of aHUS and recurrent disease. Eculizumab is indicated for the prevention and treatment of aHUS and has been used successfully in the posttransplant management of aHUS.

**Infectious Complications**

Infections are virtually unavoidable after transplantation and remain a significant cause of morbidity and mortality. The timing of specific infections is usually predictable but can be affected by antimicrobial prophylaxis, alterations in immunosuppression, or additional surgery. Most clinically important infections occur within the first 6 months. It is useful to categorize risk periods as early (posttransplant month 1), intermediate (posttransplant months 2–6), and late (beyond posttransplant month 6). These intervals provide a useful framework for preventing and diagnosing potential infectious complications.

In general, early diagnosis and prompt administration of empiric antimicrobial therapy are essential in the effective treatment of infectious complications in RTRs. Resistant organisms or coinfection with several pathogens should be considered in immunocompromised patients not responding to initial therapy. Together with the use of antimicrobial therapy, clinicians may elect to reduce or even withhold immunosuppression in the event of significant infectious complications. This is especially true in RTRs, given that renal replacement therapies can often be administrated to patients if allograft failure occurs; therefore, preventing patient death is much more important than preventing allograft failure. Because this chapter focuses on long-term management, only infections in the intermediate and late periods are reviewed.

**Intermediate Period**

Opportunistic infections generally present in the intermediate period. During this period CMV disease peaks in patients receiving no or short-course prophylaxis. Similarly, without preventive strategies, PCP and fungal infections can occur during this period, as can BK virus (BKV) viremia.

**Late Period**

Late period infection risk depends on the patient's net total and current degree of immunosuppression and exposure to pathogens. Individuals who require enhanced immunosuppression are at increased risk. The presence of comorbidities (e.g., diabetes, malignancy) may increase the risk of late period infections. In patients who have received a prolonged prophylactic antiviral course, CMV is most likely to manifest during this period. The prevalence of EBV-associated PTLD is highest in the late period. Patients continue to carry a risk of being exposed to community-acquired respiratory and GI pathogens in the late period.

**P. jiroveci Pneumonia**

Prophylaxis reduces PCP occurrence from 5%–15% to less than 1% in RTRs. Antimicrobial prophylaxis is generally used, with a duration of 3–12 months; however, it may be prolonged or reinitiated in patients with enhanced immunosuppression (e.g., treatment of rejection) or in those with immunomodulating viral infections (e.g., CMV, hepatitis, HIV).

Sulfamethoxazole/trimethoprim is the drug of choice for PCP prophylaxis; it has spectrum of activity against other, non-Pneumocystis organisms such as Toxoplasma,
### Table 2-4. Treatment and Prevention Options for PCP and CMV

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosing</th>
<th>Key Information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>P. jiroveci Pneumonia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atoquone</td>
<td>Treatment • 750 mg by mouth twice daily x 21 days • Prophylaxis • 1500 mg by mouth once daily</td>
<td>Common adverse events • Hepatic (liver function test abnormalities) • GI (nausea, vomiting, diarrhea) Clinical pearls • Available only as a liquid, which may affect patient acceptance/adherence • Administer with food</td>
</tr>
<tr>
<td></td>
<td>Prophylaxis</td>
<td></td>
</tr>
<tr>
<td>Dapsone and trimethoprim</td>
<td>Treatment • Dapsone 100 mg by mouth once daily together with trimethoprim 15 mg/kg/day orally in three divided doses x 21 days • Prophylaxis • Dapsone 50–100 mg by mouth once daily</td>
<td>Common adverse events • Hepatic (liver function test abnormalities) • Hematologic (leukopenia, methemoglobinemia) • Renal (acute interstitial nephritis) Clinical pearls • Dapsone should never be administered to a patient with a significant sulfa allergy or G6PD deficiency</td>
</tr>
<tr>
<td></td>
<td>Prophylaxis</td>
<td></td>
</tr>
<tr>
<td>Pentamidine</td>
<td>Treatment • 4 mg/kg/day IV once daily (dose reduction to 2–3 mg/kg/day may be necessary) x 21 days • Prophylaxis • 300 mg inhaled every 3–4 weeks</td>
<td>Common adverse events • Endocrine (hypoglycemia) • Hematologic (leukopenia) • Renal (increased SCr) Clinical pearls • Monthly doses require outpatient nebulization services or administration with a home nebulizer • The prophylaxis dose can be given IV if necessary</td>
</tr>
<tr>
<td></td>
<td>Prophylaxis</td>
<td></td>
</tr>
<tr>
<td>Primaquine and clindamycin</td>
<td>Treatment • Primaquine 15–30 mg by mouth once daily together with clindamycin 600–900 mg IV or by mouth every 6–8 hours x 21 days • Prophylaxis • Not recommended</td>
<td>Common adverse events • GI (nausea, vomiting, diarrhea) • Hematologic (leukopenia) Clinical pearls • Long-term clindamycin can predispose to Clostridium difficile infection; therefore, its use for prophylaxis is not warranted</td>
</tr>
<tr>
<td></td>
<td>Prophylaxis</td>
<td></td>
</tr>
<tr>
<td>Sulfamethoxazole/trimethoprim</td>
<td>Treatment • 15–20 mg/kg/day of the trimethoprim component given intravenously in divided doses every 6–8 hours x 21 days • In milder disease, two double-strength tablets can be given by mouth two or three times daily x 21 days • Prophylaxis • One single-strength tablet by mouth once daily • One double-strength tablet by mouth once daily • One double-strength tablet by mouth three times weekly</td>
<td>Common adverse events • GI (nausea, vomiting, diarrhea, dyspepsia) • Electrolyte abnormalities (hyperkalemia) • Hematologic (leukopenia, thrombocytopenia) • Renal (acute interstitial nephritis, increased SCr, crystalluria) • Skin (photosensitivity, rash) Clinical pearls • Increased SCr after initiation of sulfamethoxazole/trimethoprim is probably temporary, reflecting altered secretion of SCr • The need to withhold doses or discontinue therapy early may be necessary because of hyperkalemia and myelosuppression</td>
</tr>
</tbody>
</table>
### Table 2-4. Treatment and Prevention Options for PCP and CMV (continued)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosing</th>
<th>Key Information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cytomegalovirus</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cidofovir</td>
<td>Treatment</td>
<td>• 5 mg/kg IV once weekly × 2; then every 2 weeks thereafter&lt;br&gt;Prophylaxis</td>
</tr>
<tr>
<td></td>
<td>Prophylaxis</td>
<td></td>
</tr>
<tr>
<td>Foscarnet</td>
<td>Treatment</td>
<td>• 60 mg/kg IV every 8 hours or 90 mg/kg intravenously every 12 hours&lt;br&gt;Prophylaxis</td>
</tr>
<tr>
<td></td>
<td>Induction: 5 mg/kg IV twice daily for 3 weeks&lt;br&gt;Maintenance: 5 mg/kg IV once daily for 1–3 months&lt;br&gt;Prophylaxis</td>
<td>• 5 mg/kg IV once daily&lt;br&gt;Common adverse events</td>
</tr>
<tr>
<td>Ganciclovir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valganciclovir</td>
<td>Treatment:</td>
<td>• Induction: 900 mg by mouth twice daily for 3 weeks&lt;br&gt;Maintenance: 450–900 mg by mouth once daily for 1–3 months&lt;br&gt;Prophylaxis:</td>
</tr>
</tbody>
</table>

CMV = cytomegalovirus; G6PD = glucose-6-phosphate dehydrogenase; IV = intravenous(ly); PCP = *Pneumocystis jiroveci* pneumonia; RTR = renal transplant recipient.
Listeria, and Nocardi. Patients with a sulfa allergy, glucose-6-phosphate dehydrogenase (G6PD) deficiency, or intolerance to sulfamethoxazole/trimethoprim should be given atovaquone or pentamidine. Dapsone is another alternative, but patients with a significant sulfa allergy or G6PD deficiency should not receive it. Prophylaxis and treatment strategies for PCP and CMV are summarized in Table 2-4.

Cytomegalovirus is the infection associated with the most morbidity in RTRs. The risk of disease is highest among CMV-naive recipients who receive a CMV-positive organ. The degree of immunosuppression augments the risk of CMV disease. Cytomegalovirus disease classically occurs in the intermediate period, but delayed onset is common in patients receiving 6 months of antiviral prophylaxis. Patients may present with general symptoms such as fever, chills, aches, malaise, and fatigue. However, CMV disease may also result in myelosuppression, GI toxicity, and tissue-invasive disease.

Acyclovir, valacyclovir, ganciclovir, valganciclovir, foscarnet, and cidofovir all have activity against CMV. Ganciclovir and valganclovir are considered the drugs of choice for both prevention and treatment. Prophylaxis should be continued for 6 months in high-risk patients (Razonable 2013). In the moderate-risk groups, 3 months of prophylaxis is adequate. Use of foscarnet or cidofovir may be necessary if managing a UL97 ganciclovir-resistant infection, with foscarnet often considered first-line therapy in this situation. However, these agents are highly nephrotoxic and should be used only when the benefit outweighs the risk of renal failure.

Polyomavirus

In RTRs, the polyomavirus BKV is associated with tubulointerstitial nephritis and ureteral stenosis. Polyomavirus-associated nephritis often presents with renal dysfunction, resulting in either acute or slowly progressive allograft injury. The incidence of BKV viremia is reported to be almost 29% after renal transplantation. Polyomavirus-associated nephritis is estimated to affect 10% of RTRs, often resulting in irreversible allograft dysfunction or failure.

Currently, BKV management options are limited, and recommendations are based on individual case reports and small case series. Reducing the degree of immunosuppression in patients with BKV viremia is the first-line strategy to prevent nephritis. Despite the lack of directed antiviral options, several agents have reported anti-BKV activity, including IVIg, cidofovir, leflunomide, and fluoroquinolones. In anecdotal cases, all have shown benefit in preventing or managing BKV viremia and nephropathy.

Malignancy

Transplant recipients have a greater risk of malignancies than the general population. For example, Kaposi sarcoma is more than 200 times more likely posttransplantation. Kidney transplants carry an enhanced risk of virus-associated malignancies such as PTLD and cervical and vulvovaginal cancers. Solid tumors such as colorectal and lung cancers are 2-3 times higher in transplant recipients than the general population. Malignancy is the second most common cause of death in RTRs. The most common posttransplant malignancies are skin cancer and PTLD.

Skin Cancer

Skin cancers – especially squamous cell and basal cell carcinomas, but also melanoma, Merkel cell carcinoma, and Kaposi sarcoma – remain the most common malignancy after transplantation. The incidence of skin cancers increases with time and is as high as 35% among patients 10 years posttransplantation. Skin cancers in RTRs tend to grow more rapidly and are more likely to metastasize.

The risk factors for skin cancer include advanced age, excessive UV light exposure, high degree of immunosuppression, Fitzpatrick skin types I–III, history of skin cancers, and infection by human herpes virus and/or human papillomavirus. Data suggest that ToR inhibitors can reduce the risk of nonmelanoma skin cancers; therefore, it is advisable to consider converting from a CNI to a ToR inhibitor in this population.

Posttransplant Lymphoproliferative Disorders

The most serious and potentially fatal complication posttransplantation is PTLD. In one large case series, PTLD occurred in 1%–3% of RTRs (Fault 2005). Most PTLDs are related to EBV; however, EBV-negative disease can also occur. Risk factors for PTLD include advanced age, high degree of immunosuppression, and no prior EBV exposure. The type of immunosuppressive agents used can also influence PTLD. Belatacept carries a boxed warning regarding the increased risk of PTLD. Patients who receive T cell–depletion therapy also have a higher rate of PTLD.

The current approach to PTLD management involves therapeutic options such as reduction of immunosuppression, combination chemotherapy, and anti-B-cell monoclonal antibodies. The prognosis of PTLD varies with clonality and extent of disease, but the literature suggests a survival rate of less than 50%.

Cardiovascular Disease

Death with a functioning allograft secondary to CVD remains the leading cause of late graft loss. Traditional CVD risk factors (e.g., hyperlipidemia, hypertension,
obesity) are common in RTRs and likely contribute to the high CVD risk in this population.

**Prevention Strategies**

Prevention of CVD in RTRs should include management of modifiable risk factors. Preserving renal function is warranted given the significant effect of worsening graft function on cardiovascular events. Use of CNIs, ToR inhibitors, and corticosteroids posttransplantation contributes to the development of hypertension, hyperlipidemia, NODAT, weight gain, and impaired renal function. Use of CNI or corticosteroid minimization or withdrawal regimens may help mitigate CVD risk. Although data are lacking on aspirin or statin use in the primary prevention of CVD in RTRs, recent guidelines suggest these agents benefit select patients.

**Posttransplant Hypertension**

Hypertension is the most prevalent CVD risk factor, affecting 75%–90% of RTRs. Observational studies suggest a 1%–2% increased risk of fatal or nonfatal cardiovascular events for every 1-mm Hg increase in systolic blood pressure. Factors that contribute to the pathogenesis of posttransplant hypertension include pretransplant hypertension, immunosuppressive agents, obesity, delayed graft function, acute rejection, and transplant renal artery stenosis.

Guidelines suggest a target blood pressure of 130/80 mm Hg in RTRs but do not specify an antihypertensive drug of choice (KDIGO 2009). These guidelines advocate for ACE inhibitors/ARB use as first-line therapy in the setting of severe proteinuria (greater than 1 g/day). Choice of antihypertensive agents in RTRs should be based on comorbid disease states and other compelling indications.

The CCBs are favored in RTRs because they counteract CNI-induced vasoconstriction of the afferent arterioles. Data from a large-scale systematic review show that CCBs reduced graft loss by 25% and improved GFR by 4.5 mL/minute (Cross 2009). Dihydropyridines are the most commonly used CCBs. Non-dihydropyridines may benefit some patients, but their use is limited by significant drug interactions with the CNI and ToR inhibitors.

Outside the setting of severe proteinuria, ACE inhibitors and ARBs are often considered second-line agents in RTRs, despite their renoprotective effects. By altering renal hemodynamics, these agents cause a temporary increase in SCr that may mask rejection, especially when used early posttransplantation. Despite these concerns, several studies have shown the safety and efficacy of these agents in transplantation. In RTRs with evidence of left ventricular hypertrophy, ACE inhibitors were associated with significantly higher cardiovascular event–free survival. These agents should be strongly considered in RTRs with compelling indications such as allograft dysfunction, diabetes, heart failure, left ventricular hypertrophy, post–myocardial infarction, and high-risk coronary artery disease. There is no consensus on the best time to initiate ACE inhibitor or ARB therapy; most clinicians wait until renal function has stabilized, which may be weeks to months posttransplantation.

Transplant recipients not achieving blood pressure control with CCBs or ACE inhibitors may be candidates for β-blockers. Patients taking β-blockers pretransplantation should continue them posttransplantation. Additional candidates for β-blocker therapy include patients with angina, coronary artery disease, stable heart failure, and arrhythmias. Nebivolol and the cardioselective β-blockers are typically chosen for managing hypertension. However, nebivolol, a cardioselective β-blocker that induces endothelium-derived nitric oxide–dependent vasodilation, may have benefit in RTRs. Nebivolol reduces ischemia/reperfusion injury in rats, negates atenolol-induced alterations in renal blood flow, and preserves endothelial dysfunction in individuals with diabetes. Nebivolol is also associated with a lower incidence of fatigue, dyspnea, bradycardia, erectile dysfunction, and depression.

Alternative blood pressure–lowering agents such as α-blockers, diuretics, clonidine, hydralazine, and minoxidil are typically reserved as add-on therapy in patients intolerant of or nonresponsive to other therapies.

**Posttransplant Hyperlipidemia**

Modern immunosuppression has decreased the incidence of posttransplantation dyslipidemia from greater than 80% to less than 50%. Potential causes of posttransplant hyperlipidemia include preexisting dyslipidemia, genetic predisposition, obesity, and use of immunosuppressive agents. Corticosteroids, CNIs, and ToR inhibitors have all been associated with dyslipidemia.

In 2013, a more aggressive approach to lipid management was proposed in both the KDIGO and the American College of Cardiology/American Heart Association (ACC/AHA) guidelines (KDIGO 2013; Stone 2013). Both sets of guidelines recognize the lack of evidence to support statin use in reducing atherosclerotic CVD risk in the transplant population. However, many groups believe that because of their significant risk of cardiovascular-related mortality, RTRs should be considered the highest-risk group with respect to risk factor management. The 2013 ACC/AHA guidelines have moved away from the “treat-to-goal” approach, with a current focus on the use of clinical criteria for initiating statin therapy. The four main groups for whom robust evidence supports statin use in reducing CVD risk are as follows: (1) those with clinically evident atherosclerotic CVD, (2) those with primary LDL cholesterol (LDL-C) levels of at least 190 mg/dL, (3) patients with diabetes and an LDL-C of 70 mg/dL or higher, and (4) those with a 10-year risk of atherosclerotic CVD of at least 7.5%, according to the Pooled Cohort Equations, and an LDL-C of at least 70 mg/dL. For these high-risk patients, the guidelines recommend high-intensity statin therapy, designed to reduce LDL-C levels by greater than 50%. Moderate-intensity
statin therapy, aiming for an LDL-C reduction of 30% to less than 50%, is recommended for patients who cannot tolerate high-intensity treatment or for those with diabetes and a 10-year risk of atherosclerotic CVD of less than 7.5%. The 2013 KDIGO guidelines recommend that statin therapy be initiated in all adult RTRs.

Currently, however, it is unclear how these new guidelines will be incorporated into the clinical management of RTRs. In the non-transplant population, substantial controversy surrounds the new ACC/AHA guidelines and the reliability of the Pooled Cohort Equations. Many transplant practitioners may not feel comfortable initiating high-intensity statins in RTRs in light of the recent FDA warnings and label changes for simvastatin, lovastatin, and atorvastatin. The simvastatin label includes new contraindicated medications and dose limitations. Of particular concern in transplantation is the inclusion of cyclosporine on the contraindications list and CCBs on the dose limitation list. In 2012, the FDA required label changes for lovastatin and atorvastatin to avoid concomitant use with cyclosporine because these agents are physicochemically and pharmacokinetically similar to simvastatin. This drug interaction has been ascribed to the competitive inhibitory effect of cyclosporine on CYP3A4, Pgp, and other transporters like organic anion transport polypeptide. Pharmacokinetic studies of both atorvastatin and simvastatin in combination with tacrolimus have not shown significant drug-drug interactions. Cyclosporine inhibits both Pgp and organic anion transport polypeptide–mediated uptake of atorvastatin, whereas tacrolimus does not, which is why tacrolimus does not have a similar warning (Amundsen 2010; Lemahieu 2005). In addition to the interactions with atorvastatin and simvastatin, cyclosporine increases the exposure of all other marketed statins. Table 2-5 summarizes the relevant clinical characteristics of the statins, renal dosing recommendations, and concerns regarding concomitant dosing with cyclosporine.

