

CRITICAL CARE PHARMACY

PREPARATORY REVIEW AND
RECERTIFICATION COURSE

VOLUME 2

Society of
Critical Care Medicine
The International Council of Critical Care Medicine



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CRITICAL CARE PHARMACY EVOLUTION AND VALIDATION, PRACTICE STANDARDS, TRAINING, AND PROFESSIONAL DEVELOPMENT

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Learning Objectives

1. Describe key landmark events in the evolution of critical care pharmacy as a specialty.
2. Summarize key published documents and evidence validating critical care pharmacy as a specialty for validation to other health care professionals and stakeholders.
3. List the core knowledge areas for pharmacists caring for critically ill patients.
4. Identify the elements of fundamental, desirable, and optimal pharmacist practice and pharmacy service components.
5. Summarize the findings from key studies documenting the association of critical care pharmacy services with favorable health care outcomes.
6. List the criteria for credentialing and training of pharmacists providing critical care services at the desired and optimal levels as outlined in the 2011 American College of Clinical Pharmacy (ACCP) critical care “PRN Opinion Paper,” in addition to critical care training opportunities and growth.
7. Apply the standards of practice for clinical pharmacy to the critical care practice environment using a standard process of care.
8. Develop an approach to conducting a gap analysis relative to the principles and values of team-based care in a local critical care practice environment.
9. Differentiate between the conventional and nontraditional pathways of training to obtain knowledge, skills, and attitudes for critical care pharmacy practice.
10. Define the key features of a mentor-mentee (protégé) relationship and the important role of mentoring in developing and training critical care clinical pharmacists.
11. Develop an approach to lifelong professional learning to maintain competency in critical care pharmacy practice using the principles of continuing professional development.
12. Identify the many educational components or techniques that can be incorporated into a personal development plan.
13. Identify the avenues and processes for contributing to the critical care body of knowledge as a presenter, author, or peer reviewer.

Abbreviations in This Chapter

ACCM	American College of Critical Care Medicine
ACCP	American College of Clinical Pharmacy
ACLS	Advanced cardiac life support
ASHP	American Society of Health-System Pharmacists
BPS	Board of Pharmacy Specialties
CE	Continuing education
CPD	Continuing professional development
CPE	Continuing pharmacy education
ICU	Intensive care unit
PDP	Personal development plan
SCCM	Society of Critical Care Medicine

Self-Assessment Questions

Answers and explanations to these questions can be found at the end of the chapter.

1. Which is the journal that, in 1982, was the first to publish a critical care therapeutics column?
 - A. *Drug Intelligence and Clinical Pharmacy*
 - B. *Pharmacotherapy*
 - C. *Chest*
 - D. *Heart & Lung*
2. The scope of pharmacy practice within the intensive care unit (ICU) was outlined by two task forces focused on models of critical care delivery, the definition of an intensivist, and the practice of critical care medicine within three different proposed models in 2001. Which best depicts the professional organization that formed these two task forces?
 - A. Institute of Medicine
 - B. American College of Clinical Pharmacy (ACCP)
 - C. American College of Critical Care Medicine (ACCM)
 - D. Clinical Pharmacy and Pharmacology Section of the Society of Critical Care Medicine (SCCM)
3. Which best depicts the medical event that has been documented to be associated with a lower mortality in ICUs with clinical pharmacists compared with ICUs without clinical pharmacists?