Niacin or the fibrates are reserved for patients with significant hypertriglyceridemia (TG greater than 500 mg/dL) that has not responded to therapeutic lifestyle changes alone. Despite the known issues with intolerance, niacin may be one of the preferred agents in RTRs because new data associate fibrates with nephrotoxicity. In addition, fibrates should be cautiously combined with statins because of the increased potential for myopathy and rhabdomyolysis. Ezetimibe has some triglyceride-lowering abilities and is a safe alternative for use in RTRs with elevated triglycerides. Bile-acid sequestrants are often avoided in RTRs because of the interactions discussed earlier.

Endocrine Complications
New-Onset Diabetes After Transplantation

Development of NODAT is associated with impaired long-term graft function, reduced allograft and patient survival, and increased cardiovascular morbidity and mortality. In patients without a history of diabetes, the reported incidence of NODAT is 5%–25%. Risk factors include advanced age, obesity, African American or Hispanic race, hepatitis C, and use of immunosuppressants.

Posttransplant immunosuppression accounts for up to 74% of the NODAT risk (Montori 2002), with tacrolimus and corticosteroids the greatest contributors. Both

<table>
<thead>
<tr>
<th>Medication</th>
<th>Lipophilicity a</th>
<th>Metabolic Pathway b</th>
<th>Renal Dosing</th>
<th>Cyclosporine Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pravastatin</td>
<td>+</td>
<td>(3A4)</td>
<td>Significant impairment: Initial dose 10 mg/day</td>
<td>Initiate at 10 mg, NTE 20 mg daily</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>+++</td>
<td>2C9</td>
<td>Severe impairment: Use with caution (doses &gt; 40 mg/day have not been studied)</td>
<td>NTE 20 mg daily</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>++++</td>
<td>3A4, 2C8</td>
<td>CrCl &lt; 30 mL/minute: use caution with doses &gt; 20 mg/day</td>
<td>Avoid use with cyclosporine</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>++++</td>
<td>3A4, 2C8</td>
<td>Severe renal impairment: Initial dose 5 mg/day</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>+++</td>
<td>3A4 (2C8)</td>
<td>No adjustment necessary</td>
<td>Avoid use with cyclosporine</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>++</td>
<td>2C9 (2C19)</td>
<td>CrCl &lt; 30 mL/minute: Initial dose 5 mg/day; NTE 10 mg/day</td>
<td>NTE 5 mg with cyclosporine</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>++++</td>
<td>(2C9)</td>
<td>CrCl &lt; 60 mL/minute: Initial dose 1 mg/day, NTE 2 mg/day</td>
<td>Contraindicated</td>
</tr>
</tbody>
</table>

aFour plus signs indicate most lipophilic; one plus sign indicates most hydrophilic.
bParentheses indicate minor significance.
CrCl = creatinine clearance; NTE = not to exceed; RTR = renal transplant recipient.
CNIs can induce NODAT by reducing insulin secretion, whereas corticosteroids can increase insulin resistance and weight gain. The effect of corticosteroids on NODAT is linked to the cumulative dose and duration of use. More recently, sirolimus has been shown to cause a defect in the compensatory beta-cell response and a decline in insulin sensitivity. Long-term data on the benefit of belatacept with respect to NODAT development are lacking.

Managing NODAT begins with optimizing modifiable risk factors. The immunosuppressive regimen should be modified if this will not increase the risk of rejection. Suggested interventions include withdrawing or minimizing steroids and converting tacrolimus to cyclosporine. Lifestyle modifications include patient referral to a nutritionist and an exercise program.

If risk factor modification does not achieve adequate glycemic control, medical intervention is recommended. Oral hypoglycemic agents can be used alone or in combination and with or without insulin. Although oral hypoglycemic agents are effective in RTRs, insulin therapy is required in almost 40% of patients. Choice of pharmacologic therapy should be based on the potential advantages and disadvantages of the different classes of agents. Although metformin is recommended as first-line therapy in overweight patients, use should be avoided in patients with impaired allograft function because of metformin’s potential to cause lactic acidosis. Sulfonylureas should be used cautiously in those with impaired allograft function or advanced age because of the risk of hypoglycemia. The glinides and incretin-based therapies have been studied in RTRs.

The glinides act on beta-cells to stimulate rapid insulin secretion dependent on ambient glucose. Repaglinide and nateglinide reduce hemoglobin A1C (A1C) levels by 1%–1.5% and are mainly indicated to cover postprandial hyperglycemic peaks, thus requiring three or four times/daily dosing. Both glinides are metabolized by CYP and are susceptible to drug interactions. Repaglinide and nateglinide have been studied in RTRs, showing favorable responses.

The incretin class of agents, which includes the glucagon-like peptide-1 agonists and the dipeptidyl peptidase-4 inhibitors, may be particularly beneficial in transplant recipients. These agents stimulate beta-cell function and decrease insulin resistance, making them good candidates for treating NODAT. However, the glucagon-like peptide-1 agonists are associated with GI intolerance and should be avoided in patients with gastroparesis. Moreover, caution is advised regarding their use in patients with low GFR. Oral dipeptidyl peptidase-4 inhibitors may be ideal for RTRs because of their more flexible GFR cutoffs, minimal GI adverse events, and low hypoglycemia potential.

In 15 RTRs with NODAT and a GFR greater than 30 mL/minute receiving concomitant tacrolimus and sirolimus, sitagliptin use was well tolerated, caused no drug interactions, and did not result in impaired kidney function (Lane 2011). In patients receiving sitagliptin for 3 months, A1C improved to 6.7% from a baseline of 7.2% (p=0.002). In a small case series, liraglutide showed good efficacy and a favorable adverse event profile in five RTRs (Pinelli 2013). In a randomized, double-blind, placebo-controlled trial, vildagliptin 50 mg daily for 3 months reduces 2-hour plasma glucose levels and A1C compared with placebo (Haidinger 2014). Overall, preliminary data on the safety, efficacy, and tolerability of glucagon-like peptide-1 agonists and dipeptidyl peptidase-4 inhibitors are promising. Table 2-6 reviews the therapeutic options for NODAT.

Reproductive Health

Sexual dysfunction remains a common problem post-transplantation, affecting more than 50% of RTRs. The etiology of erectile dysfunction is multifactorial and may be linked to the transplant surgery itself as well as to the use of various drugs. Therapy with 5-phosphodiestrase inhibitors may be effective; however, men should be cautioned about the risks of coadministration with α-adrenergic antagonists.

Evidence has emerged suggesting that immunosuppressive regimens containing sirolimus lead to impaired male fertility. One analysis discovered that men using sirolimus had reduced total sperm counts, a decreased proportion of motile spermatozoa, and a lower fathered pregnancy rate than those receiving a non–sirolimus-based immunosuppressive regimen (Zuber 2008).

Pregnancy after transplantation is a viable option for female RTRs. Health care providers should discuss family planning issues with patients in the pretransplant evaluation and throughout posttransplant care. The dialogue should include the optimal timing of pregnancy, known pregnancy and fertility rates, appropriate contraceptive options, risks of immunosuppression to the fetus, and impact of pregnancy on graft function and immunosuppressive concentrations. Women of child-bearing potential should be informed that regular menses and fertility are restored shortly after successful transplantation (in some reports, as early as 3 weeks posttransplantation).

An effective method of contraception should be initiated in the immediate posttransplant period because of the significant risk of fetal malformations with some immunosuppressive agents. The Centers for Disease Control and Prevention recommendations include guidance on contraceptive options for transplant recipients that are based on whether the patient’s case is considered complicated (e.g., history of acute or chronic rejection) or uncomplicated. Use of barrier methods and progesterone-based hormonal contraceptives are preferred in complicated female transplant recipients. Combined oral contraceptives containing estrogen are believed to pose an unacceptable health risk and should be avoided in complicated female RTRs. All forms of contraception are believed to be acceptable in the uncomplicated transplant recipient. Additional guidance on appropriate contraception was provided in 2012 when the Mycophenolate...
<table>
<thead>
<tr>
<th>Medication Class</th>
<th>Agents</th>
<th>Renal Dosing</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanides</td>
<td>Metformin</td>
<td>Contraindicated:</td>
<td>Cost</td>
<td>Risk of lactic acidosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Men with SCr &gt; 1.5 mg/dL</td>
<td>Cardiovascular benefits</td>
<td>GI adverse events</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Women with SCr &gt; 1.4 mg/dL</td>
<td>Weight loss</td>
<td></td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Glipizide</td>
<td>No adjustment necessary</td>
<td>Nonrenal clearance</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Caution with CrCl &lt; 50 mL/minute</td>
<td>Cost</td>
<td>Weight gain</td>
</tr>
<tr>
<td></td>
<td>Glyburide</td>
<td>Avoid with CrCl &lt; 50 mL/minute</td>
<td>Weight gain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glimperide</td>
<td>CrCl &lt; 40 mL/minute, start at 1 mg/day</td>
<td>Hypoglycemia in patients with renal insufficiency</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td></td>
<td>Acarbose</td>
<td>• Avoid:</td>
<td>Weight loss</td>
<td>GI adverse events</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• SCr &gt; 2.0 mg/dL</td>
<td>No hypoglycemia</td>
<td></td>
</tr>
<tr>
<td>Thiazolidinedione</td>
<td>Pioglitazone</td>
<td>None needed</td>
<td>Studied in RTRs</td>
<td>Increased risk:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Possible cardiovascular benefit</td>
<td>• Congestive heart failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Fractures</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Liver failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Bladder cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Peripheral edema</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>Repaglinide</td>
<td>No adjustment necessary</td>
<td>Beneficial for postprandial excursions</td>
<td>Weight gain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Caution in severe renal impairment:</td>
<td>Studied in RTRs</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Initiate at 0.5 mg/day</td>
<td></td>
<td>Cost</td>
</tr>
<tr>
<td></td>
<td>Nateglinide</td>
<td>None needed</td>
<td></td>
<td>Frequency of dosing CYP3A4 substrate:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Potential interactions</td>
</tr>
<tr>
<td>Amylin analog</td>
<td>Pramlintide</td>
<td>None needed</td>
<td>Beneficial for postprandial excursions</td>
<td>Injection</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Weight loss</td>
<td>Cost</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GI adverse events</td>
</tr>
<tr>
<td>Glucagon-like peptide-1 agonists</td>
<td>Liraglutide</td>
<td>Use caution with CrCl &lt; 50 mL/minute</td>
<td>Minimal hypoglycemia</td>
<td>Injection</td>
</tr>
<tr>
<td></td>
<td>Exenatide</td>
<td></td>
<td>Weight loss</td>
<td>Cost</td>
</tr>
<tr>
<td></td>
<td>Exenatide ER</td>
<td>Use caution with CrCl &lt; 50 mL/minute</td>
<td>Some benefit in patients with hypertension/ hyperlipidemia</td>
<td>GI adverse events</td>
</tr>
<tr>
<td></td>
<td>Albiglutide</td>
<td>Use caution with CrCl &lt; 15 mL/minute</td>
<td>Once-weekly injection</td>
<td>Questionable pancreatitis and thyroid cancer risk</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Avoid in patients with gastroparesis</td>
</tr>
</tbody>
</table>
Risk Evaluation and Mitigation Strategies (REMS) program was implemented. This program was developed in response to the 2007 change in the MPA pregnancy risk factor from C to D. The REMS program is detailed later in this chapter.

The 2009 KDOQI guidelines and the American Society of Transplantation recommend that women have at least 1 year free of rejection before planning a pregnancy. They also recommend that kidney function be stable (SCr of less than 1.5 mg/dL) with proteinuria of less than 1 g/day. Pregnancy during the first year would be considered high risk given the possibility of rejection, infection, and fetal exposure to immunosuppressants.

Changes in immunosuppressive drugs may be a necessary part of some women's pregnancy planning. Women stable on sirolimus or MPA will need to be converted to a CNI or azathioprine, respectively, at least 6 weeks before a planned pregnancy. It may be prudent to consider adding a small dose of prednisone to avoid the risk of rejection in those previously on a steroid withdrawal regimen. Throughout the pregnancy, graft function and immunosuppressive concentrations must be monitored closely because of the potential for significant alterations in drug clearance.

**Pharmacist and Patient Education Points**

**Nonadherence**

Nonadherence can significantly worsen long-term allograft outcomes. After renal transplantation, nonadherence rates are 15%–40%. Identifying barriers to adherence and intervening accordingly is necessary for improving outcomes. About 25% of RTRs who are nonadherent to their immunosuppressive medications develop late acute rejection compared with 8%–10% of adherent patients. Even temporary nonadherence can initiate the rejection process, and medication adherence thereafter does not mitigate allograft damage. It has been suggested that nonadherence greatly affects chronic rejection. In a 2007 meta-analysis, nonadherent patients had a 7-fold increased risk of graft failure compared with adherent patients (Dew 2007).

Patients and families should understand the significance of lifelong drug therapy and proper adherence. Adherence should be addressed by clinicians at every patient interaction posttransplantation. Clinical pharmacy services positively affect medication adherence in RTRs and directly affect transplant outcomes as well as health-related quality of life (Taber 2013; Chisholm-Burns 2008).

**Controversies with Generic Immunosuppressants**

The question of whether clinically relevant changes in drug exposure occur with use of generic immunosuppressants has culminated in the approval of generic formulations for the CNIs, sirolimus, and the MPA products. Generic products are considered therapeutically equivalent if they are both bioequivalent and pharmaceutically equivalent to the innovator product. However, because bioequivalence is determined in a small group of healthy volunteers, some investigators are concerned that bioequivalence may not be met in RTRs because of their many comorbid conditions. Another concern is that, given the narrow therapeutic windows of the CNIs, generic conversion could result in significant changes in drug exposure, potentially causing rejection or toxicities.
In several reports, generic CNIs in RTRs show similar efficacy and safety but require close monitoring after conversion because almost 25% of patients required a dose adjustment. In a prospective, randomized, crossover trial, generic tacrolimus was compared with the innovator product in stable RTRs and met all requirements to be deemed bioequivalent (Alloway 2012). The mean C0 values were also similar between the two products. These data show that the pharmacokinetic profile of generic tacrolimus is similar to that of the innovator product.

**Risk Evaluation and Mitigation Strategies**

The process of managing known or potential serious risks associated with medications is known as REMS. Belatacept and all the MPA formulations, both brand and generic, have FDA-approved REMS. The ToR inhibitors previously had REMS that centered on a communication plan to warn prescribers about their potential risks (e.g., hyperlipidemia, proteinuria, graft thrombosis, wound-healing complications, increased nephrotoxicity) when coadministered with full-dose cyclosporine. The FDA removed the REMS requirements after this message was communicated with potential prescribers. Despite not being indicated for transplantation, eculizumab has REMS requirements that must be followed when this medication is used. Table 2-7 contains a review of the REMS requirements for the immunosuppressants used in RTRs.

**Conclusion**

Successful outcomes in renal transplantation are measured by several end points, including sustaining 1-year allograft survival rates, preventing rejection and immunosuppressive-related complications, and enhancing long-term allograft and patient survival. The short-term goals of reducing rejection rates and attaining good graft survival can be achieved through the appropriate use of immunosuppression and an examination of the patient’s therapeutic and toxic-monitoring values. The long-term goals of maximizing the functionality of the allograft and preventing immunosuppressive-related complications are not as easily achieved. In the long-term care of RTRs, pharmacists must be focused on identifying and treating the adverse sequelae associated with lifelong immunosuppression, including CVD, malignancy, infection, and endocrine disorder. Limiting drug misadventures and ensuring adherence to pharmacotherapy are of utmost importance.

**References**


<table>
<thead>
<tr>
<th>Medication/Medication Class</th>
<th>REMS Objective(s)</th>
<th>REMS Elements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belatacept</td>
<td>Inform patients and providers about the potential risks of PTLD and serious infections</td>
<td>Medication guide Communication plan</td>
</tr>
</tbody>
</table>
| MPA derivatives             | Minimize fetal exposure to MPA Prevent unplanned pregnancies in patients using MPA Collect data on MPA use in pregnancy through a pregnancy registry Educate patients about the risks associated with MPA therapy | Medication guides ETASU:  
  • Special training for prescribers regarding the risk of miscarriage and birth defects with MPA  
  • Information on the risks of MPA during pregnancy (miscarriage and fetal malformations), pregnancy prevention (birth control options), importance of family planning, and need to discontinue MPA at least 6 weeks before trying to get pregnant  
  • Establishment of the voluntary “Mycophenolate Pregnancy Registry” |
| Eculizumab                  | Minimize the risk of serious infection (i.e., meningococcal infection) Ensure the medication’s proper use | Medication guide ETASU:  
  • Prescriber required to be certified with the manufacturer  
  • Prescribers will educate patients, provide them with the medication guide, and comply with the directions for safe use  
  • Medication is only distributed to certified prescribers |

ETASU = elements to assure safe use; MPA = mycophenolic acid; PTLD = posttransplant lymphoproliferative disorder.


SELF-ASSessment QUESTIONS

Questions 21–23 pertain to the following case.
T.G. is a 49-year-old Hispanic man (weight 74 kg, height 5’9”) who received a deceased donor kidney transplant at your institution 4 months ago. His end-stage renal disease was secondary to his IgA nephropathy. He received induction therapy with antithymocyte globulin rabbit, and his maintenance therapy consisted of tacrolimus, mycophenolate mofetil, and prednisone; however, T.G.’s steroids were completely withdrawn on postoperative day 10. His regimen was converted to cyclosporine because of the intolerable neurologic complications associated with tacrolimus (i.e., hand tremors and headaches). T.G. has had no rejection episodes or other immunologic complications to date. He currently receives antimicrobial prophylaxis with sulfamethoxazole/trimethoprim and valganciclovir. His other drugs include amlodipine, metoprolol, atorvastatin, levothyroxine, sitagliptin, and famotidine.