- A. Corrected QT (QTc)-interval prolongation
 - B. Preventable adverse drug interactions
 - C. Drug-drug interactions
 - D. Nosocomial-acquired infections
4. Which best describes what is deemed a core knowledge base area for pharmacists caring for critically ill patients?
- A. Infectious diseases
 - B. Oncology
 - C. Transplantation
 - D. Obstetrics
5. Which most accurately reflects the journal that published a landmark study documenting a decrease in preventable adverse drug reactions after the inclusion of pharmacists on interdisciplinary medical rounds?
- A. *New England Journal of Medicine*
 - B. *Lancet*
 - C. *Journal of the American Medical Association*
 - D. *Annals of Internal Medicine*
6. There were eight American Society of Health-System Pharmacists (ASHP)-accredited critical care pharmacy residencies in 2001. Assuming linear growth, which most accurately represents the approximate yearly increase in ASHP-accredited critical residencies between 2001 and 2014?
- A. 6
 - B. 8
 - C. 10
 - D. 12
7. Which best reflects the current conventional or preferred postgraduate training pathway to clinical pharmacy practice in an ICU providing level I services?
- A. Postgraduate year 1 (PGY1) residency with focused critical care rotations
 - B. PGY1 residency followed by on-the-job mentored training
 - C. PGY1 and PGY2 critical care residency
 - D. PGY1 and critical care traineeship
8. Which element would best be considered a differentiator between the provision of an optimal level of pharmacy practice and a desirable level of practice as defined in the 2000 ACCP/SCCM position paper?
- A. Publishes research and program evaluations
 - B. Participates in experiential training of pharmacy students and residents
 - C. Participates in interdisciplinary patient care rounds
 - D. Maintains advanced cardiac life support (ACLS) certification, and participates in code responses
9. When considering the five principles of team-based health care delineated in the Institute of Medicine discussion paper, which of the other four principles is effective communication most tightly linked to?
- A. Shared goals
 - B. Clear roles
 - C. Mutual trust
 - D. Measurable processes and outcomes
10. Which statement is most accurate concerning the mentor-mentee relationship as it pertains to the training and development of critical care pharmacists?
- A. Formal mentoring relationships are restricted to residency and fellowships.
 - B. Voluntary relationships that evolve and develop through mutual interests have the greatest likelihood of success.
 - C. Mentored training programs are the only reliable pathway for the nonconventional training of critical care pharmacists.
 - D. Most successful critical care pharmacists have a single relevant mentor-mentee relationship during their training and development.
11. Which is the most accurate description of the relationship between the continuing pharmacy education (CPE) and the continuing professional development (CPD) of clinical pharmacists?
- A. CPE and CPD are two distinctly different processes for continuing development.
 - B. CPD is an individualized, self-directed, and iterative process of development that replaces traditional CPE.

- C. CPE is strictly a didactic process, whereas CPD incorporates many different learning strategies and techniques.
 - D. CPD is an individualized, self-directed process that typically incorporates relevant CPE as one of the learning strategies.
12. Which statement is most accurate relative to the recently published standards of care and standardized process of care for clinical pharmacy when considering critical care pharmacy practice?
- A. ICUs are highly individualized practice environments that cannot easily conform to broad-based, discipline-wide standards.
 - B. Critical care pharmacists have knowledge and skill sets that are specific to their practice style and environment and are not consistent with the standards.
 - C. The standards of care and standardized process of care are very consistent with critical care pharmacy practice standards and expectations.
 - D. The standard process of care, which has evolved around the “provider status” efforts, is primarily applicable to the ambulatory, primary care environment of practice.
13. Which is the best example of an audience that has not traditionally been an important focus of critical care pharmacists’ educational and teaching efforts?
- A. Patients and families
 - B. Pharmacy students
 - C. Critical care physicians
 - D. Critical care nurses
14. As part of the reflection stage of the CPD process, which would be the best example of an episodic opportunity for self-assessment?
- A. An annual 360-degree peer evaluation providing feedback that your coworker believes you do not contribute adequately on departmental initiatives
 - B. Recognition that the usual approach to training and assessing a challenging student on rotation was ineffective
 - C. A self-evaluation of the past year’s accomplishments for your direct supervisor
 - D. An annual performance evaluation with specific goals for the coming year
15. Which would be considered the most valid reason for recommending the rejection of a manuscript as a scientific reviewer?
- A. Poor syntax and word choices
 - B. A methodological flaw that results in incorrect data
 - C. A disagreement concerning the statistical analysis presented in the manuscript
 - D. Results presented in the abstract that are inconsistent with results presented in a table