21. T.G. developed new-onset diabetes after transplantation (NODAT), which has persisted despite the changes in his immunosuppressive regimen. Since his transplant, he has been receiving sitagliptin therapy. Which one of the following is the most likely contributing factor to T.G.’s NODAT?
A. Obesity.
B. Tacrolimus.
C. Cyclosporine.
D. Race/ethnicity.

22. In a follow-up visit about 2 weeks later, T.G.’s laboratory values reveal an elevation in SCr from 1.1 mg/dL to 1.7 mg/dL. He has no other laboratory abnormalities. T.G. undergoes an outpatient renal biopsy that reveals cyclosporine nephrotoxicity despite concentrations in the therapeutic range (289 ng/dL; goal trough range is 200–300 ng/dL). Which one of the following is the best management strategy for T.G.?
A. Increase the amlodipine dose from 5 mg once daily to 10 mg once daily.
B. Lower the mycophenolate dose.
C. Convert cyclosporine to belatacept.
D. Lower the cyclosporine dose.

23. T.G. comes to his 6-month clinic visit with a blood pressure of 162/98 mm Hg (confirmed at 158/88 mm Hg) and evidence of proteinuria on urine dipstick, confirmed by a high protein/creatinine ratio on urinalysis. Which one of the following would be best to initiate in T.G.?
A. Hydrochlorothiazide.
B. Lisinopril.
C. Diltiazem.
D. Clonidine.

Questions 25 and 26 pertain to the following case.
B.C. is a 47-year-old woman who received a deceased donor kidney transplant 6 months ago. This was her second renal transplant; the first transplant lasted 17 years. B.C. was given antithymocyte globulin rabbit and received maintenance tacrolimus, mycophenolate mofetil, and prednisone. She was scheduled to finish a 6-month course of antimicrobial prophylaxis. During your clinic interview, she states that she has taken sulfamethoxazole/trimethoprim daily as prescribed but has not been taking valganciclovir 450 mg once or twice weekly (the prescribed dose was 900 mg once daily). B.C.’s husband lost his job and insurance about 3 months ago, and she has been trying to stretch her last refill of valganciclovir because it is expensive. She did not contact the transplant clinic for help because she was embarrassed that she could not afford her medications. She reports adherence to her other medications. Her tacrolimus C0 today is 8.1 ng/dL, which is within her goal concentration.

25. B.C. has a 10-day history of low-grade fevers, malaise, myalgias, and fatigue. She believes her symptoms have worsened during the past few days. Her laboratory test results show a white blood cell count of 1.9 x 10³ cells/mm³. She is admitted to the hospital to be evaluated for infection. Of note, she is at high risk of cytomegalovirus (CMV) disease because her donor was CMV positive and she was CMV negative at the time of transplantation. A CMV viral load after admission reveals a viral load of 35,000 copies/mL. All bacterial blood cultures are negative. B.C. is initiated on intravenous ganciclovir 5 mg/kg every 12 hours. Her symptoms continue to worsen during the next 5 days. Further testing reveals
that she has UL97 ganciclovir-resistant CMV. Which one of the following is best to recommend for B.C.?

A. Cidofovir 5 mg/kg intravenously once weekly.
B. Cidofovir 5 mg/kg intravenously every 24 hours.
C. Foscarnet 90 mg/kg intravenously every 12 hours.
D. Foscarnet 60 mg/kg intravenously every 12 hours.

26. As part of B.C.’s workup for CMV disease, other viral screens are sent. Her BKV viral load in the blood is positive with 175,000 copies/mL. Which one of the following is the best initial treatment for BKV viremia in B.C.?

A. Convert mycophenolate mofetil to leflunomide 40 mg once daily.
B. Add levofloxacin 500 mg once daily for 30 days.
C. Add intravenous immunoglobulin (IVIg) 2 g/kg for one dose.
D. Reduce tacrolimus by 25%.

27. A 56-year-old man underwent kidney transplantation with a living related donor organ 18 months ago. He has been maintained on belatacept, mycophenolate mofetil, and prednisone with good short-term results. At the time of transplantation, he weighed 88 kg. He has intentionally lost 7 kg through lifestyle modifications and visits with a nutritionist. He is due for another belatacept dose in the next few days. Which one of the following is the optimal belatacept dose for this patient?

A. 440 mg.
B. 437.5 mg.
C. 405 mg.
D. 400 mg.

28. You see a male transplant recipient in the clinic for a posttransplant follow-up. He is 8 years post–kidney transplantation with chronic allograft nephropathy and stage 5 CKD. His immunosuppressive regimen consists of cyclosporine, mycophenolate, and prednisone. His most recent fasting lipid panel values are as follows: TC 320 mg/dL, LDL cholesterol 145 mg/dL, TG 320 mg/dL, and HDL cholesterol 45 mg/dL. Which one of the following is the best option for treating this patient’s dyslipidemia?

A. Initiate atorvastatin 10 mg.
B. Initiate pravastatin 20 mg.
C. Initiate pravastatin 10 mg.
D. Initiate lovastatin 20 mg.

29. A 67-year-old white man received a living related renal transplant from his son about 9 years ago. He is currently maintained on tacrolimus 2 mg twice daily, azathioprine 100 mg once daily, and prednisone 5 mg once daily. His transplant history is unremarkable except for significant GI intolerance to enteric-coated MPA, despite his taking doses lower than 720 mg/day, which has necessitated a conversion in his regimen to azathioprine. He comes to the clinic today for his yearly evaluation and states that he just finished a steroid taper for treating a gout flare – his third flare-up in the past 3 months. His primary care physician would like to initiate allopurinol 100 mg once daily. You agree that this therapy should help prevent future gout flares but are concerned about the drug-drug interaction (DDI) with azathioprine. After discussing this with the patient, it is agreed that he will begin allopurinol therapy and return for follow-up visits at 1 week and 1 month from the allopurinol start date. Which one of the following is best to recommend for this patient?

A. Lower azathioprine to 25 mg once daily and monitor the CBC.
B. Lower azathioprine to 50 mg once daily and monitor the CBC.
C. Lower azathioprine to 75 mg once daily and monitor the CBC.
D. Convert to mycophenolate mofetil 500 mg twice daily and monitor the CBC.

**Questions 30 and 31 pertain to the following case.**

J.A. is a 28-year-old woman scheduled to receive a living donor renal transplant from her father. She has a history of systemic lupus erythematosus that was previously managed with steroids and hydroxychloroquine. She is not taking any drugs for lupus and has never received cyclophosphamide. J.A.’s lupus has been quiescent since she began hemodialysis about 6 months ago. The immunosuppressive plan for her is to induce basiliximab and keep her on maintenance tacrolimus and mycophenolate mofetil. Given J.A.’s history of weight gain with corticosteroids, the clinician decides to try withdrawing steroids completely.

30. J.A., who was recently married, looks forward to starting a family once she recovers from transplantation. She has been warned about pregnancy risks posttransplantation and those specifically related to lupus. Which one of the following education points regarding the MPA REMS and the use of MPA posttransplantation is best to provide J.A.?

A. All MPA formulations increase the risk of miscarriage and fetal malformations.
B. Family planning is discouraged posttransplantation because the most important concern is maintaining kidney function and preventing allograft failure.
C. It is mandatory that all patients who become pregnant after transplantation be enrolled in the Mycophenolate Pregnancy Registry to track outcomes.
D. The patient can be converted to enteric-coated MPA because only mycophenolate mofetil carries risk during pregnancy.

31. J.A. does well after transplantation and returns to the clinic 5 months later. During the past few months, you have decreased her tacrolimus and MPA doses because of a hand tremor and leukopenia, both of which have resolved. At today’s clinic visit, she is concerned about increased alopecia because her friends and family comment about her “starting to go bald.” She has read all the package inserts that came with her most recent refills. The only medications she currently takes are tacrolimus (3 mg twice daily; C0 6.1 ng/dL; goal is 8–10 ng/dL, but at higher doses, she has hand tremors), mycophenolate mofetil (750 mg twice daily), and an oral contraceptive. J.A. states that she could live with any of the other adverse effects listed in the package inserts, just not the cosmetic adverse effects, because she is now back at work full-time and “needs to look presentable.” You are concerned about nonadherence should her alopecia continue. Which one of the following is best to recommend for J.A.?

A. Decrease tacrolimus to 2 mg twice daily.
B. Convert tacrolimus to cyclosporine 125 mg twice daily.
C. Advise the patient to try topical minoxidil 2% solution as directed to increase hair growth.
D. Decrease mycophenolate mofetil to 500 mg twice daily.

32. A 37-year-old man received a kidney transplant 7 years ago. His current regimen is tacrolimus 5 mg twice daily, azathioprine 100 mg once daily, prednisone 5 mg once daily, amlopidine 10 mg once daily, rosuvastatin 10 mg once daily, and omeprazole 20 mg once daily. This patient is an attorney and has been working increasingly longer hours for the past few years. He admits forgetting to take his morning medications (tacrolimus) several times during the past 1½ years. Which one of the following is best to recommend for this patient?

A. Convert from tacrolimus 5 mg twice daily to tacrolimus extended release 10 mg once daily.
B. Convert from tacrolimus 5 mg twice daily to tacrolimus extended release 5 mg once daily.
C. Convert from tacrolimus to belatacept 5 mg/kg intravenously once monthly.
D. Convert from tacrolimus to sirolimus 2 mg once daily.

33. A patient with a diagnosis of NODAT and known gastroparesis presents for a follow-up. The patient is 2 years posttransplantation with an SCr of 3.2 and an estimated CrCl of 25 mL/minute/1.73m². Which one of the following would be most appropriate to initiate in this patient?

A. Glyburide.
B. Metformin.
C. Liraglutide.
D. Linagliptin.

34. One concern regarding the use of generic calcineurin inhibitors (CNIs) in renal transplant recipients (RTRs) is that, given their narrow therapeutic windows, generic conversion could result in significant changes in drug exposure, potentially causing rejection or toxicities. Which one of the following best describes the reasoning behind this concern?

A. The excipients of the generic formulation may be different from those of the innovator product and have a significant DDI with the other immunosuppressive medication.
B. Bioequivalence is determined in a small group of healthy volunteers, and there is apprehension regarding the actual bioequivalence in RTRs with common comorbid disease states that are often present in kidney failure (e.g., diabetes, cardiovascular disease, peripheral vascular disease).
C. Many generic medications are manufactured outside the United States, and the FDA does not monitor these outside facilities for good manufacturing practices.
D. The cost savings associated with generic medications will decrease the profit margins of those who manufacture innovator products and subsequently reduce future research in transplantation.

35. A patient is admitted to the hospital for a renal biopsy secondary to a rapid increase in SCr and a sharp decline in urine output. The patient is 4 months posttransplantation and is considered high immunologic risk because this is his third transplant in the past 28 years. He had several rejection episodes after his two previous kidney transplants. The biopsy results confirm T cell–mediated rejection (TCMR) Banff Ia (low-severity rejection). Which one of the following is best to recommend for this patient?

A. Methylprednisolone 500 mg intravenously daily for 3 days.
B. Prednisone 250 mg orally daily for 3 days.
C. Alemtuzumab 30 mg subcutaneously x 1.
D. Antithymocyte globulin rabbit 1.5 mg/kg intravenously daily for 4 days.

Questions 36 and 37 pertain to the following case.

B.R. is admitted to the hospital for a renal biopsy secondary to a slow rise in SCr during the past few weeks. The
patient is 2 months posttransplantation and is considered at high immunologic risk, given that she has preformed antihuman antibodies because of multiple pregnancies and blood transfusions. She has no donor-specific antibodies, but antibody-mediated rejection (AMR) is a concern. The renal biopsy confirms AMR.

36. Which one of the following is best to recommend for B.R.?
   A. Plasmapheresis (three to five sessions) with IVIg 10 g after each plasma exchange.
   B. Plasmapheresis (three to five sessions) with IVIg 2 g/kg after each plasma exchange.
   C. Rituximab 1000 mg intravenously x 1 dose.
   D. Eculizumab 1200 mg intravenously x 1 dose, followed 1 week later by four weekly doses of 900 mg, with a final dose of 1200 mg at week 5.

37. Despite your best efforts at initially treating her AMR, B.R. shows no signs of improvement and is given a diagnosis of refractory AMR. Which one of the following is best to recommend for B.R.?
   A. Plasmapheresis (three to five sessions) with IVIg 10 g after each plasma exchange.
   B. Plasmapheresis (three to five sessions) with IVIg 10 g after each plasma exchange and rituximab 1000 mg intravenously x 1 dose.
   C. Plasmapheresis (three to five sessions) with 10 g of IVIg after each plasma exchange and bortezomib 1.3 mg/m² intravenously on days 1, 4, 8, and 11.
   D. Plasmapheresis (three to five sessions) with IVIg 10 g after each plasma exchange; eculizumab 1200 mg intravenously x 1 dose, followed 1 week later by four weekly doses of 900 mg with a final dose of 1200 mg at week 5; and rituximab 1000 mg intravenously x 1 dose (administered before the first eculizumab dose).

38. A man received a deceased donor renal transplant 7 months ago. Alemtuzumab was induced, and he is currently maintained on tacrolimus 6 mg twice daily (C₀ 7.6 ng/dL; goal C₀ 8–10 ng/dL) and mycophenolate mofetil 500 mg twice daily. His posttransplant course has been complicated only by persistent hyperkalemia, despite good graft function. He has tried diet modifications and pharmacotherapy using sodium polystyrene sulfonate and loop diuretics, but without improvement. Which one of the following is best to recommend for this patient?
   A. Admit him for intravenous insulin and calcium therapy.
   B. Convert tacrolimus to cyclosporine.
   C. Convert tacrolimus to belatacept.
   D. Add fludrocortisone 0.1 mg once daily.

39. A 49-year-old man has type 1 diabetes mellitus and end-stage renal disease. He has a history of hypertension, hyperlipidemia, peripheral neuropathy, retinopathy, and peripheral vascular disease. He is being worked up for a living donor renal transplant from his wife. He is CMV negative and Epstein-Barr virus (EBV) negative. His potential donor is CMV negative and EBV positive. The patient is considered at low immunologic risk. Which one of the following maintenance immunosuppressive regimens would provide this patient the best long-term benefit?
   A. Tacrolimus and enteric-coated MPA.
   B. Belatacept, mycophenolate mofetil, and prednisone.
   C. Tacrolimus, enteric-coated MPA, and prednisone.
   D. Everolimus, mycophenolate mofetil, and prednisone.

40. A man presents with a history of steroid-resistant TCMR that required treatment with antithymocyte globulin rabbit. He was never reinitiated on antimicrobial prophylaxis after treatment of this rejection episode. Five weeks later, he is admitted for treatment of *Pneumocystis jiroveci* pneumonia and is given intravenous sulfamethoxazole/trimethoprim. After 24 hours of therapy, the patient continues to be febrile with extreme hypoxia (Pao₂ 65 mm Hg). Which one of the following is the best treatment option for this patient?
   A. Increase the sulfamethoxazole/trimethoprim dose.
   B. Add valganciclovir because this patient could have CMV pneumonia as well.
   C. Add atovaquone 750 mg twice daily.
   D. Add prednisone.

41. A woman received a deceased donor renal transplant 6 months ago. Her kidney failure was secondary to lithium toxicity. She received an induction of antithymocyte globulin rabbit, tacrolimus, mycophenolate mofetil, and prednisone. Having received early steroid withdrawal, she is now maintained on only tacrolimus and MPA. The patient has a history of several squamous cell carcinomas. Her transplant history is unremarkable. She has an estimated GFR of 110 mL/minute and her urine protein/creatinine ratio is 0.05. Which one of the following is the best option for this patient’s maintenance immunosuppressive therapy?
   A. Continue with her current therapy.
   B. Convert tacrolimus to belatacept.
   C. Convert tacrolimus to sirolimus.
   D. Convert mycophenolate mofetil to azathioprine.
LEARNING OBJECTIVES

1. Design evidence-based treatment regimens for the management of gastrointestinal disease, especially inflammatory bowel disease.
2. Distinguish the role of biologic therapies, including safety concerns, in the treatment of inflammatory bowel disease.
3. Evaluate appropriate treatment recommendations with health care providers regarding the use of biologic therapies in inflammatory bowel disease.
4. Justify important drug education with patients regarding the use of biologic therapies in the treatment of inflammatory bowel disease.

INTRODUCTION

Biologic therapies, as defined in Section 351 of the Public Health Services act, are created from living cells and/or organisms and are used to prevent, treat, and/or cure a disease. Biologics are regulated by both the U.S. Food and Drug Administration (FDA) Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research. Biologic agents differ from drugs in that they are typically much larger, more complex molecules. In some cases, they are immunogenic and may be of a heterogeneous mixture (e.g., proteins, nucleic acids, sugars). Although biologics emerged in the early 1900s, their development has recently expanded. The approval of infliximab in 1998 has been followed by several new agents that target a variety of pathways in the treatment of gastrointestinal diseases. These advances have been key in preventing surgery, inducing and maintaining remission, and treating refractory disease including inflammatory bowel disease (IBD), the most common; Crohn’s disease (CD); and ulcerative colitis (UC).

Inflammatory Bowel Disease

Typically presenting in the second and third decade of life, IBD may also present in patients aged 60 to 80
years (Friedman 2012). The exact pathogenesis of IBD is unclear, although the consensus is that a mix of environmental and host factors lead to an inappropriate immune response within the intestines. This dysregulated inflammatory response is the target of therapy. Typical treatment before biologic therapy may include aminosalicylates, sulfasalazine or corticosteroids (first-line), and/or immunosuppressants (second-line). This treatment course is considered a stepwise or step-up approach (Figure 3-1, Figure 3-2). Patients with difficulty to treat or refractory disease can be considered for step-down or top-down therapy, which introduces biologics (e.g., anti-tumor necrosis factor [TNF] agents) earlier and may prevent complications and improve patient outcomes. A recent study evaluated top-down therapy (infliximab alone or in combination with azathioprine) in patients with a new CD diagnosis who were naïve to corticosteroids, immunomodulators, and anti-TNF agents (Colombel 2010). Top-down therapy was associated with better outcomes (corticosteroid-free at week 26 and mucosal healing) than azathioprine alone. However, significant benefit of this therapy remains to be validated in prospective clinical trials in high-risk patients (e.g., refractory disease).