I. LANDMARK EVENTS IN CRITICAL CARE MEDICINE/PHARMACY

- A. First ICU: Three-Bed Neurosurgical Unit in Baltimore, Maryland (1930s) (Ann Pharmacother 2006;40:612-8)
- B. First Pharmacists Assigned to ICUs in a Limited Number of Hospitals – Occurred in the late 1960s (Ann Pharmacother 2006;40:612-8)
- C. Establishment of several Critical Care Pharmacists ICU Practices (in or around the 1970s; clinical research conducted in a wide array of therapeutic specialty areas [e.g., pharmacokinetics, infectious diseases, nutrition support, ACLS]) (Ann Pharmacother 2006;40:612-8; Practice of Critical Care Pharmacy, Rockville, MD: Aspen Publications, 1985)
 - 1. Cardiovascular ICUs
 - 2. Pediatric/neonatal ICUs
 - 3. Medical ICUs
 - 4. Emergency medicine
 - 5. Trauma
 - 6. Surgical ICUs
 - 7. Neurosurgical ICUs
- D. Formation of SCCM with 100 Members (1970)
 - 1. Multidisciplinary model stressed by founding SCCM President Max Harry, M.D.
 - 2. Subsequent inclusion of pharmacists as permanent members of the SCCM governing council
- E. Emergence of Critical Care Specialty Journals and Publications
 - 1. *Heart & Lung* (1972)
 - 2. *Intensive Care Medicine* (1972)
 - 3. *Critical Care Medicine* (1973)
 - 4. *Critical Care Clinics* (1984)
 - 5. Critical care therapeutics column in *Drug Intelligence and Clinical Pharmacy* (1982)
 - 6. First critical care pharmacy textbook: *Critical Care Pharmacy* (1985)
- F. Formation of Critical Care Pharmacists Specialty Groups
 - 1. SCCM Clinical Pharmacy and Pharmacology Section (1989)
 - 2. ACCP Critical Care Practice and Research Network (PRN) (1992)

II. VALIDATION OF CRITICAL CARE PHARMACY AS A SPECIALTY

- A. Chapter Titled “Role of the Pharmacist in Caring for the Critically Ill Patient,” Published in *The Pharmacologic Approach to the Critically Ill Patient*, 3rd ed. Baltimore, MD: Williams & Wilkins, 1994:156-66.
- B. Publication of “Position Paper on Critical Care Pharmacy Services” (Crit Care Med 2000;28:3746-50); establishment of three levels of pharmacy services (fundamental, desirable, optimal) for the provision of pharmaceutical care in critically ill patients (see specifics that follow)

- C. SCCM Recognition of Critical Care Pharmacists as an Integral Member of the Multidisciplinary Team Together with Physicians, Nurses, and Respiratory Therapists (Crit Care Med 2001;29:2007-19)
- D. Scope of Pharmacy Practice Within ICU Outlined by Two ACCM Task Forces: Models of critical care delivery and definition of an intensivist and the practice of critical care medicine within three different proposed models (critical care pharmacy and pharmacist services deemed “essential” within level I critical care centers as endorsed by ACCM (Crit Care Med 2003;31:2677-83) (see specifics that follow)
- E. Awarding of FCCM Status by ACCM: Almost 80 pharmacists from an overall total of 1014; six MCCMs (Master Critical Care Medicine) (2016) Receipt of Several Honors and Awards by Critical Care Pharmacists Within SCCM, ACCM, and ACCP
 - 1. SCCM/ACCM: Distinguished Investigator Award, Shubin-Weil Master Clinician, Excellence in Bedside Teaching Award, Distinguished Service Award
 - 2. ACCP: Russell R. Miller Award, Paul F. Parker Medal, Clinical Practice Award, Robert M. Elenbaas Service Award, Education Award
 - 3. Creation of the Joseph F. Dasta Critical Care Pharmacy Outcomes Research Grant by the Clinical Pharmacy and Pharmacology Section of SCCM (2000)
- F. Leadership Roles in Major Multidisciplinary and Pharmacy Organizations
 - 1. SCCM: President Judith Jacobi (2010)
 - 2. ACCP: Presidents Robert Elenbaas, Barbara Zarowitz, Bradley Boucher, Curtis Haas, Judith Jacobi
- G. Prescriber Perceptions of Pharmacist-Provided Patient Care–Related Clinical Functions: Decreased efficiencies of 40%–65% in the absence of pharmacy services (Pharmacotherapy 2013;33:401-10).

III. CRITICAL CARE PHARMACY GROWTH

- A. SCCM Membership: About 15,900. Clinical pharmacist practitioner (CPP) membership: 2377 (1339 with pharmacy credentials). ACCP Critical Care PRN: About 2340 (2016).
- B. Provision of Direct Patient Care Services: 62.2% of ICUs responding to hospital survey (Ann Pharmacother 2006;40:612-8)

IV. STUDIES DOCUMENTING THE ASSOCIATION OF CRITICAL CARE PHARMACY SERVICES WITH FAVORABLE HEALTH CARE OUTCOMES

- A. Reduction in Drug Costs in ICU with the Inclusion of a Pharmacist as a Member of the Multidisciplinary Team
 - 1. Medical-surgical ICU: Annual savings of \$67,664 in 1994 dollars (Crit Care Med 1994;22:1044-8)
 - 2. Neurosurgical ICU: Reduction in pharmacy acquisition costs from \$4833 to \$3239 per patient after the addition of a pharmacist to the neurosurgery team; reduction in ICU days from 8.56 to 7.24 days (p=0.003) (Neurosurgery 2009;65:946-50; discussion 950-1)

3. Burn ICU: Annual savings of \$22,162 in 2003 dollars (J Burn Care Res 2006;310-13)
 4. Several other studies in a wide range of ICU settings (see Intensive Care Med 2003;29:691-8)
- B. Reduction in Adverse Drug Effects/Drug-Drug Interactions
1. Decrease in preventable adverse drug effects after the inclusion of a pharmacist on interdisciplinary medical ICU rounds: 66%, ($p<0.001$) (JAMA 1999;282:267-70); supported by meta-analysis of three studies (odds ratio (OR) 0.23, 95% confidence interval (0.11, 0.48) (J Crit Care 2015).
 2. Decreased incidence of QTc-interval prolongation with ICU monitoring by a pharmacist using a standard algorithm: 19% versus 39% ($p=0.006$) (Ann Pharmacother 2008;42:475-82)
 3. Reduction in drug-drug interactions by 65% ($p<0.01$) in medical ICUs with a pharmacist (J Crit Care 2011;26:104.e101-106)
- C. Improvement in Infectious Diseases Morbidity, Mortality, and Costs (Crit Care Med 2008;36:3184-9)
1. Mortality higher in ICUs without clinical pharmacists than in ICUs with clinical pharmacists: 23.6% for nosocomial-acquired infections in ICUs without clinical pharmacists, 16.2% for community-acquired infections in ICUs without clinical pharmacists, 4.8% for sepsis in ICUs without clinical pharmacists ($p\leq 0.008$)
 2. Length of stay longer for ICUs without clinical pharmacists than for ICUs with clinical pharmacists: 7.9% for nosocomial-acquired infections in ICUs without clinical pharmacists, 5.9% for community-acquired infections in ICUs without clinical pharmacists, 8.1% for sepsis in ICUs without clinical pharmacists ($p\leq 0.03$)
 3. Medicare bills increased the number of patients in ICUs without clinical pharmacists compared with ICUs with clinical pharmacists: 12% for nosocomial-acquired infections in ICUs without clinical pharmacists, 11.9% for community-acquired infections in ICUs without clinical pharmacists, 12.9% for sepsis in ICUs without clinical pharmacists ($p<0.001$)
- D. Improvement in Thromboembolic and Infarction-Related Event (TIE) Clinical and Economic Outcomes (Pharmacotherapy 2009;29:761-8)
1. Mortality increased in ICU patients with TIE without clinical pharmacy services compared with ICU patients with clinical pharmacy services: 37%, ($p<0.0001$).
 2. Bleeding complications increased by 49% ($p<0.001$), with 39% more patients receiving transfusions ($p<0.001$) in ICUs without clinical pharmacy services.
 3. Length of ICU stays and costs were significantly higher in patients with TIE in ICUs without clinical pharmacy services.
- E. Impact of ICU Protocols on Patient Outcomes
1. Significant improvement in sedation and analgesia monitoring targets with the use of protocol versus empiric therapy ($p\leq 0.01$); no difference in length of ICU stay (Pharmacotherapy 2000;20:662-72)
 2. Pharmacist-enforced ICU sedation protocol reduced mechanical ventilator duration as well as ICU, hospital length of stay ($p<0.001$) (Crit Care Med 2008;36:427-33)
 3. Improvement Mortality with Inclusion of Clinical Pharmacist Following Multicomponent Intervention in Tertiary Care Medical ICU (also included increase in ICU beds, larger rooms, 24-hour critical care specialist coverage, decrease in respiratory therapist/patient ratio) (Crit Care Med 2011;39:284-93)
 4. ICU Mortality decrease from 18.4% to 14.9% ($p=0.006$), hospital mortality decrease 25.8% to 21.7% ($p=0.005$)
 5. Increase in median ICU length of stay; no difference in hospital length of stay
 6. Increase in median 28-day ventilator-free days in mechanically ventilated patients
 7. Mean decrease in daily dosing of fentanyl and lorazepam