Surgery should be considered when pharmacologic therapies fail or to avoid further complications of disease (e.g., cancer). Timeline of failure is difficult to estimate, although 38% of patients will require surgery within 1 year of initiating corticosteroids. When disease does not improve in 7 to 10 days with intensive medical management, surgery should be considered.

The primary goals of biologic therapy in CD and UC are to achieve and maintain remission, defined as having few or no symptoms of disease. Secondary goals for CD include: (1) maintaining steroid-free remission, (2) resolving fistulizing disease, (3) decreasing complications and surgery, (4) preserving intestinal function, (5) improving patient quality of life, and (6) minimizing adverse drug events (ADEs) of therapy (Nielsen 2012). Secondary goals for UC include: (1) reducing the need for long-term corticosteroids, (2) improving patient quality of life, and (3) decreasing the risk of cancer (Kornbluth 2010). The severity of CD may be scored using the Crohn’s Disease Activity Index (CDAI) (Table 3-1), whereas the severity of UC may be determined by the Mayo Score (Table 3-2) or the Lichtiger Score (Table 3-3).

Overview of Biologic Therapy

Biologic therapies have several targets and mechanisms of action. These include TNF-α, interleukins (ILs), cluster of differentiation, Janus kinase (JAK), and other miscellaneous targets.

Tumor necrosis factor-alpha is an inflammatory cytokine produced primarily by lymphocytes with macrophage activation, although many cells of the immune system are capable of TNF-α synthesis. It is, in part, responsible for proinflammatory cytokine induction and an inflammatory host response through TH1 (Friedman 2012; Peake 2013). This response can cause tissue damage as seen in CD and UC (Peake 2013). Antagonists of TNF-α block the interaction between a TNF precursor and its membrane receptor, whereas agonists of TNF-α may lead to “reverse signaling” (Peake 2013). Both of these pathways may lead to cytokine suppression, thereby decreasing the inflammatory response. Anti-TNF agents are generally reserved for moderate to severe disease or for disease refractory to standard CD or UC therapies. They may be used as induction agents or to maintain remission of disease. Anti-TNF agents discussed in this chapter include infliximab, adalimumab, certolizumab pegol, golimumab, and etanercept.

The ILs are cytokines produced by lymphocytes that regulate inflammatory and immune responses. The International Union of Immunological Societies and the World Health Organization Nomenclature Subcommittee developed a nomenclature that includes a number after the abbreviation IL. The agents to be discussed in this chapter are antagonists of IL-12/23, IL-17a, and IL-5. Currently, there are no FDA-approved IL agents for treatment of gastrointestinal diseases, but two IL agents (ustekinumab and secukinumab) have been investigated in CD.

Cluster of differentiation is a nomenclature protocol that has helped organize cell surface molecules, many of which are on lymphocytes and play a role in the immune system. Monoclonal antibodies are being developed to target these molecules and treat a variety of diseases. No agents within this class are approved to treat gastrointestinal disease, but they have been studied in CD. Discussed in this chapter are abatacept and visilizumab.

Kinases are enzymes that are responsible for phosphorylation. More specifically, JAK are a family of intracellular enzymes that mediate cytokine signals through the JAK-STAT (Janus kinase signal transducer and activator of transcription) pathway. This pathway is an alternative to the secondary messenger system cells employ; however,
the JAK-STAT pathway is expressed in lymphocytes, so they are specific to functions of the immune system. Tofacitinib, which carries FDA-approved labeling for moderate to severe rheumatoid arthritis but not for gastrointestinal disease, has been studied in CD and UC.

Other miscellaneous agents include natalizumab, vedolizumab, and fontolizumab. Natalizumab, a recombinant humanized immunoglobulin (Ig)G4κ monoclonal antibody produced in murine cells, binds the adhesion molecules, integrins α4β7 and α4β1. Integrins are expressed on leukocytes, with the exception of neutrophils. In theory, this monoclonal antibody would inhibit the ability of immune system cells to bind to the intestines. Crohn’s disease, in part, results from the migration of leukocytes to the intestines, which causes inflammation. Natalizumab is approved for inducing and maintaining response and remission in patients with moderate to severe CD that has not improved with conventional therapies and anti-TNF agents. Natalizumab should not be used in combination with immunosuppressants or anti-TNF agents. Vedolizumab is a more selective version of natalizumab, binding only α4β7. It was recently approved by the FDA for patients with CD and UC. Vedolizumab and natalizumab will likely compete for their place in therapy.

Interferon-γ (IFN-γ) is a cytokine that plays an important role in the immune system, activating macrophages. Production of IFN-γ is upregulated in CD. Fontolizumab, a monoclonal antibody that binds to and inhibits IFN-γ, does not have FDA label approval but has been studied in CD.

This chapter reviews clinical study data and guidelines for biologic therapies in CD and UC. Drug classes are grouped by mechanism of action, with discussions of safety and place in therapy for each agent. Where the data are more limited, the immunologic basis of the therapies is discussed together with trial data. Mechanism of action and specific information on each class of agents (e.g., approved indications, dosing, clinical pearls) are described in Table 3-4. Pivotal trial data for CD and UC is summarized in Table 3-5 and Table 3-6, respectively.

**Anti-TNF-α Agents**

**Infliximab**

Infliximab is the most studied of the agents in this class and has label approval for both CD and UC. Standard dosing of infliximab for both CD and UC is 5 mg/kg administered intravenously; however, for patients with CD who lose response to infliximab, the dose may be increased to 10 mg/kg. If a patient experiences a mild to moderate infusion reaction, the infusion may be slowed or interrupted and reinitiated after resolution of the reaction. Patients may be pre-medicated with acetaminophen,
antihistamines, and/or corticosteroids. Serum sickness (a delayed hypersensitivity infusion-related reaction) has been reported and usually presents as rash, fever, chills, polyarthralgias, or polyarthritis. Administration of infliximab induction at weeks 0, 2, and 6 can reduce the development of antibodies to infliximab and infusion-related reactions.

**Crohn’s Disease**

Infliximab’s label approval for the treatment of moderate to severe CD was based on two major studies. A single-dose study showed 81% of patients treated with 5 mg/kg infliximab had a clinical response versus 17% of patients treated with placebo (p<0.001) (Targan 1997). This was followed by ACCENT I, an induction and maintenance trial of infliximab (Hanauer 2002). Nearly 60% of patients responded after a single infusion, with 39% and 45% in the 5 mg/kg and 10 mg/kg dosing groups, respectively, achieving remission by week 30 (p=0.03) versus 21% in the placebo group (p=0.0002) (Hanauer 2002). Patients in the infliximab 10 mg/kg group sustained their response for more than 54 weeks versus 19 weeks for the placebo group (p=0.0002). However, these studies did not include patients with fistulizing disease, which was the focus of the ACCENT 2 study.

Patients enrolled in ACCENT 2 had a single or multiple draining fistulas for at least 3 months and were randomized by fistula response or nonresponse to placebo or infliximab through week 54 (Sands 2004). The trial group was 49% women (n=138), of whom 25 had rectovaginal fistulas. Excluded were patients who had received anti-TNF therapy within 3 months of randomization. At week 14, 44.8% of women with draining rectovaginal fistulas (13 of 29) had closure of their fistula. Among patients who responded, 72.2% of fistulas had stopped draining. Additionally, the median duration of fistula closure was longer with infliximab (46 weeks) than in the placebo group (33 weeks) (Sands 2004).

The use of anti-TNF therapy in combination with more conventional therapies was evaluated in the SONIC trial. Patients with moderate to severe CD were randomized to infliximab monotherapy, azathioprine monotherapy, or the combination versus placebo. At week 26, more patients treated with combination therapy achieved steroid-free remission than those treated with infliximab alone (p=0.02) or azathioprine alone (p<0.001). Infectious complications were not increased with the addition of infliximab to azathioprine (Colombel 2010).

A recent meta-analysis of six studies including SONIC supported these results, finding that combination therapy was more effective at inducing remission (p=0.0009), and maintaining early (weeks 24-26) and late remission (weeks 48-54) (p<0.00001). Additionally, no greater risk of ADEs was seen with combination therapy than with either agent alone (Lin 2011). However, the authors found publication bias when analyzing infections (p=0.095). The immunosuppressants included were azathioprine,
6-mercaptopurine, and methotrexate; however, data were insufficient to analyze these agents separately, so they were analyzed as a group. This analysis included patients with fistulizing disease but did not discuss the more difficult-to-treat patients who previously received anti-TNF agents or who required surgery.

Data are conflicting on prevention of disease recurrence by ileocolic or ileal resections. One study (n=31) found a significant improvement with infliximab based on International Organization for the Study of Inflammatory Bowel Disease scores (p<0.03) but not with CDAI scores (p=0.70) (Yoshida 2012). Similar results were found with infliximab maintenance therapy in 62 patients with a seton placed in the fistula to help in healing. Treatment with or without infliximab produced similar failure rates (15.4% vs. 27.8%; p=0.25) and partial improvement (88.5% vs. 72.2%; p=0.25), respectively. Overall short-term improvement was seen in 77.4% of patients; however no advantage in long-term benefit was found for infliximab (Uchino 2011).

Another small study (n=32) compared infliximab plus seton placement with infliximab alone. Patients with seton placement before infliximab treatment were more likely to have a better initial response (100% vs. 83%; p=0.014), a lower recurrence rate (44% vs. 79%; p=0.001), and a longer time to recurrence (14 vs. 4 months; p=0.0001) (Regueiro 2003).

Patients failed by other anti-TNF agents are difficult to treat. In one small study (n=15), all patients who discontinued adalimumab because of loss of response (n=7) achieved response with infliximab. However, none of the patients who achieved only a partial response to

---

**Table 3-1. Crohn’s Disease Activity Index Scoring**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
<th>Score</th>
<th>Multiplier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of liquid stools</td>
<td>Sum of 7 days</td>
<td>0 = none</td>
<td>X2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 = mild</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 = moderate</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 = severe</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Sum of 7 days</td>
<td>0 = generally well</td>
<td>X5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 = slightly under par</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 = poor</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 = very poor</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 = terrible</td>
<td></td>
</tr>
<tr>
<td>Well-being</td>
<td>Sum of 7 days</td>
<td>0 = generally well</td>
<td>X7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 = slightly under par</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 = poor</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 = very poor</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 = terrible</td>
<td></td>
</tr>
<tr>
<td>Extra-intestinal complications</td>
<td>Number of listed complications (one point for each complication)</td>
<td>Arthritis or arthralgia, iritis or uveitis, erythema, nodosum, pyoderma, gangrenosum, aphthous stomatitis, anal fissure or fistula or abscess, fever &gt; 37.8°C</td>
<td>X20</td>
</tr>
<tr>
<td>Anti-diarrheal drugs</td>
<td>Use in previous 7 days</td>
<td>0 = no</td>
<td>X30</td>
</tr>
<tr>
<td>(diphenoxylate/atropine, loperamide, or opiates)</td>
<td></td>
<td>1 = yes</td>
<td></td>
</tr>
<tr>
<td>Abdominal mass</td>
<td></td>
<td>0 = no</td>
<td>X10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 = questionable</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 = definite</td>
<td></td>
</tr>
<tr>
<td>Hematocrit</td>
<td>Expected-observed hematocrit</td>
<td>Males: 47 – observed</td>
<td>X6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Females: 42 – observed</td>
<td></td>
</tr>
<tr>
<td>Body weight</td>
<td>Ideal/observed ratio</td>
<td>[1-(ideal/observed)] x 100</td>
<td>X1</td>
</tr>
</tbody>
</table>

Response: ≥ 70 point decrease in CDAI score
Remission: CDAI < 150
Moderate Activity: CDAI 200-450
Severe Activity: CDAI > 450
Maximum Score: CDAI 600
adalimumab responded to infliximab (Chaparro 2012a). Failure of adalimumab therapy may also indicate loss of response to infliximab. In one study (n=74), about one-half of the patients lost response to infliximab. This resulted in longer disease duration and exposure to infliximab, which could lead to possible antibody development to infliximab, thereby increasing drug clearance (Sono 2012).

**Ulcerative Colitis**

A 3-year open-label extension of ACT-1 and ACT-2 demonstrated that infliximab was safe and effective in the treatment of UC (Reinisch 2012). Patients with moderate to severe UC who achieved clinical benefit, based on the opinion of the treating physician (Rutgeerts 2005), received up to 3 more years of infliximab. Only 5% of patients discontinued therapy because of a lack of efficacy, and about 90% of patients had no disease or mild disease. The overall rate of infliximab discontinuation was 30.6% (Reinisch 2012).

**Adalimumab**

Adalimumab is a fully human, recombinant IgG1 monoclonal antibody with label approval in the treatment of CD and UC. Patients with CD should notify their physician if there is no clinical response within 12 weeks of therapy. In patients with UC, adalimumab should be discontinued if there is no evidence of remission within 8 weeks of therapy. The package insert states that patients should be instructed to properly self-administer a subcutaneous injection including sterile technique and rotating the injection site.

**Crohn’s Disease**

Three major trials examined the use of adalimumab in patients with moderate to severe CD that did not respond to conventional therapies. CLASSIC-I, an induction study, reported a significant increase in remission rates at 4 weeks of adalimumab versus placebo (36% vs. 12%; p=0.001) (Hanauer 2006). CHARM was a long-term maintenance study in which patients treated with adalimumab were more likely to achieve and maintain clinical remission than those receiving placebo (p≤0.005) (Colombel 2007). The GAIN re-induction and maintenance study found that treatment with adalimumab resulted in a 21% remission rate versus 7% for placebo (p<0.001) (Sandborn 2007a).

These trials were followed by several others. The CLASSIC-II maintenance and dosing study enrolled patients from CLASSIC-I and assessed maintenance therapy after induction with adalimumab. In the randomized arm, patients treated with adalimumab were more likely

---

**Table 3-2. Mayo Scoring for Ulcerative Colitis**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stool frequency</td>
<td>0 = normal number for patient</td>
</tr>
<tr>
<td></td>
<td>1 = 1 to 2 stools more than normal for patient</td>
</tr>
<tr>
<td></td>
<td>2 = 3 to 4 stools more than normal for patient</td>
</tr>
<tr>
<td></td>
<td>3 = 5 or more stools more than normal for patient</td>
</tr>
<tr>
<td>Rectal bleeding</td>
<td>0 = no blood seen</td>
</tr>
<tr>
<td></td>
<td>1 = streaks of blood with stool less than half the time</td>
</tr>
<tr>
<td></td>
<td>2 = obvious blood with stool most of the time</td>
</tr>
<tr>
<td></td>
<td>3 = blood alone passes</td>
</tr>
<tr>
<td>Findings on endoscopy</td>
<td>0 = normal or inactive disease</td>
</tr>
<tr>
<td></td>
<td>1 = mild disease (erythema, decreased vascular pattern, mild friability)</td>
</tr>
<tr>
<td></td>
<td>2 = moderate disease (marked erythema, lack of vascular pattern, friability, erosions)</td>
</tr>
<tr>
<td></td>
<td>3 = severe disease (spontaneous bleeding, ulceration)</td>
</tr>
<tr>
<td>Physician’s global assessment</td>
<td>0 = normal</td>
</tr>
<tr>
<td></td>
<td>1 = mild disease</td>
</tr>
<tr>
<td></td>
<td>2 = moderate disease</td>
</tr>
<tr>
<td></td>
<td>3 = severe disease</td>
</tr>
</tbody>
</table>

Remission: ≤2  
Mild disease: 3 – 5  
Moderate disease: 6 – 10  
Severe disease: 11 – 12  
Range 0 to 12
to develop remission (79%–83%) than those treated with placebo (44%) at week 56 (p<0.05). In the open-label portion of the study, 46% of patients were in remission at week 56 (Sandborn 2007b). The EXTEND long-term maintenance study used a patient group (n=135) similar to previous trials but the primary end point was mucosal healing after adalimumab induction. Healing rates at weeks 12 and 52 were higher with adalimumab (27% and 24%; p=0.056) than with placebo (13% and 0%; p<0.001) (Rutgeerts 2012a). The results of these trials were confirmed by a meta-analysis of 1402 patients (Huang 2011).

Another open-label trial assessed the efficacy of adalimumab in anti-TNF naïve and experienced patients (n=304). Adalimumab maintained steroid-free remission in all patients. However, anti-TNF experienced patients had lower rates of remission (36% vs. 53%) and fistula healing (26% vs. 48%) than anti-TNF naïve patients, although there was significant improvement from baseline (Panaccione 2011). Two other open-label trials showed conflicting results for adalimumab use in anti-TNF experienced patients. The SWITCH study showed that switching from infliximab to adalimumab was associated with increased intolerance and decreased efficacy within 1 year. Authors recommended continuing the first anti-TNF agent initiated (van Assche 2012). The CHOICE trial evaluated safety, quality of life, work productivity, and patient satisfaction.

### Table 3-3. Lichtiger Scoring System for Ulcerative Colitis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea (number of daily stools)</td>
<td>0 = 0 to 2</td>
</tr>
<tr>
<td></td>
<td>1 = 3 to 4</td>
</tr>
<tr>
<td></td>
<td>2 = 5 to 6</td>
</tr>
<tr>
<td></td>
<td>3 = 7 to 9</td>
</tr>
<tr>
<td></td>
<td>4 = 10 or more</td>
</tr>
<tr>
<td>Nocturnal diarrhea</td>
<td>0 = no</td>
</tr>
<tr>
<td></td>
<td>1 = yes</td>
</tr>
<tr>
<td>Visible blood</td>
<td>0 = 0</td>
</tr>
<tr>
<td></td>
<td>1 = less than 50% of movements</td>
</tr>
<tr>
<td></td>
<td>2 = more than 50% of movements</td>
</tr>
<tr>
<td></td>
<td>3 = 100% of movements</td>
</tr>
<tr>
<td>Fecal incontinence</td>
<td>0 = no</td>
</tr>
<tr>
<td></td>
<td>1 = yes</td>
</tr>
<tr>
<td>Abdominal pain or cramping</td>
<td>0 = none</td>
</tr>
<tr>
<td></td>
<td>1 = mild</td>
</tr>
<tr>
<td></td>
<td>2 = moderate</td>
</tr>
<tr>
<td></td>
<td>3 = severe</td>
</tr>
<tr>
<td>General well-being</td>
<td>0 = perfect</td>
</tr>
<tr>
<td></td>
<td>1 = very good</td>
</tr>
<tr>
<td></td>
<td>2 = good</td>
</tr>
<tr>
<td></td>
<td>3 = average</td>
</tr>
<tr>
<td></td>
<td>4 = poor</td>
</tr>
<tr>
<td>Abdominal tenderness</td>
<td>0 = none</td>
</tr>
<tr>
<td></td>
<td>1 = mild and localized</td>
</tr>
<tr>
<td></td>
<td>2 = mild to moderate and diffuse</td>
</tr>
<tr>
<td></td>
<td>3 = severe or rebound</td>
</tr>
<tr>
<td>Need for anti-diarrheal medications</td>
<td>0 = no</td>
</tr>
<tr>
<td></td>
<td>1 = yes</td>
</tr>
<tr>
<td>Response: &lt;10 for 2 consecutive days</td>
<td></td>
</tr>
<tr>
<td>Remission: &lt;4</td>
<td></td>
</tr>
<tr>
<td>Severe Disease: &gt;10</td>
<td></td>
</tr>
<tr>
<td>Agent (Pharmacology)</td>
<td>Approved and Investigational Indication(s)</td>
</tr>
<tr>
<td>-----------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Anti-tumor necrosis factor-α</td>
<td></td>
</tr>
<tr>
<td>Infliximab (chimeric (human constant region, murine variable region) IgG1 monoclonal antibody)</td>
<td>CD – induction and maintenance of remission in patients with moderate to severe disease that failed conventional therapies; reduce signs and symptoms of disease, reduce the number of draining enterocutaneous and rectovaginal fistulas, maintain closure of fistulas</td>
</tr>
<tr>
<td></td>
<td>UC – induction and maintenance of remission and mucosal healing in patients with moderate to severe disease that failed conventional therapies; reducing signs and symptoms of disease, decrease the need for corticosteroids Also approved for pediatric CD and UC</td>
</tr>
<tr>
<td>Adalimumab (fully human, recombinant IgG1 monoclonal antibody)</td>
<td>CD – induction and maintenance of remission in patients with moderate to severe disease after conventional therapies fail; reduce signs and symptoms of CD and induce remission after infliximab fails</td>
</tr>
<tr>
<td></td>
<td>UC – induction and maintenance of remission in patients with moderate to severe disease with inadequate response to conventional therapies</td>
</tr>
<tr>
<td>Certolizumab pegol (pegylated, recombinant humanized antibody Fab fragment)</td>
<td>CD – reduction of signs and symptoms of disease and maintenance of remission for patients with moderate to severe disease refractory to conventional therapies</td>
</tr>
<tr>
<td>Agent (Pharmacology)</td>
<td>Approved and Investigational Indication(s)</td>
</tr>
<tr>
<td>----------------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td><strong>Golimumab (fully human, recombinant IgG1 monoclonal antibody)</strong></td>
<td>UC – patients with moderate to severe disease that failed conventional therapies or requires chronic corticosteroids; induction and maintenance of response and remission, and improvement of endoscopic appearance of mucosa</td>
</tr>
<tr>
<td><strong>Etanercept (engineered dimeric Fc fusion protein)</strong></td>
<td>Not FDA approved for a GI indication Studied in CD</td>
</tr>
<tr>
<td><strong>Interleukin antagonists</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Ustekinumab (fully human, recombinant IgG1 monoclonal antibody to IL-12 and IL-23)</strong></td>
<td>Not FDA approved for a GI indication Studied in CD</td>
</tr>
<tr>
<td><strong>Secukinumab (fully human, recombinant IgG1 monoclonal antibody to IL-17A)</strong></td>
<td>Not FDA approved Studied in CD</td>
</tr>
<tr>
<td><strong>Cluster of differentiation agents</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Abatacept (soluble fusion protein that inhibits T cell activating by binding cluster of differentiation-80 and -86)</strong></td>
<td>Not FDA approved for GI indications Studied in CD and UC</td>
</tr>
<tr>
<td><strong>Visilizumab (humanized IgG2 monoclonal antibody to cluster of differentiation-3)</strong></td>
<td>Not FDA approved Studied in UC</td>
</tr>
<tr>
<td><strong>Agent (Pharmacology)</strong></td>
<td><strong>Approved and Investigational Indication(s)</strong></td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td><strong>Janus kinase inhibitor</strong></td>
<td>Tofacitinib (citrate salt of tofacitinib, reduces IL-2 activation of helper T cells and attenuates IL-6 and IFN-γ)</td>
</tr>
<tr>
<td><strong>Integrin inhibitors</strong></td>
<td>Natalizumab (recombinant humanized IgG4 monoclonal antibody that binds integrins α4β7 and α4β1)</td>
</tr>
<tr>
<td></td>
<td>Vedolizumab (humanized Act-1 monoclonal antibody that binds integrin α4β7)</td>
</tr>
<tr>
<td><strong>Interferon-γ inhibitor</strong></td>
<td>Fontolizumab (humanized, recombinant monoclonal antibody)</td>
</tr>
</tbody>
</table>

*Based on prescribing information.

CD = Crohn’s disease; GI = gastrointestinal; Ig = immunoglobulin; IL = interleukin; IV = intravenous; UC = ulcerative colitis; SC = subcutaneous; TNF = tumor necrosis factor.
and fistula healing in 673 patients failed by or intolerant of infliximab therapy (including primary non-responders). After adalimumab induction and maintenance therapy, fistulas healed in 39% of patients and all patients had improved quality of life and work productivity that was sustained from week 4 to week 24 (Lichtiger 2010).

A historical cohort study (n=380) showed that with longer use of adalimumab (up to 48 months in a Kaplan-Meier estimate), only 42% of patients maintained response. Loss of response was 18% per patient-year of follow-up, and was more likely in anti-TNF experienced patients than anti-TNF naive patients (Chaparro 2012b). A family history of IBD, higher BMI, male sex, or previous response to infliximab are predictors for needing dose escalation (Cohen 2012; Bultman 2012).

Cost and quality of life data should also be considered when recommending the use of adalimumab in patients with moderate to severe CD. In one study, patients treated with adalimumab (n=623) had lower health care costs over a 6-month period than patients treated with infliximab (n=623) ($18,885 vs. $24,355; p<0.0001). This difference was most likely caused by administration routes (subcutaneous vs. intravenous, respectively). The largest cost difference (about $2000) was seen in outpatient visits (p<0.0001) (Sussman 2012). Quality of life was also evaluated in a meta-analysis of 1202 patients enrolled in the ACCESS, CARE, CHOICE, and EXTEND trials. Results showed that patients with CD treated with adalimumab had better work productivity (improved rates of absenteeism, presenteeism, and total work productivity impairment). The authors suggested that these results translate into indirect cost savings for employers (Binion 2011).

**Ulcerative Colitis**

The approval of adalimumab for the treatment of moderate to severe UC was based on two major multicenter, randomized, double-blind, placebo-controlled studies. The 8-week ULTRA 1 study included anti-TNF treatment naive patients with UC that failed to improve on corticosteroids or immunosuppressant therapy. Remission was achieved in 18.8% on high-dose adalimumab (p=0.031) and 10% on low-dose adalimumab (p=0.833) compared with 9% in the placebo group (Reinsch 2011). In the ULTRA 2 study, a similar patient group was stratified by previous anti-TNF agent use or no previous use. More patients in the adalimumab group than the placebo group achieved remission at week 8 (16.5% vs. 9.3%; p=0.019) and at week 52 (17.3% vs. 8.5%; p=0.004). Remission rates for patients naive to anti-TNF agents were higher at week 8 (21.3% vs. 9.2%) and week 52 (22% vs. 10.2%) than for patients with previous anti-TNF therapy (Sandborn 2012a). The ULTRA 1 and 2 trials showed that high-dose adalimumab was safe and effective at inducing and maintaining clinical remission of moderate to severe UC that failed to improve on conventional therapy.

A recent review that included data mostly from ULTRA 1 and 2 determined that adalimumab improved mucosal healing, clinical response, and health-related quality of life, while reducing hospitalizations and corticosteroid use (Burness 2013).

Although ULTRA 2 remission rates were low in the anti-TNF experienced group, evidence suggests that adalimumab is effective in these patients. One uncontrolled, open-label retrospective case series (n=30) showed a positive clinical response at week 4 (53%) and week 12 (60%). Long-term follow-up found that 50% of patients remained on adalimumab, and those with clinical response at week 12 avoided colectomy over a 4-year span (Taxonera 2011). Careful interpretation of this study is warranted given its uncontrolled, retrospective nature and short duration. Another small prospective observational study (n=23) found that adalimumab loses effectiveness over time; 79% of patients discontinued adalimumab and 65% of patients experienced treatment failure. The authors estimated cumulative failure rates of 50% at 6 months, 65% at 1 year, and 72% at 2 years (median follow-up, 22 months). They also reported colectomy-free survival of 59% at 2 years (McDermott 2013). It should be noted that 87% of patients had received infliximab previously, making this a more difficult to treat population.

**Certolizumab Pegol**

Certolizumab pegol is a pegylated, recombinant humanized antibody fragment (Fab) with label approval for the treatment of severe CD refractory to conventional therapies. The dosage for certolizumab pegol is 400 mg (two 200-mg injections at separate sites) every 4 weeks; if symptoms respond after three doses, the regimen should be continued.

**Crohn’s Disease**

The PRECISE trials evaluated the efficacy of certolizumab pegol in CD, enrolling anti-TNF naive patients as well as patients who had received infliximab. The PRECISE 1 induction and maintenance study found certolizumab pegol produced a response rate than placebo (35% vs. 27%; p=0.02); however, remission rates at weeks 6 and 26 were not significantly different (10% vs. 14%; p=0.07). Infliximab naive patients had significantly higher response (p=0.01) and remission rates (p=0.03) than placebo; however, the difference was not significant in patients who previously received infliximab (Sandborn 2007c).

In PRECISE 2, a maintenance trial, 64% of patients treated with certolizumab pegol achieved response at week 6; of these 428 patients, 48% achieved remission at week 26 versus 29% in the placebo group (p<0.001) (Schreiber 2007). In PRECISE 3, an open-label 18-month extension of PRECISE 2, certolizumab’s long-term safety, efficacy, and immunogenicity were evaluated. At week 80, 63%–66% of patients who achieved remission in PRECISE 2
were still responding; however, sustained remission rates were low (30.9% vs. 33%) (Lichtenstein 2010). In PRECISE 4, an open-label re-induction study for patients who relapsed during PRECISE 2, response was seen in 63%–65% of patients by week 4, with 55%–59% of these patients maintaining response at week 52 (Sandborn 2010a).

In a meta-analysis of more than 1000 patients (including PRECISE 2-4 as well as patients previously treated with infliximab), certolizumab proved effective for induction and maintenance of clinical response or remission in CD, improved quality of life for patients with CD, and for CD nonresponsive to infliximab. About 21% of patients receiving certolizumab achieved remission by week 4 (relative risk 1.95; 95% confidence interval 1.41–2.70; p <0.0001) versus 11% in the placebo group. For the patient with a flare on maintenance therapy, reinduction may have minimal value, although this is according to data from PRECISE 4, an open-label study with low remission rates. Disease may respond to certolizumab after infliximab fails, although remission rates for these patients are, as expected, lower than for infliximab-naive patients (Shao 2009).

Since this meta-analysis, several trials have examined the utility of certolizumab. One trial of certolizumab in 439 anti-TNF treatment naive patients with moderate to severe CD reported remission rates of 32% and 25% for the certolizumab and placebo groups, respectively; however, they did not reach significance. When patients were stratified by baseline c-reactive protein (CRP) levels, those with higher CRP were more likely to achieve remission; however, this still did not reach significance (Sandborn 2011a). The WELCOME trial enrolled patients in whom infliximab failed and found response rates of 62% and remission rates of 39.3% at week 6; at week 26, 36.6%–39% responded to therapy and 29.2%–30.4% achieved remission (Sandborn 2010b). A separate analysis of PRECISE 2 confirmed the WELCOME findings (certolizumab response rates 44.2% vs. 25.5% with placebo; p=0.018) (Hanauer 2010).

The development of fistulas can complicate treatment. A small, prospective questionnaire-based study of 50 patients determined that response rates were 54% and remission rates were 40% in complicated patients (Schoepfer 2010). These patients had prior exposure to immunosuppressants (96%), infliximab (78%), and adalimumab (50%). More than one-half had strictures or fistulas and had undergone surgery. A 50% fistula response, defined as a decrease of at least 50% in the number of draining fistulas, was seen in 8 of 11 patients treated with certolizumab. Albeit a small observational study, these data support the use of certolizumab for complicated patients with fistulizing disease.

Two secondary analyses of the PRECISE 2 trial examined health-related quality of life and work productivity. Results showed that there were significant improvements in three quality of life scales in patients treated with certolizumab compared with placebo (the Inflammatory Bowel Disease Questionnaire [p<0.001], Short-Form 36 [p<0.001], and the mental component summary responses [p=0.016]) (Feagan 2009). Additionally, there was a significant improvement in work productivity in patients treated with certolizumab (Feagan 2010). Similar results were reported in the WELCOME study (Feagan 2011).

**Golimumab**

The most recent anti-TNF agent to be approved for UC is golimumab, a fully human monoclonal antibody. Golimumab has not been studied in CD.

**Ulcerative Colitis**

The PURSUIT-SC and PURSUIT-M were major studies that led to FDA label approval of golimumab. The PURSUIT-SC (induction study) was a blended phase 2 and phase 3 safety and efficacy study that included anti-TNF naïve patients with UC who were failed by or intolerant of conventional therapies, or who were steroid dependent. Clinical response at week 6 was achieved by 52%–55% in the golimumab group versus 30% in the placebo group (p<0.0001). Patients treated with golimumab were more likely to achieve remission (18% vs. 6%), mucosal healing, and improved quality of life (Sandborn 2014a).

The PURSUIT-M (maintenance study) included patients who completed an induction study, either PURSUIT-SC or PURSUIT-IV; the latter study was terminated by the sponsor based on efficacy rather than safety concerns. In PURSUIT-M, maintenance of clinical response through week 54 was significantly higher in the golimumab-induction responders groups (47% with 50-mg dose and 49.7% with 100-mg dose) than with placebo (31.2%; p≤0.010). At weeks 30 and 54, rates of clinical remission (27.8% with 100-mg dose vs. 15.6% with placebo; p=0.004) and mucosal healing (42.4% with 100-mg dose vs. 26.6% with placebo; p=0.002) were significantly higher in the golimumab-induction responders groups than with placebo. Rates of clinical remission and mucosal healing were similar for the 100-mg and 50-mg doses.

**Etanercept**

Etanercept, an engineered dimeric Fc fusion protein, is less immunogenic than other anti-TNF agents; it has been studied in CD but does not have FDA label approval.

**Crohn’s Disease**

Two small studies compared etanercept with placebo in patients with CD. In a pilot trial, clinical response occurred in 7 out of 10 patients by week 12; however, clinical remission occurred in only 4 patients. Study patients did not appear to have prior exposure to an anti-TNF agent (D’Haens 2001). The second study, a placebo-controlled trial, found no significant increase in clinical response with etanercept versus placebo. In fact, the placebo group had higher rates of clinical response than the etanercept group (45% vs. 39%; p=0.763) (Sandborn 2001). However, the lower dose approved for rheumatoid arthritis was used in these studies. It is possible that higher doses of etanercept...
may benefit patients with CD because it appears less immunogenic than other anti-TNF agents; however, no studies have investigated this hypothesis.

**Safety**

Common ADEs include infusion or injection site reactions, upper respiratory tract infections, nasopharyngitis, and headache (see Table 3-4). Compared with infliximab, adalimumab appears to be well tolerated. Rates of ADEs with certolizumab tend to be lower than with adalimumab or infliximab. Golimumab studies also report low rates of ADEs.

Serious ADEs of the anti-TNF agents include infections and malignancies. All anti-TNF agents have a boxed warning for serious infections and malignancies, risks supported by trial data. One retrospective cohort study compared postoperative abdominal surgery complications in CD patients exposed or not exposed to anti-TNF agents. Patients treated with anti-TNF agents within 8 weeks of surgery were more likely to develop an infection than the unexposed group (36% vs. 25%; p=0.05). Multivariate analysis determined that anti-TNF exposure was an independent predictor for infections and surgical site complications (Syed 2013). Of note, more patients were treated with infliximab (69.3%) than adalimumab (19.3%) and certolizumab (11.3%).

The general warnings for all three anti-TNF agents for CD include: infections, reactivation of tuberculosis (regardless of vaccination status with Bacille Calmette-Guerin [BCG]), malignancies, hypersensitivity reactions, hepatitis B reactivation, heart failure, and hematologic and neurologic complications. Although the warnings include hepatitis B reactivation, one study showed that rates of hepatitis B and C infection in patients with IBD are similar to the general population, and no patients experienced virus reactivation during anti-TNF treatment (Papa 2013; Viganò 2012). Appropriate testing for hepatitis B and C infection should precede initiation of anti-TNF therapy regardless of prior treatment status.

Malignancies, especially lymphomas, have been reported with anti-TNF therapy and the risk is increased with concomitant azathioprine or 6-mercaptopurine therapy. In a single-center study, 2% of patients experienced malignancy (Hamazoglou 2010). Therefore, risk/benefit should be assessed before initiation, and it may be preferable to avoid therapy in patients with a history of malignancy (especially active disease).

Also, anti-TNF agents should be avoided in patients with NYHA class III or IV heart failure. The package insert cites higher mortality with infliximab 10 mg/kg dosing, and increased cardiovascular events with both the 5- and 10-mg/kg dosing.

The use of anti-TNF agents for IBD in women who are pregnant or breastfeeding presents important safety concerns. All anti-TNF agents are listed as pregnancy category B. A recent systematic review examined 462 pregnant women who received infliximab, adalimumab, or certolizumab. Anti-TNF agents cross the placenta at the end of the second trimester, and an increase in infections has been shown in infants exposed in utero. In this review, however, these agents were given in combination with immunomodulators. Data suggested that interrupting therapy in the second trimester is appropriate (Gisbert 2013).

Anti-TNF agents have been detected in breast milk, although case reports have not linked this to toxicity in breastfed infants. Of note, certolizumab may be an option in pregnancy because its Fab fragment may prevent it from crossing the placenta. Untreated, active CD in pregnancy may increase poor obstetric outcomes (Gisbert 2013). Animal studies showed lower levels of PEGylated Fab versions of hamster antimurine TNF antibody in fetal samples compared with murinized IgG1.