V. PRACTICE STANDARDS FOR CRITICAL CARE PHARMACY

- A. Standards of Practice for Clinical Pharmacists (Pharmacotherapy 2014;34:794-7): The Standards of Practice for Clinical Pharmacists were recently published by ACCP, incorporating a standardized process of care endorsed by all major pharmacy organizations. This document defines expectations of clinical pharmacists delivering comprehensive medication management in team-based, collaborative practice settings, including the ICU.
1. Qualifications
 - a. Licensed pharmacists
 - b. Advanced education, training, and experience
 - i. Advanced, accredited residency in critical care pharmacy (PGY2);
 - ii. Fellowship in critical care research; or
 - iii. Equivalent, relevant clinical experience
 - c. Clinical and personal competencies to practice in a team-based collaborative environment
 - d. Board certification
 2. Process of care
 - a. Assess the patient.
 - b. Evaluate medication therapy.
 - c. Develop and implement therapeutic plan.
 - d. Provide follow-up evaluation and monitoring.
 - e. Document clinical activities.
 - i. Medication history
 - ii. Problem list and assessment
 - iii. Plan of care and follow-up
 3. Collaborative, team-based care and privileging
 4. Professional development and maintenance of competence
 - a. Board certification and recertification
 - b. CPE
 - c. Maintenance of licensure
 - d. Participation in formal and informal development activities
 5. Professionalism and ethics – Demonstrate the traits of:
 - a. Responsibility
 - b. Commitment to excellence
 - c. Respect for others
 - d. Honesty and integrity
 - e. Care and compassion for others
 - f. High ethical standards
 - g. Legal and regulatory compliance
 6. Research and scholarship
 7. Other
 - a. Education and training
 - b. Mentorship
 - c. Management and leadership
 - d. Policy and service development and implementation
 - e. Consultation

- B. Scope of Critical Care Pharmacy Services (Crit Care Med 2000;28:3746-50; Task Force on Critical Care Pharmacy Services [a joint effort of SCCM and ACCP])
1. The task force defined parameters within six domains:
 - a. Clinical activities
 - b. Drug distribution
 - c. Education
 - d. Research
 - e. Documentation
 - f. Administration
 2. Recommendations were further organized into two areas:
 - a. Pharmacist activities: This referred to the activities of clinical pharmacists with training and/or experience in providing for the specific pharmaceutical care needs of complex ICU patients in a team-based environment, with the pharmacist taking shared responsibility and accountability for patient outcomes.
 - b. Pharmacy services: This referred to the departmental and institutional infrastructure to support and facilitate the pharmacist, including systems, operations, and personnel to provide safe and effective pharmacy care in the ICU.
 3. Gradations of pharmacy practice (see Table 1 for details)
 - a. Fundamental: Practice and operation recommendations that are considered vital to the safe provision of care to ICU patients
 - b. Desirable: Offers clinical practice and service expectations that are more specialized and specific to the ICU beyond the fundamental recommendations
 - c. Optimal: Represents an integrated, highly specialized, and dedicated model of pharmacy practice that is focused on optimizing outcomes through incorporating education, research, and advanced pharmacy practice into the ICU
 4. Commentary/updates
 - a. Many of the pharmacy service expectations related to technology are increasingly outdated because meaningful use requirements and other incentives for the modernization of technology are introducing integrated or interoperable information systems in most institutions. Optimal characteristics are becoming fundamental.
 - b. Alternatives to traditional unit-of-use distribution systems using decentralized, automated dispensing are reasonable today but are not included in these guidelines. In addition, the need to maintain dispensing ICU pharmacy satellites may be negated by the use of technology.
 - c. There is no mention of important “sharp-end” (at the point of drug administration) patient safety technologies like bar code medication administration and smart pumps with medication libraries or profiles. These should be considered at least desirable now.
 - d. Several of the fundamental recommendations are not practical or likely for small institutions with level III ICUs (see concerning levels of ICU care later in the chapter). For example, it is unlikely that having dedicated ICU pharmacists with limited commitment outside the ICU will be possible.