**Place in therapy**

**Crohn’s Disease**

Although no trials have compared anti-TNF agents, individual studies of these agents had similar patient populations, durations of therapy, and end points (clinical response and remission). Overall results support the use of anti-TNF agents, with the exception of etanercept and golimumab.

Compared with other anti-TNF agents, data with infliximab support its use in combination with immunosuppressants in patients with moderate to severe CD naive to immunosuppressants and anti-TNF agents. However, infliximab’s efficacy in patients with a history of ileocolic or ileal resection is uncertain.

Two Cochrane reviews and a meta-analysis evaluated anti-TNF agents use in CD. Infliximab and possibly certolizumab pegol were found useful for inducing remission but etanercept was not (Akobeng 2009). Infliximab, adalimumab, and certolizumab were effective at maintaining remission in patients who responded to initial therapy (Behm 2009). The meta-analysis included 27 studies of patients with CD treated with infliximab, adalimumab, and certolizumab. Only infliximab and adalimumab were effective at inducing remission of active non-fistulizing CD. Infliximab and certolizumab prevented relapse of non-fistulizing CD, although the certolizumab data was from only one trial. Infliximab was the only agent to heal fistulizing disease better than placebo (Ford 2011).

A small retrospective study (n=60) compared infliximab, adalimumab, and certolizumab in treating patients at one site (Patil 2013). More infliximab-treated patients were in remission at 1 year compared with the other agents (88% vs. 53%; p≤0.01). However, history of anti-TNF agent use was higher in the adalimumab and certolizumab groups, confounding results. After controlling for this data, there was no difference in remission rates or quality of life. The study is limited by its single-center, retrospective design and small sample size.
<table>
<thead>
<tr>
<th>Study and Design (n)</th>
<th>Patient Population</th>
<th>Intervention</th>
<th>Primary End Point</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infliximab</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Targan 1997 R, PC, DB, MC (108)</td>
<td>Moderate to severe CD refractory to conventional therapies (anti-TNF naïve)</td>
<td>Single dose of 5, 10, or 20 mg/kg IV infliximab or placebo</td>
<td>Clinical response at week 4</td>
<td>81% of infliximab treated patients vs. 17% of placebo treated patients achieved primary end point</td>
</tr>
<tr>
<td>ACCENT 1 (Hanauer 2002) R, PC, DB, MC (573)</td>
<td>Moderate to severe CD refractory to conventional therapies (anti-TNF naïve)</td>
<td>5 mg/kg IV infliximab at week 0, followed by (1) repeat placebo infusions, (2) repeat infliximab infusions at weeks 2 and 6 then every 8 weeks, or (3) repeat infliximab infusions at weeks 2 and 6, followed by 10 mg/kg infusions every 8 weeks</td>
<td>Clinical response at week 2 and remission at week 30</td>
<td>60% of patients responded with single infusion 39%–45% of infliximab treated patients achieved remission by week 30 (vs. 21% with placebo; p≤0.03)</td>
</tr>
<tr>
<td>ACCENT 2 (Sands 2004) R, PC, DB, MC (282)</td>
<td>Patients with single or multiple draining fistulas for at least 3 months (anti-TNF naïve)</td>
<td>5 mg/kg IV infusions at weeks 0, 2, and 6 followed by 5 mg/kg infusions every 8 weeks or placebo</td>
<td>Fistula response (defined as at least 50% closure)</td>
<td>72.2% of fistulas stopped draining among those who responded; duration of fistula closure was 46 weeks (vs. 33 weeks with placebo)</td>
</tr>
<tr>
<td>SONIC (Colombel 2010) R, PC, DB, MC (508)</td>
<td>Moderate to severe CD (anti-TNF and immunosuppressant naïve)</td>
<td>Infliximab monotherapy 5 mg/kg IV infusions at weeks 0, 2, 6 followed by every 8 weeks infusions, azathioprine monotherapy 2.5 mg/kg daily, or combination infliximab and azathioprine</td>
<td>Steroid-free remission at week 26</td>
<td>Combination therapy more likely to reach end point (56.8%) than infliximab monotherapy (44.4%; p=0.02) or azathioprine monotherapy (30%; p&lt;0.001)</td>
</tr>
<tr>
<td><strong>Adalimumab</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLASSIC 1 (Hanauer 2006) R, PC, DB, MC Phase 3 (299)</td>
<td>Moderate to severe CD (anti-TNF naïve)</td>
<td>Adalimumab induction at week 0 and maintenance dose at week 2 of 40 mg/20 mg, 80 mg/40 mg, and 160 mg/80 mg SC, or placebo</td>
<td>Remission at week 4</td>
<td>Adalimumab 40 mg/20 mg, 80 mg/40 mg, and 160 mg/80 mg had increase in remission rates at 4 weeks (18% [p=0.36], 24% [p=0.06], and 36% [p=0.001], respectively) vs. placebo (12%)</td>
</tr>
<tr>
<td>CHARM (Colombel 2007) R, PC, DB, MC Phase 3 (854)</td>
<td>Moderate to severe CD that responded to adalimumab induction</td>
<td>80 mg adalimumab SC at week 0 and 40 mg at week 2, followed by (1) adalimumab 40 mg weekly, (2) every other week, or (3) placebo</td>
<td>Remission at weeks 26 and 56</td>
<td>Adalimumab-treated patients were more likely to achieve remission regardless of dose compared with placebo (at week 26: 40%–47% vs. 17%; p&lt;0.001 and at week 56: 36%–41% vs. 12%; p&lt;0.001)</td>
</tr>
<tr>
<td>GAIN (Sandborn 2007a) R, PC, DB, MC (301)</td>
<td>Moderate to severe CD in patients failed by or intolerant of infliximab</td>
<td>Adalimumab 160 mg at week 0 and 80 mg at week 2, or placebo</td>
<td>Remission at week 4</td>
<td>21% of adalimumab-treated patients achieved remission vs. 7% with placebo (p&lt;0.001)</td>
</tr>
</tbody>
</table>
Table 3-5. Pivotal Studies in Crohn’s Disease (continued)

<table>
<thead>
<tr>
<th>Study and Design (n)</th>
<th>Patient Population</th>
<th>Intervention</th>
<th>Primary End Point</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLASSIC 2 (Sandborn 2007b) R, PC, MC Open-label (276)</td>
<td>Enrolled patients from CLASSIC I</td>
<td>40 mg adalimumab at weeks 0 and 2, followed by (1) 40 mg weekly, (2) every other week, or (3) placebo; also an open-label arm</td>
<td>Remission at week 56</td>
<td>Patients treated with adalimumab were more likely to achieve remission (79%–83% vs. 44% with placebo; p&lt;0.05)</td>
</tr>
<tr>
<td>SWITCH (van Assche 2012) R, SC Open-label (73)</td>
<td>Patients responding to infliximab for at least 6 months</td>
<td>Continuation of infliximab or switch to adalimumab 80 mg at week 0, followed by 40 mg every other week</td>
<td>Impact of elective switching (dose intensification or early treatment termination)</td>
<td>Dose optimization needed in 47% vs. 6% of adalimumab- and infliximab-treated patients, respectively (p=0.006) 10 adalimumab patients vs. 1 infliximab patient interrupted therapy (p=0.003), largely because of a loss of response</td>
</tr>
<tr>
<td>Certolizumab pegol</td>
<td>Moderate to severe CD (included prior anti-TNF treated patients)</td>
<td>Certolizumab 400 mg at weeks 0, 2, and 4, then every 4 weeks, or placebo</td>
<td>Response at week 6 and remission at weeks 6 and 26</td>
<td>Certolizumab-treated patients more likely to have induction response (35% vs. 27%; p=0.02) Remission rates not significantly different</td>
</tr>
<tr>
<td>PRECISE 2 (Schreiber 2007) R, PC, DB, MC (668)</td>
<td>Moderate to severe CD (included prior anti-TNF treated patients)</td>
<td>Certolizumab 400 mg or placebo every 4 weeks in patients who responded to induction (CDAI score reduction of at least 100 from baseline)</td>
<td>Response at week 26</td>
<td>48% of certolizumab-treated patients achieved response (vs. 29% with placebo; p&lt;0.001)</td>
</tr>
<tr>
<td>PRECISE 3 (Lichtenstein 2010) MC Open-label (241)</td>
<td>Patients who responded to induction at week 6 in PRECISE 2</td>
<td>Extension study of PRECISE 2</td>
<td>Long-term safety and efficacy (response and remission at week 80)</td>
<td>63%–66% of patients maintained response at week 80, although remission rates at week 80 were 30.9%–33%</td>
</tr>
<tr>
<td>WELCOME (Sandborn 2010b) R, DB, MC, active control Open-label Phase 3b (539)</td>
<td>Patients who failed infliximab (defined as loss of response or hypersensitivity to infliximab)</td>
<td>Certolizumab induction 400 mg at weeks 0, 2, and 4, then certolizumab 400 mg every 2 or 4 weeks</td>
<td>Response at week 6</td>
<td>Response rate of 62%, remission rate of 39.3% at week 6 36.6%–39% response rate and 29.2%–30.4% remission rate at week 24</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>Moderate to severe CD (included prior anti-TNF treated patients)</td>
<td>Natalizumab induction 300 mg or placebo at weeks 0, 4, 8</td>
<td>Response at week 10</td>
<td>56% vs. 49% of natalizumab vs. placebo responded by week 10 (p=0.05)</td>
</tr>
</tbody>
</table>
U.S. guidelines recommend reserving anti-TNF agents for induction and maintenance of moderate to severe CD refractory to conventional therapy (Lichtenstein 2009). However, European guidelines recommend drug therapy depending on disease site, disease activity, and disease course; they also endorse anti-TNF agents in patients with moderately active localized ileocecal disease (refractory or steroid dependent), severe and localized ileocecal disease (after a relapse on steroids), relapsed colonic disease, relapsed extensive small bowel disease, and severe or refractory esophageal or gastroduodenal disease (Dignass 2010).

Neither set of guidelines delineate preferred agents. Adalimumab or certolizumab may be preferred over infliximab because subcutaneous administration is more convenient and less costly than infusion administration. Adalimumab has more robust efficacy data than certolizumab (e.g., prolonging time to colectomy) and a similar ADE profile. Infliximab may be reserved for fistulizing disease. Data support the use of certolizumab or infliximab after failure of the other, although these agents are more effective in patients who are naïve to these biologic agents. When anti-TNF therapy fails, surgery should be considered, if appropriate. There is no genetic marker that consistently predicts patient response to anti-TNF therapy (Roberts 2012). The TAXIT study (maintenance phase) showed that trough-level based dosing of infliximab maintained drug levels better than clinical-based dosing, although this did not improve clinical remission rates (Vande Casteele 2013).

**Ulcerative Colitis**

Compared with CD, the use of biologic agents in UC is less established. Studies included patients with moderate to severe disease (regardless of disease location) and patients who failed standard therapies. Most studies were placebo-controlled; however, there were no head-to-head trials of anti-TNF agents. Authors of a recent review, which did not include golimumab, found anti-TNF agents...
to have efficacy in mucosal healing, achieving corticosteroid-free remission, and prolonging time to colectomy. They suggest earlier use of these agents because UC is not a “benign” disease, and also recommend studies of combination therapy and the use of anti-TNF agents earlier in disease progression (Danese 2013).

The European guidelines recommend infliximab over adalimumab for its increase in steroid-free remission rate (Dignass 2012). The American College of Gastroenterology guidelines support the use of infliximab as induction and maintenance therapy for patients with refractory disease; however, these guidelines were established before adalimumab and golimumab were approved (Kornbluth 2010). The guidelines are supported by a Cochrane Review that found infliximab effective in inducing clinical remission in moderate to severe UC unimproved by conventional therapies (Lawson 2009).

Overall, anti-TNF agents should be considered earlier rather than later in the course of disease; the risk of cancer with UC may warrant more aggressive treatment (Danese 2013). Response is seen in one-half of patients treated with golimumab or infliximab. Although no head-to-head trials exist, trial data on remission rates may favor infliximab over golimumab (28%–39% vs. 18%) (Sandborn 2013a, b).

**INTERLEUKIN ANTAGONISTS**

**Ustekinumab**

Ustekinumab is an IgG1 human monoclonal antibody approved to treat plaque psoriasis; this agent binds to IL-12 and IL-23, inflammatory cytokines implicated in CD.

A double-blind cross-over study evaluated ustekinumab in 104 patients with moderate to severe CD that showed inadequate response to conventional therapies or anti-TNF agents. One group received ustekinumab 90 mg subcutaneously at weeks 0, 1, 2, and 3, and placebo at weeks 8, 9, 10, and 11, or vice versa. A second group received open-label subcutaneous ustekinumab 90 mg at weeks 0, 1, 2, and 3, or intravenous 4.5 mg/kg ustekinumab at week 0. Clinical remission at week 8 was achieved in 49% of patients treated with ustekinumab versus 40% with placebo (p=0.34). A subgroup of patients previously treated with infliximab also achieved better response with ustekinumab than with placebo (p<0.05) (Sandborn 2008).

The CERTIFI study evaluated ustekinumab as induction and maintenance therapy in 526 patients with primary or secondary nonresponse or unacceptable adverse effects from anti-TNF agents. Patients received intravenous ustekinumab 1, 3, or 6 mg/kg or placebo at week 0; those with a response at week 6 (n=145) received subcutaneous ustekinumab 90 mg or placebo at weeks 8 and 16; those with nonresponse (n=219) received subcutaneous ustekinumab 270 mg at week 8 and 90 mg at week 16. Clinical response at week 6 was reached by 34%–40% with ustekinumab induction versus 23.5% with placebo (p=0.005 for the 6 mg/kg induction group). Response rates (69.4% vs. 42.5%, p<0.001) and remission rates (41.7 vs. 27.4%, p=0.03) were significantly higher with ustekinumab maintenance than placebo. This data show induction with intravenous ustekinumab followed by subcutaneous maintenance to be effective for patients with moderate to severe CD that failed anti-TNF agents (Sandborn 2012b).

**Secukinumab**

Secukinumab is a human monoclonal antibody that antagonizes IL-17A, which promotes intestinal inflammation. This agent is not approved for any indication but has been studied in patients with CD.

In a double-blind, randomized, placebo-controlled safety and efficacy trial, patients with moderate to severe CD (n=59) were given two 10 mg/kg infusions of secukinumab or placebo on days 1 and 22. The primary end point was mean effect on CDAI scores. Unfortunately, 31% of patients discontinued the study early because of a lack of efficacy and high rate of ADEs, and the change in CDAI scores favored placebo. This study showed that not all IL pathways have a positive effect on the treatment of CD (Hueber 2012).

**Safety and Place in Therapy**

The IL-antagonists may increase the risk of infections and malignancies, but this has not been proven in the literature. The most common ADEs for ustekinumab are nasopharyngitis, upper respiratory tract infections, headache, and fatigue. Infection and malignancy are rare (Elliott 2009). Ustekinumab use has been associated with an increased risk of major adverse cardiovascular events (Tzellos 2012). Secukinumab was not well tolerated: 74% of patients experienced an ADE, and 28% were severe. Forty-four percent of patients experienced an infection; in the placebo group, 50% experienced an ADE, 15% experienced a severe ADE, and 0% experienced an infection (Hueber 2012).

Currently, none of the three agents studied have label approval for use in CD. Two studies have ustekinumab effective for induction and maintenance therapy (remission rates 41%–49% vs. 27.4%–40% with placebo). However, further studies of long-term safety and efficacy in fistulizing disease and in post-surgical patients are warranted. Data do not support secukinumab use in CD. These agents should not be recommended for use in patients with CD.

**CLUSTER OF DIFFERENTIATION**

**Abatacept**

Abatacept has labeled indications for rheumatoid arthritis and juvenile idiopathic arthritis but not for gastrointestinal disease.
### Table 3-6. Pivotal Studies in Ulcerative Colitis

<table>
<thead>
<tr>
<th>Study and Design (n)</th>
<th>Patient Population</th>
<th>Intervention</th>
<th>Primary End Point</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infliximab</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACT 1 and 2 Extension Studies (Reinisch 2012) R, PC, DB, MC Open-label (229)</td>
<td>Moderate to severe UC (as defined by Mayo score 4 of 6-12) despite corticosteroid monotherapy or combination with an immunosuppressant</td>
<td>Infliximab infusions 5 mg/kg every 8 weeks, but investigators could increase the dose to 10 mg/kg in patients who lost response</td>
<td>Long-term efficacy and safety</td>
<td>90% had no disease or mild disease by Physician’s Global Assessment 30.6% of patients discontinued therapy (10.5% for ADEs, 4.8% for lack of efficacy, 0.4% for surgery, 14.8% for other reasons)</td>
</tr>
<tr>
<td><strong>Adalimumab</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ULTRA 1 (Reinisch 2011) R, PC, DB, MC Phase 3 (576)</td>
<td>Moderate to severe UC that failed corticosteroid or immunosuppressants (anti-TNF naïve)</td>
<td>Adalimumab high dose (160 mg week 0, 80 mg week 2, 40 mg weeks 4 and 6), low dose (80 mg week 0, 40 mg weeks 2, 4, and 6), or placebo</td>
<td>Remission at week 8</td>
<td>18.5% of high dose adalimumab (p=0.031 vs. placebo) and 10% of low dose adalimumab (p=0.833 vs. placebo) achieved remission</td>
</tr>
<tr>
<td>ULTRA 2 (Sandborn 2012a) R, PC, DB, MC Phase 3 (494)</td>
<td>Moderate to severe UC that failed corticosteroids or immunosuppressants (included anti-TNF treated patients)</td>
<td>Induction and maintenance with high-dose adalimumab from ULTRA 1 or placebo</td>
<td>Remission at weeks 8 and 52</td>
<td>Adalimumab-treated patients had higher remission at week 8 (16.5% vs 9.3%; p=0.019) and week 52 (17.3% vs. 8.5%; p=0.004) than placebo</td>
</tr>
<tr>
<td><strong>Golimumab</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PURSUIT-SC (Sandborn 2014a) R, PC, DB, MC Phase 2 and 3, blended (771)</td>
<td>Moderate to severe UC in patients failed by or intolerant of conventional therapies or steroid dependent (anti-TNF naïve)</td>
<td>Dosing groups (induction) were 200 mg and 100 mg vs. 400 mg and 200 mg 2 weeks apart, or placebo</td>
<td>Response at week 6</td>
<td>52%–55% with golimumab versus 30% with placebo (p&lt;0.0001)</td>
</tr>
<tr>
<td>PURSUIT-M (Sandborn 2014b) R, PC, DB, MC Phase 3 (464)</td>
<td>Enrolled PURSUIT-SC and PURSUIT-IV patients</td>
<td>Golimumab maintenance 50 mg or 100 mg every 4 weeks, or placebo</td>
<td>Response through week 54</td>
<td>47%–49.7% with golimumab versus 31.2% with placebo (p≤0.01)</td>
</tr>
<tr>
<td><strong>Vedolizumab</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GEMINI 1 (Feagan 2013) R, PC, DB, MC Phase 3 (374 blinded induction) (521 open label induction) (373 maintenance)</td>
<td>Patients with unsuccessful treatment for UC (included adalimumab, infliximab, or certolizumab)</td>
<td>Vedolizumab 300 mg or placebo at weeks 0 and 2; responders randomized to placebo or vedolizumab every 4 or 8 weeks</td>
<td>Induction study: response and remission at week 6 Maintenance study: remission at week 52</td>
<td>47.1% vs. 25.5% in vedolizumab and placebo groups responded at week 6 (p&lt;0.001) 41.8%–44.8% in vedolizumab group versus 15.9% in placebo group were in remission (p&lt;0.001)</td>
</tr>
</tbody>
</table>

DB = double-blind, MC = multi-center, PC = placebo-controlled, R = randomized
Patients with CD (n=451) or UC (n=490) were enrolled in a randomized, double-blind, placebo-controlled trial of abatacept as induction and maintenance therapy. Patients had moderate to severe disease with a history of inadequate or intolerable response to conventional therapies, which may or may not have included anti-TNF agents. Patients were randomized to one of four groups: intravenous abatacept 30 mg/kg, 10 mg/kg, 3 mg/kg, or placebo at weeks 0, 2, 4, and 8. Results for both disease states did not reach statistical significance for either induction or maintenance efficacy end points, and response rates did not vary by subgroup (prior treatments, disease duration, concomitant immunosuppressant use, baseline CRP) (Sandborn 2012c).