- C. Critical Care Pharmacist as Educator: The critical care pharmacist has several educational missions and obligations (Pharmacotherapy 2011;31:135e-175e; Ann Pharmacother 2006;40:612-8; Pharmacotherapy 2002;22:1484-8; Crit Care Med 2000;28:3746-50), and teaching methods and techniques vary depending on intended audience and content. The clinical pharmacist must develop comfort and expertise with a wide range of teaching styles and techniques to be successful as an educator in the ICU setting.
1. Pharmacy students and residents: Content has to be at a level appropriate to learners who may or may not have a primary interest in critical care. Active learning strategies must be incorporated with didactic approaches that are more traditional. For this audience, the clinical pharmacist has primary responsibility for assessment/grading.
 - a. Clinical practice training
 - i. Role modeling (I do, you watch)
 - ii. Coaching (I do, you help ... then ... you do, I help)
 - iii. Mentoring (You do, I watch)
 - b. Case-based teaching (point-of-care teaching)
 - c. Hands-on demonstrations of equipment, technology, and devices used in the ICU
 - d. Clinical conferences/topic discussions
 - e. Assigned readings
 - f. Journal club
 - g. Quality improvement projects
 - h. Writing assignments
 - i. Case reports
 - ii. Guideline/protocol development
 - iii. Pharmacy and therapeutics (P&T) monographs
 2. Critical care team: More heavily focused on the specifics of critical care therapeutics. Content and sophistication will vary depending on audience (e.g., physicians vs. nurses). Audience is assumed to have a primary interest in critical care.
 - a. Case-based, point-of-care teaching (bedside rounds)
 - b. Didactic teaching
 - i. Teaching rounds/conferences
 - ii. In-service education
 - iii. Grand rounds
 - iv. Basic science lectures
 - c. Critical care-specific journal club
 - d. Collaboration on guidelines/protocols
 - e. Quality improvement projects
 3. Pharmacist colleagues: May not have a primary focus or interest in critical care. Content may be focused on specific pharmacotherapeutic issues (e.g., pharmacokinetic principles in the critically ill) that often arise during cross-coverage. May include pharmacists taking a nonconventional path to critical care practice.
 - a. Didactic lectures (e.g., clinical conferences, topic-specific lectures)
 - b. Hands-on demonstration of equipment, technology, and devices used in the ICU
 - c. Case-based, point-of-care teaching
 - d. Journal club
 - e. Competency-based programs – Lead to credentialing according to demonstrated skills

4. Other trainees: Often includes a mix of backgrounds and interests (e.g., critical care fellows, anesthesia residents, medicine residents, emergency department (ED) residents, fourth-year medical students, nursing students, physician assistant (PA) students). Content has to be appropriate for the predominant audience and baseline understanding of the topic.
 - a. Didactic lectures
 - i. Teaching rounds
 - ii. Clinical conferences
 - b. Point-of-care teaching – Bedside rounds
 5. Patients and families: Education of patients and family members has not been a traditional realm of clinical pharmacist involvement in the ICU because of an assumption that patients were not awake and alert enough and that patients were almost never discharged from the ICU. However, with an increasing emphasis on patient and family satisfaction and a greater involvement of the patient and family in decision-making, the need to educate around pharmacotherapy in the ICU has increased.
 - a. Techniques
 - i. Simple language, basic content
 - ii. Teach-back technique to assess understanding
 - iii. Frequent reinforcement
 - iv. Motivational interviewing techniques
 - v. Open-ended questions to understand what is important to the patient and family
 - b. Content
 - i. Medications being initiated in the ICU
 - ii. Why the medication is being used – Have goals different from home medications
 - iii. What to expect – Effects, adverse effects, changes in patient interaction, etc.
 - iv. Expected duration of new medications
 - v. What factors are monitored to see whether medications are helping or hurting
- D. Critical Care Services (Crit Care Med 2003;31:2677-83): ACCM recommended critical care services and personnel according to the level of care being provided. ICUs were defined as levels I, II, and III.
1. Levels of ICU services
 - a. Level I
 - i. Comprehensive critical care for a wide variety of patient populations with a high level of specialization
 - ii. Requires broad range of comprehensive support, including pharmacy services, respiratory therapy, clinical nutrition, pastoral care, and social services
 - iii. Often fulfills an academic mission
 - b. Level II
 - i. Comprehensive critical care but may not provide care for certain patient populations
 - ii. Must have transfer protocols in place for patients with special needs
 - iii. Comprehensive support services must be available.
 - iv. May or may not have an academic mission
 - c. Level III
 - i. Provides stabilization, but has limited ability to provide comprehensive critical care
 - ii. Must have transfer protocols in place for patients requiring level I and II critical care services
 - iii. Support services are often limited in scope.
 2. Critical care pharmacy services (level I and II ICUs)
 - a. Reiterates pharmacist and pharmacy services defined in 2000 guideline
 - b. Emphasizes the importance of clinical pharmacists as required members of the patient care team