Visilizumab
Visilizumab, administered intravenously, has been studied in UC; however, it is not approved for any indication (Sandborn 2010c).

A 3-month, randomized, placebo-controlled trial evaluated the efficacy of visilizumab in 127 patients with severe, corticosteroid-refractory UC. Patients received either placebo or intravenous visilizumab at 5 mcg/kg on 2 consecutive days. Patients had to be hospitalized at the time of enrollment and refractory to corticosteroids within 1 day of randomization. The primary end point was response at day 45 using the Lichtiger score (see Table 3-3). Response rates were similar in both groups (55% with visilizumab, 47% with placebo; p=0.475) as were remission rates (8% vs. 9%). Overall, visilizumab was not effective at inducing response or remission in patients with severe, corticosteroid-refractory UC (Sandborn 2010c).

Safety and Place in Therapy
Similar to other immunomodulating agents, safety of the cluster of differentiation agents is a concern. One study reported overall infections (20%–36.4%) and serious infections (3.1%–7%) of patients with CD who were treated with abatacept, respectively (compared with 32.8%–39.1% and 2.2%–2.3%, respectively, with placebo). In patients with UC, overall infection and serious infection rates were 11.4%–60% and 0%–7.7%, respectively, with abatacept (17.9%–54.4% and 0%–3%, respectively, with placebo). Overall, ADE rates were similar among abatacept and placebo treated patients (Sandborn 2012c).

Patients treated with visilizumab were more likely to have any ADE or serious ADE, compared with placebo, but rates of infection were similar. The most common ADEs among visilizumab-treated patients were nausea, pyrexia, chills, and headache (Sandborn 2010c).

Targeting the cluster of differentiation for treating gastrointestinal diseases does not appear to be as effective as other biologic targets. Based on current data, none of these agents should be recommended for use in CD or UC.

**Janus Kinase Inhibitors**

**Tofacitinib**
Tofacitinib is approved for treatment of moderate to severe rheumatoid arthritis; it has also been studied in patients with CD and UC. Tofacitinib is primarily metabolized by CYP3A4, with renal elimination of mostly unchanged drug. A single-dose pharmacokinetic study of patients with mild, moderate, severe, and end-stage renal disease showed increases in AUC and prolongation of half-life with increasing severity of renal impairment (Krishnaswami 2013). Recommendations for dose adjustments cannot be made from these data, although they are informative relative to the pharmacokinetic properties of tofacitinib.

**Crohn’s Disease and Ulcerative Colitis**
Tofacitinib was investigated in two phase 2 trials. In a 4-week trial in patients with moderate to severe CD (n=139), there were no significant improvements with tofacitinib over placebo (Sandborn 2011b). In an 8-week trial in patients with moderate to severe UC (n=194), only the patients given tofacitinib 15 mg twice daily (the highest dose) were more likely to reach the primary end point (clinical response at 8 weeks) compared with placebo. Remission rates were not as robust, but tofacitinib 3-mg, 10-mg, and 15-mg dosing groups had significantly higher remission rates than placebo. Overall, tofacitinib was effective at inducing clinical response and maintaining remission in moderate to severe UC (Sandborn 2012d).

**Safety and Place in Therapy**
Authors of the CD study stated the rates of ADEs and serious ADEs were similar between placebo and tofacitinib, although no specific safety information was reported (Sandborn 2011b). In the UC trial, two patients in the 10-mg group had serious ADEs related to infections (both were abscesses). Infection, influenza and nasopharyngitis were the most common ADEs. The rest of the ADE profile was similar across all groups, including the placebo group (Sandborn 2012d). The most common ADEs with tofacitinib use in other indications provided are upper respiratory tract infections, headache, diarrhea, and nasopharyngitis, all occurring in more than 2% of patients. The package insert states tofacitinib should not be used in patients with hepatic impairment, lymphocyte count less than 500/mm³, absolute neutrophil count less than 1000/mm³, or hemoglobin less than 9 g/dL. A dose-dependent increase in LDL cholesterol and HDL cholesterol has been reported with tofacitinib; however, levels normalized after discontinuation of the medication.

The use of tofacitinib for treatment of UC seems promising; however, further studies are warranted and under way. Safety data should also be considered if more efficacy data becomes available. Patients should be educated on the risk of infectious complications and have their lipid panels monitored.
**Integrin Inhibitors**

**Natalizumab**

Natalizumab is approved for inducing and maintaining response and remission in patients with moderate to severe CD failed by conventional therapies and anti-TNF agents. It should not be used in combination with immunosuppressants or anti-TNF agents. If a patient has not had a response by week 12 or remains steroid dependent after 6 months, natalizumab should be discontinued.

The TOUCH restricted distribution program was implemented to help manage the risk of progressive multifocal leukoencephalopathy (PML). Symptoms of PML include clumsiness, visual or speech changes, and progressive weakness. Only pharmacies associated with infusion centers are able to dispense this medication.

**Crohn’s Disease**

Three pivotal, phase 3 trials investigated natalizumab in CD. ENACT 1 evaluated natalizumab induction therapy, and ENACT 2 evaluated maintenance therapy. Response rates to induction therapy were significantly higher in the natalizumab group compared with placebo (56% and 49%; p=0.05). Sustained response and remission to maintenance therapy was significantly higher in the natalizumab group compared with placebo (61% vs. 28% [p<0.001]; 44% vs. 26% [p=0.003]) (Sandborn 2005). The ENCORE trial evaluated natalizumab induction therapy in CD with active inflammation. Induction of response was significantly higher with natalizumab than placebo (48% vs. 32%; p<0.001) (Targan 2007).

A small retrospective study evaluated natalizumab in 69 patients with CD. Patients had complicated disease (e.g., long disease duration, prior surgery, fistulas) and 94% had prior treatment with anti-TNF agents. About one-third of patients maintained response for at least 1 year; of the rest, 37% were primary nonresponders, 13% lost response, 8% had an allergic reaction, and 14% discontinued for other reasons (Juillerat 2013).

A Cochrane review evaluated the use of natalizumab as induction therapy in patients with CD. Natalizumab 300 mg induced clinical response and remission in patients with moderate to severe CD who did not respond adequately to conventional therapies (MacDonald 2009). Certain subgroups may have greater benefit, including patients with active or chronically active disease. These data were supported by a recent trial (n=36) in which 46% of patients had a clinical response; however, all patients in this study suffered from at least one ADE (Kane 2012). The patients in these trials have typically been failed by anti-TNF therapy, making them a more difficult population to treat.

Improvement of health-related quality of life with natalizumab has been evaluated in the difficult-to-treat population. One study measured Inflammatory Bowel Disease Questionnaire (IBDQ) data from the ENACT and ENCORE trials. At week 60, patients who received natalizumab were more likely to score higher on IBDQ than those who received placebo (p<0.001) (Dudley-Brown 2009).

The benefit of natalizumab therapy should be weighed against the risks. Most studies were not adequately powered to detect more infrequent, but serious ADEs such as PML. To date, PML has only been reported in patients receiving natalizumab for multiple sclerosis. In a recent report, 20 patients with multiple sclerosis developed central nervous system herpes virus infections. This heightens awareness of other possible central nervous system opportunistic infections (Fine 2013). Other serious ADEs occurring more often with natalizumab include intestinal obstruction or stenosis (2%), hypersensitivity reactions (0.5%), abdominal adhesions (0.3%), and cholelithiasis (0.3%) (see Table 3-4).

Natalizumab should only be used to treat patients with moderate to severe CD that has failed to improve with standard therapies (including anti-TNF agents). Based on their robust efficacy data and better ADE profile, treatment with two anti-TNF agents is recommended before natalizumab (Juillerat 2013; Kane 2012). In patients with progressive disease, consideration should also be given to surgical interventions before natalizumab treatment (Juillerat 2013; Kane 2012). If patients agree to the use of this agent, they should be educated on the risk of PML and enrolled in the TOUCH prescribing program.

**Vedolizumab**

Vedolizumab recently received label approval for use in management of both CD and UC.

**Crohn’s Disease and Ulcerative Colitis**

The GEMINI I trial evaluated vedolizumab therapy in patients with unsuccessful treatment of UC. Patients who responded in the induction phase were enrolled in the maintenance phase. Clinical response rates at week 6 were significantly higher with vedolizumab than placebo (47.1% vs. 25.5%; p<0.001). At the end of the maintenance phase, 41.8% and 44.8% in the vedolizumab groups were in remission versus 15.9% in the placebo group (p<0.001 for both vedolizumab groups) (Feagan 2013).

The GEMINI II counterpart enrolled patients with CD. Primary end points were clinical remission at weeks 6 and 52 for the induction and maintenance phases, respectively. At week 6, remission rates were more than two-fold higher with vedolizumab than with placebo (14.5% vs. 6.8%; p=0.02). In the maintenance phase, patients in the every-4-week and every-8-week vedolizumab groups had significantly higher remission rates than placebo (36.4% and 39.0% vs. 21.6%; p≤0.004 for both groups) (Sandborn 2013). A steroid-sparing effect was seen in both GEMINI trials, and vedolizumab was effective in patients who were anti-TNF naive and those that had failed anti-TNF therapy. Data from a small long-term study confirmed these
results for every-8-week vedolizumab use in CD (n=19; 21% achieving remission) and in UC (n=53; 72% achieving remission) (Parikh 2013).

About 3000 patients have been treated with vedolizumab with no reported cases of PML; the most common ADEs are nasopharyngitis, headache, cough, and arthralgia (Mosli 2013; Parikh 2013). In clinical trials, ADE rates were similar between vedolizumab and placebo, with the exception of nasopharyngitis (about 12% of patients receiving vedolizumab) (Feagan 2013, Sandborn 2013). Overall, limited and less serious ADEs with the use of vedolizumab are a significant advantage over natalizumab, although cases of PML may emerge as more patients are treated. Therefore, strong consideration should be given to vedolizumab use before natalizumab for patients with moderate to severe CD failed by anti-TNF therapies. It is also an option for patients with moderate to severe UC after anti-TNF therapies have been exhausted.

**Interferon-γ Inhibitor**

Fontolizumab does not have label approval but has been studied in CD. It is administered first by intravenous infusion, then subcutaneous injections for maintenance therapy.

In early studies, fontolizumab was well-tolerated with little immunogenicity (Reinisch 2006). Single doses failed to show a significant benefit; however, multiple doses of 4 mg/kg and 10 mg/kg demonstrated significant improvement over placebo (Hommes 2006). A later phase 2 randomized, placebo-controlled trial enrolled 201 patients with moderate to severe CD; patients were randomized to 1 or 4 mg/kg of fontolizumab or placebo. Initial intravenous doses of fontolizumab were followed by up to 3 subcutaneous maintenance doses of 0.1 or 1.0 mg/kg. The primary end point was reduction in CDAI scores after one dose of drug. There was no significant difference in the primary end point between the groups. However, similar to the previous phase 2 study, there was a significant difference in CDAI score reduction in patients who received several doses of fontolizumab (p<0.034) (Reinisch 2010).

Fontolizumab was generally well-tolerated with only one infection reported (Reinisch 2010). Other ADEs reported include vomiting (1%–8.9%), abdominal pain (6.7%–13.3%), dry skin (2%–8%), rash (2%–8%), and sinusitis (2%–7%) (Hommes 2006; Reinisch 2010). Further studies are warranted to evaluate long-term safety and efficacy of fontolizumab.

**Early Clinical Trials**

Several biologic agents with poor or limited response have undergone early phase clinical trials. Briakinumab failed to show a significant difference in patients with moderate to severe CD versus placebo (Mannon 2004). In a phase I study, priliximab showed promise in reducing CDAI scores in patients with corticosteroid-refractory CD (Stronkhorst 1997). However, the manufacturer halted development, possibly because its other product, infliximab, proved to be an effective agent in IBD.

Tuvirumab showed lack of efficacy and increased ADEs in patients with chronic HBV infection (Heijtink 2001; van Nunen 2001). In a phase I study, etrolizumab was well-tolerated and was more likely to produce the secondary efficacy end points than placebo; however, no further studies are being conducted (Rutgeerts 2012b). Reslizumab was shown to decrease eosinophil counts in the esophagus in patients with eosinophilic esophagitis;
however, this was not associated with better symptom improvement or physician grading than placebo (Spergel 2012). Reslizumab was well-tolerated; ADEs were mild and included headache, cough, and nasal congestion.

Investigational agents in early clinical trials yet to be published include anrakizumab (UC), actoxoumab/bezoltuxumab (Clostridium difficile), eldelumab (CD and UC), exbivirumab/libivirumab (hepatitis B virus infection), setoxaximab (Shiga toxin-producing Escherichia coli), simtuzumab (liver fibrosis), and vatelizumab (UC).

**Conclusion**

Biologic therapies have given patients another option before surgical intervention. With the introduction of infliximab, advancements in biologic therapies have steadily increased. Agents targeting areas outside of IBD are being developed and studied in clinical trials. When recommending biologic therapies for gastrointestinal disorders, it is paramount for the practitioner to evaluate the latest study data. Many of these agents were approved after the publication of the most recent guidelines (e.g., golimumab). Despite the lack of head-to-head comparisons, important factors to consider include the available data on each agent, previous therapies (including anti-TNF agents), risk of infection and immunosuppression (vs. the benefit), type and location of disease (CD or UC), need for surgical intervention. Patient factors such as cost, drug administration, and ADEs should also be considered. Overall, the data for other gastrointestinal diseases is extremely limited, and current recommendations can only be made on the use of biologic agents in IBD.

**References**


---

**Practice Points**

The use of biologic therapies in patients with CD may be optimized with the following information:

- Golimumab has not been studied in CD and etanercept has not been shown to be effective
- Fistulizing disease may be best treated with adalimumab or infliximab
- Adalimumab may prolong time to colectomy
- Post-surgical CD patients may be best treated with adalimumab or infliximab
- Certolizumab re-induction may be considered in patients who relapse while on certolizumab maintenance; alternately, infliximab may be considered after certolizumab failure
- Natalizumab should be reserved for patients who fail at least two anti-TNF agents
- Vedolizumab may compete for its place in therapy with natalizumab

The use of biologic therapies in patients with UC may be optimized with the following information:

- The use of biologic therapy should be considered early in the course of treatment
- Adalimumab, golimumab, infliximab, and vedolizumab are the approved agents to treat UC
- Remission rates favor the use of infliximab, although patient preference should be considered when initiating biologic therapy (e.g., cost, route of administration, risk of ADEs)


SELF-ASSESSMENT QUESTIONS

Questions 42 and 43 pertain to the following case.
F.Q. is a 26-year-old woman (height 5’6”, weight 55 kg) who presents to the emergency department with severe abdominal pain, diarrhea, and fever. She reports that her overall condition is very poor and states that she had about five watery bowel movements per day over the last week. She admits using diphenoxylate/atropine to treat her diarrhea, with only mild improvement in symptoms. Her medical history is significant for Crohn’s disease (CD), (diagnosed 5 years ago and for which she received multiple courses of corticosteroids) and diet-controlled diabetes mellitus. Physical examination is benign with the exception of a perianal fistula. Vital signs are recorded as a temperature of 101.8°F, heart rate 98 beats/minute, respiratory rate of 21 breaths/minute, and blood pressure of 124/72 mm Hg. Her laboratory results include SCr 1.3 mg/dL, BUN 26 mg/dL, potassium 3.6 mEq/L, hematocrit 32%, and WBC count of 5.1 x 103 cells/mm3. Her current drugs include diphenoxylate/atropine 5 mg (two tablets) as needed for diarrhea, mercaptopurine 75 mg daily, and norethindrone acetate/ethinyl estradiol daily. F.Q. was vaccinated with Bacille Calmette-Guerin (BCG) when she was 5 years old.

42. The team decides to initiate anti-tumor necrosis factor (TNF) therapy. Which one of the following is best to obtain before initiating anti-TNF agents in F.Q.?
A. Chest radiography and tuberculin skin testing.
B. Results of thiopurine s-methyltransferase gene testing.
C. Echocardiography.
D. Malignancy status.

43. Which one of the following would be best to initiate for the induction of severe CD in F.Q.?
A. Adalimumab 160 mg by subcutaneous administration at day 1 and 80 mg day 15.
B. Infliximab 275 mg by intravenous infusion at weeks 0, 2, and 6.
C. Methylprednisolone 50 mg intravenously daily until resolution of symptoms.
D. Natalizumab 300 mg intravenously every 4 weeks.

44. A patient has been prescribed infliximab 5 mg/kg to be administered intravenously over 2 hours. Which one of the following statements is the best treatment recommendation regarding infliximab therapy?
A. Discontinue the infusion if the patient becomes febrile with chills and headache
B. Administer the next dose of infliximab 1 week after this infusion if moderate infusion-related reaction occurs.
C. Intravenous infliximab should be administered as two separate infusions.
D. Infliximab should not be combined with immunosuppressant therapy.

45. A patient with an 8-year history of CD was successfully treated with infliximab therapy (5 mg/kg every 8 weeks) for 3 years but has since lost response. Which one of the following would be the most appropriate choice for this patient?
A. Give infliximab dose 10 mg/kg one time by intravenous infusion, followed by infliximab 5 mg/kg every 8 weeks by intravenous infusion.
B. Change to certolizumab pegol 400 mg at weeks 0, 2, and 4 by subcutaneous administration.
C. Change to adalimumab 160 mg at day 1 and 80 mg at day 15 by subcutaneous administration.
D. Recommend surgical evaluation.

Questions 47 and 48 pertain to the following case.
O.N. is a 30-year-old man (height 5’11”, weight 74 kg) with ulcerative colitis (UC). He presents to the emergency department with tenesmus and rectal bleeding. He states he has been passing red liquid stool with what appears to be pus. These symptoms have been on and off for the last 2 months. He reports a 7-kg weight loss over that period. His initial workup is negative for infection. A CT scan reveals inflammation of the distal colon. Colonoscopy is performed to find ulceration. The patient currently takes no drugs. O.N.’s laboratory test results are significant only for SCr of 1.7 mg/dL and BUN of 28 mg/dL.

47. Which one of the following is the most appropriate initial treatment for O.N.?
A. Methylprednisolone 60 mg intravenously.
B. Cyclosporine 300 mg intravenously.
C. Infliximab 370 mg intravenously.
D. Infliximab 740 mg intravenously.

48. O.N. is administered infliximab, and 7 days later disease shows no response. Which one of the following is best to recommend for O.N.?
A. Colectomy.
B. Methylprednisolone 60 mg intravenously.
C. Change to golimumab 200 mg subcutaneously followed by 100 mg 2 weeks later.
D. Change to adalimumab 160 mg subcutaneously followed by 80 mg 2 weeks later.

49. In which one of the following patients would the use of golimumab therapy be most appropriate?
A. Mayo Score of 6 in a patient with ulcerative proctitis and rectal bleeding.
B. Mayo Score of 7 in a newly diagnosed patient with ulcerative colitis.
C. Mayo Score of 8 in a patient on prednisone 40 mg daily.
D. Mayo Score of 9 in a patient status-post kidney transplant 1 year ago.

50. A 35-year-old man presents to his physician with visual disturbances, mild confusion, and ataxia. Which one of the following is most likely causing this patient’s symptoms?
A. Briakinumab.
B. Natalizumab.
C. Infliximab.
D. Etanercept.

51. You receive a call from a gastroenterologist inquiring about a 33-year-old man. This patient has had CD for 8 years; last year he became corticosteroid refractory. The patient has a distant history (5 years ago) of hepatitis C virus (HCV) infection for which he was treated. He is currently positive for antibodies against HCV (anti-HCV positive). In the past, he tested negative for hepatitis B virus infection. The physician asks if this patient can be treated with an anti-TNF agent. Which one of the following best answers the physician’s question?
A. No, regardless of HCV RNA levels, there is a risk of reactivating HCV.
B. Yes, this patient can be treated because he was treated for HCV in the past.
C. More information is needed; this patient should be tested for HCV RNA.
D. Yes, this patient can be treated and should receive concomitant treatment for HCV.

52. A 47-year-old man (height 6’0”, weight 79 kg) presents to his gastroenterologist with complaints of abdominal pain and four watery stools per day with minimal relief from loperamide. His overall condition is poor. His medical history is significant for heart failure (NYHA Functional Class III), CD, and depression. Physical examination is negative except for abdominal tenderness. His current drugs include infliximab 5 mg/kg intravenously every 8 weeks, lisinopril 10 mg daily, digoxin 125 mcg daily, carvedilol 6.25 mg twice daily, spironolactone 25 mg daily, and fluoxetine 20 mg daily. He is not a candidate for surgical intervention. Which one of the following would be best to recommend for this patient?
A. Increase infliximab dose to 10 mg/kg intravenously every 8 weeks.
B. Change to certolizumab induction and maintenance therapy every 4 weeks.
C. Change to natalizumab induction and maintenance therapy every 4 weeks.
D. Change to adalimumab induction and maintenance therapy every week.

53. A 47-year-old woman has a history of breast cancer (status post mastectomy), CD (25 years; experienced treatment failure with corticosteroids, infliximab, adalimumab, and certolizumab), and uncontrolled hypertension. Today she presents to her gastroenterologist for a routine appointment. Which agent, regardless of label indication, is best to recommend for this patient?
A. Ustekinumab.
B. Tofacitinib.
C. Secukinumab.
D. Vedolizumab.

54. An adolescent boy presents to the emergency room with his parents. He is currently suffering from moderate eosinophilic esophagitis. The normal treatment protocol was started; however, a resident physician inquires about the potential use of reslizumab in this patient. Which one of the following best answers this question?
A. Reslizumab has been shown to be effective in treating eosinophilic esophagitis.
B. The serious risk of adverse drug events with reslizumab outweigh the possible benefits.
C. Reslizumab should only be used for patients with life-threatening esophagitis.
D. Reslizumab effectively lowered eosinophil counts in a clinical trial.

55. A 40-year-old man has severe CD, first diagnosed at age 22. He has been treated with adalimumab for the
last 5 years. He has corticosteroid-refractory disease and is presenting with another flare on adalimumab therapy. He has no other significant medical or surgical history. Which one of the following is best to recommend for this patient?

A. Change to azathioprine plus certolizumab.
B. Change to azathioprine plus infliximab.
C. Change to infliximab.
D. Change to natalizumab.

56. A 33-year-old woman with UC was enrolled in and continued on a trial of tofacitinib 5 mg twice daily. She has developed seizures (determined to be genetic) and needs to be started on an antiepileptic regimen. Which one of the following is best to recommend for this patient?

A. Phenytoin and increase tofacitinib to 5 mg three times a daily.
B. Levetiracetam.
C. Carbamazepine.
D. Valproic acid and decrease tofacitinib to 5 mg daily.

57. A 34-year-old man with UC (diagnosed at age 21) presents with a breakthrough flare on infliximab. The course of treatment for his UC includes corticosteroids, mesalamine, and azathioprine. He has no other significant medical history. Which one of the following would best to induce remission of this patient’s UC?

A. Natalizumab.
B. Vedolizumab.
C. Abatacept.
D. Golimumab.

58. A 25-year-old woman has moderate to severe CD and is being treated with natalizumab 300 mg intravenously every 4 weeks. Which one of the following statements best summarizes natalizumab therapy in this patient?

A. Discontinue natalizumab if she remains steroid dependent for 12 weeks.
B. Natalizumab has been studied in combination with immunosuppressant therapy.
C. Her pharmacy can dispense natalizumab if she and her prescriber enroll in the TOUCH program.
D. Natalizumab should be interrupted if her hemoglobin decreases more than 2 g/dL.

59. One month ago, a patient was prescribed infliximab 5 mg/kg maintenance therapy. Which one of the following is now most appropriate for this patient?

A. Obtain a genetic marker to assess response to therapy.
B. Adjust infliximab dosing on the basis of trough levels.
C. Monitor clinical response and adjust infliximab accordingly.
D. Obtain and monitor infliximab trough levels to assess safety of infliximab.

60. A patient with UC has been stable on 20 mg of prednisone daily and golimumab maintenance therapy. However, 2 months ago he started to require higher doses of corticosteroid to maintain response. Which one of the following is the best next step in this patient’s therapy?

A. Re-induction with golimumab.
B. Change to adalimumab.
C. Change to infliximab.
D. Recommend surgery.

61. A 31-year-old woman with severe CD becomes pregnant. Her gastroenterologist asks you for a recommendation on how to manage her disease during and after pregnancy. The patient is currently maintained on infliximab. Which one of the following is best to recommend for this patient?

A. Maintain infliximab, and interrupt therapy at the second trimester.
B. Switch to certolizumab and maintain therapy throughout.
C. Maintain the current infliximab regimen unchanged.
D. Discontinue infliximab and change to high-dose corticosteroids.
### Serum Chemistries Reference Ranges SI Units

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Reference Range</th>
<th>SI Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin (adults)</td>
<td>3.5–5.0 g/dL</td>
<td>35–50 g/L (adults)</td>
</tr>
<tr>
<td></td>
<td>3.4–4.2 g/dL (children 1–3 years)</td>
<td>34–42 g/L (children 1–3 years)</td>
</tr>
<tr>
<td>Ammonia</td>
<td>30–70 mcg/dL</td>
<td>30–70 µmol/L</td>
</tr>
<tr>
<td></td>
<td>60–180 U/L</td>
<td>60–180 µkat/L</td>
</tr>
<tr>
<td>Alanine aminotransferase (ALT)</td>
<td>0–35 IU/L</td>
<td>0–35 µkat/L</td>
</tr>
<tr>
<td>Alkaline phosphatase (ALP)</td>
<td>Varies with age:</td>
<td>Varies with age:</td>
</tr>
<tr>
<td></td>
<td>30–120 IU/L (adults)</td>
<td>0.50–2.00 µkat/L</td>
</tr>
<tr>
<td></td>
<td>150–420 IU/L (children)</td>
<td>2.51–7.01 µkat/L</td>
</tr>
<tr>
<td>Aspartate aminotransferase (AST)</td>
<td>8–42 IU/L</td>
<td>0.130–0.700 µkat/L</td>
</tr>
<tr>
<td>Bilirubin, direct</td>
<td>0.1–0.3 mg/dL</td>
<td>1.7–5.0 µmol/L</td>
</tr>
<tr>
<td>Bilirubin, total</td>
<td>0.3–1.0 mg/dL</td>
<td>5–17 µmol/L</td>
</tr>
<tr>
<td>Blood urea nitrogen (BUN)</td>
<td>8–20 mg/dL (adults)</td>
<td>2.9–7.1 mmol/L</td>
</tr>
<tr>
<td></td>
<td>Lower in children</td>
<td></td>
</tr>
<tr>
<td>Calcium, ionized</td>
<td>4.4–5.1 mg/dL</td>
<td>1–1.3 mmol/L</td>
</tr>
<tr>
<td>Calcium, total serum</td>
<td>8.5–10.8 mg/dL</td>
<td>2.1–2.7 mmol/L</td>
</tr>
<tr>
<td>Carbon dioxide (venous)</td>
<td>24–30 mEq/L</td>
<td>24–30 mmol/L</td>
</tr>
<tr>
<td>Chloride</td>
<td>96–106 mEq/L</td>
<td>96–106 mmol</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>&lt; 0.8 mg/dL</td>
<td>&lt; 0.76 mmol/L</td>
</tr>
<tr>
<td>Creatine kinase</td>
<td>25–90 IU/L (men)</td>
<td>42–1.50 µkat/L (men)</td>
</tr>
<tr>
<td></td>
<td>10–70 IU/L (women)</td>
<td>1.7–1.7 µkat/L (women)</td>
</tr>
<tr>
<td>Creatinine, serum (SCr)</td>
<td>0.7–1.5 mg/dL (adults)</td>
<td>62–133 µmol/L (adults)</td>
</tr>
<tr>
<td></td>
<td>0.2–0.7 mg/dL (children)</td>
<td>18–62 µmol/L (children)</td>
</tr>
<tr>
<td>Creatinine (clearance) (CrCl)</td>
<td>90–140 mL/minute/1.73mL²</td>
<td>1.50–2.34 mL/second/m²</td>
</tr>
<tr>
<td>Ferritin</td>
<td>22–322 ng/mL</td>
<td>49–724 pmol/L</td>
</tr>
<tr>
<td>γ-Glutamyl transpeptidase</td>
<td>0–30 IU</td>
<td>0–30 IU</td>
</tr>
<tr>
<td>Glucose, serum</td>
<td>70–110 mg/dL</td>
<td>3.9–6.2 mmol/L</td>
</tr>
<tr>
<td>Hemoglobin A1C (glycolated hemoglobin)</td>
<td>4%–6%</td>
<td>0.04–0.06</td>
</tr>
<tr>
<td>Lactate dehydrogenase (LDH)</td>
<td>100–210 IU/L</td>
<td>1.7–3.5 µkat/L</td>
</tr>
<tr>
<td>Lipase</td>
<td>&lt; 160 U/L</td>
<td>0.04–0.06</td>
</tr>
<tr>
<td>Magnesium</td>
<td>1.5–2.2 mEq/L</td>
<td>0.75–1.1 mmol/L</td>
</tr>
<tr>
<td>Osmolality, serum</td>
<td>280–295 mOsm/kg</td>
<td>280–295 mmol/kg</td>
</tr>
<tr>
<td>Phosphorus (inorganic)</td>
<td>2.6–4.5 mg/dL (adults)</td>
<td>0.84–1.45 mmol/L</td>
</tr>
<tr>
<td></td>
<td>3.8–6.5 mg/dL (children)</td>
<td>1.22–2.1 mmol/L</td>
</tr>
<tr>
<td>Potassium</td>
<td>3.5–5.0 mEq/L</td>
<td>3.5–5.0 mmol/L</td>
</tr>
<tr>
<td>Prealbumin</td>
<td>20–36 mg/dL</td>
<td>200–360 mg/L</td>
</tr>
<tr>
<td>Sodium</td>
<td>135–145 mEq/L</td>
<td>135–145 mmol/L</td>
</tr>
<tr>
<td>Uric acid, serum</td>
<td>3.4–7 mg/dL (men)</td>
<td>202–416 µmol/L (men)</td>
</tr>
<tr>
<td></td>
<td>2.4–6 mg/dL (women)</td>
<td>143–357 µmol/L (women)</td>
</tr>
</tbody>
</table>

### Hematology/Coagulation Reference Ranges SI Units

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Reference Range</th>
<th>SI Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit (men)</td>
<td>42%–50%</td>
<td>0.42–0.5 (men)</td>
</tr>
<tr>
<td></td>
<td>36%–45% (women)</td>
<td>0.36–0.45 (women)</td>
</tr>
<tr>
<td>Hemoglobin (men)</td>
<td>14–18 g/dL</td>
<td>4.2–5.5 mmol/L (men)</td>
</tr>
<tr>
<td></td>
<td>12–16 g/dL (women)</td>
<td>3.6–4.5 mmol/L (women)</td>
</tr>
<tr>
<td>International normalized ratio (INR)</td>
<td>0.9–1.1</td>
<td></td>
</tr>
<tr>
<td>Mean corpuscular hemoglobin (MCH)</td>
<td>27–33 pg/cell</td>
<td>1.66–2.09 fmol/cell</td>
</tr>
<tr>
<td>Mean corpuscular hemoglobin concentration (MCHC)</td>
<td>33–36 g/dL</td>
<td>20.3–22 mmol/L</td>
</tr>
<tr>
<td>Mean corpuscular volume (MCV)</td>
<td>80–960 fl/cell</td>
<td>80–960 fl</td>
</tr>
<tr>
<td>Partial thromboplastin time (PTT)</td>
<td>21–45 seconds</td>
<td>21–45 seconds</td>
</tr>
<tr>
<td>Platelet count</td>
<td>150,000–450,000/mm³</td>
<td>150–450 × 10⁹/L</td>
</tr>
<tr>
<td>Prothrombin time (PT)</td>
<td>10–13 seconds</td>
<td>10–13 seconds</td>
</tr>
<tr>
<td>Red blood cell (RBC) count</td>
<td>4.5–5.9 × 10⁹ cells/mm³ (men)</td>
<td>4.5–5.9 × 10⁹/L (men)</td>
</tr>
<tr>
<td></td>
<td>4.1–5.1 × 10⁹ cells/mm³ (women)</td>
<td>4.1–5.1 × 10⁹/L (women)</td>
</tr>
<tr>
<td>Reticulocyte count</td>
<td>0.5%–2.5%</td>
<td>0.005–0.025</td>
</tr>
<tr>
<td>White blood cell (WBC) count</td>
<td>4.4–11.3 × 10⁹ cells/mm³</td>
<td>4.4–11.3 × 10⁹/L</td>
</tr>
</tbody>
</table>

### Serum Lipids Reference Ranges SI Units

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Reference Range</th>
<th>SI Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol, total (TC)</td>
<td>&lt; 200 mg/dL</td>
<td>&lt; 5.18 mmol/L</td>
</tr>
<tr>
<td>High-density lipoprotein (HDL) cholesterol</td>
<td>&gt; 40 mg/dL</td>
<td>&gt; 1.04 mmol/L</td>
</tr>
<tr>
<td>Low-density lipoprotein (LDL) cholesterol</td>
<td>&lt; 130 mg/dL</td>
<td>&lt; 3.36 mmol/L</td>
</tr>
<tr>
<td>Triglycerides (TG)</td>
<td>&lt; 150 mg/dL</td>
<td>&lt; 1.26 mmol/L</td>
</tr>
</tbody>
</table>

### Blood Gases Arterial and Venous

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Arterial (mm Hg)</th>
<th>Venous (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial pressure of carbon dioxide (PCO₂)</td>
<td>35–45 mm Hg</td>
<td>42–55 mm Hg</td>
</tr>
<tr>
<td>Partial pressure of oxygen (PO₂)</td>
<td>&gt; 70 (80–100 mm Hg)</td>
<td>30–50 mm Hg</td>
</tr>
<tr>
<td>Oxygen saturation (Sao₂)</td>
<td>&gt; 90%</td>
<td>60–85%</td>
</tr>
<tr>
<td>Serum bicarbonate</td>
<td>24–30 mEq/L</td>
<td>24–30 mmol/L</td>
</tr>
</tbody>
</table>

### Urinalysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SI Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocyte esterase, nitrite, protein, blood, ketones, bilirubin, glucose</td>
<td>Negative</td>
</tr>
<tr>
<td>pH</td>
<td>4.5–8.0</td>
</tr>
<tr>
<td>Specific gravity</td>
<td>1.010–1.025</td>
</tr>
</tbody>
</table>