- c. Qualifications and competence of the critical care pharmacist in ICU therapeutics are defined as essential. Acknowledges several pathways, including advanced degrees, residency, fellowship, and other specialized practice experiences.
 - d. ICUs with an academic mission should provide protected time for pharmacist participation in scholarly activities and appropriate knowledge and skills to provide education to critical care nurses, physician trainees, and physicians.
 - e. Nonacademic centers should provide time for maintenance of competence and maintain current certification.
- E. Principles and Values of Team-Based Health Care
 1. SCCM and ACCP have long promoted the team-based care model for critical care as a standard, including clinical pharmacists as essential staff.
 2. A recent Institute of Medicine discussion paper delineated the core principles and values of highly functioning interprofessional health care teams (see www.iom.edu/Global/Perspectives/2012/TeamBasedCare.aspx).
 - a. Definition of team-based care: *Team-based health care is the provision of health services to individuals, families, and/or their communities by at least two health providers who work collaboratively with patients and their caregivers—to the extent preferred by each patient—to accomplish shared goals within and across settings to achieve coordinated, high-quality care.*
 - b. Five personal values of effective members of high-functioning teams:
 - i. Honesty: Includes effective, transparent communication. Essential to building mutual trust.
 - ii. Discipline: Each team member carries out roles and responsibilities in a highly disciplined approach, even when inconvenient or difficult.
 - iii. Creativity: Maintains excitement around addressing new and difficult challenges. Sees opportunity in both successes and failures.
 - iv. Humility: Equal respect of all members, regardless of level of training or role – Not tied to traditional hierarchical thinking in health care. Recognizes that all members of the team are susceptible to mistakes.
 - v. Curiosity: Dedicated to reflection and continuous improvement
 - c. Five principles of team-based health care
 - i. Shared goals: Clearly articulated, understood, and supported goals are established by the team that are consistent with the patient and family wishes. The patient and family are actively involved in establishing the goals of care as members of the team.
 - ii. Clear roles: Each team member's functions, responsibilities, and accountabilities are clearly established and understood by the team. Efficiency and logical division of labor are achieved. Although autonomy is important, flexibility of roles and collaboration exist as needed.
 - iii. Mutual trust: Establishing and maintaining trust, as well as openness to address questions about or breaches of trust, are essential. Mutual trust permits individual team members to function to their highest potential and rely on other team members to follow through on their commitments.
 - iv. Effective communication: Tightly linked to mutual trust. The team has consistent channels for candid and complete communication by all team members and in all situations.
 - v. Measurable processes and outcomes: The team develops and implements accurate and timely measures of successes and failures and uses the results to track and improve performance. Measures fall into two categories: Process/outcome measures and measures of team function. This principle is typically the most challenging for a team to implement and sustain effectively.

3. Critical care teams – Gap analysis: When considering the core principles of team-based care, critical care team members should evaluate their team structure and performance against these five principles. Effective teams are much more than patient care rounds by a mix of health care professionals. Common questions to consider when evaluating potential gaps should include:
- a. Shared goals
 - i. Are the patient and family goals for critical care routinely incorporated into the care plan?
 - ii. Are the patient and family viewed as active members of the team during the establishment of goals?
 - iii. Are there clearly articulated and understood goals that are agreed on by all members of the team during the provision of care to all ICU patients and the work of the team in the care of that patient?
 - iv. Is progress toward the goals routinely reevaluated in light of the changing course and evolving perspective of the patient and family? Are goals adjusted or refined throughout the dynamic course of the critical care admission as needed?
 - v. Are there adequate organizational resources and commitments to permit effective establishment of shared goals in the treatment of ICU patients?
 - b. Clear roles
 - i. Are each team member's functions, responsibilities, and accountabilities clearly defined? Can each team member articulate and understand the role of the other team members?
 - ii. Are the roles and responsibilities of each team member focused on the shared goals of the team and patient?
 - iii. Is there clear respect for the contributions of each team member from a nonhierarchical, interdependent perspective?
 - iv. Is each team member introduced (and reintroduced) to the patient and family, including a lay description of each member's role and responsibility?
 - v. Does each team member go about his or her responsibilities with a reasonable degree of autonomy?
 - vi. Is there a clear team leader? Does the leadership role vary according to individual circumstances, problems, or environment?
 - vii. Does the team have a reasonable balance between autonomous functions and collaboration?
 - viii. Are there adequate organizational resources and commitments for professional development, team education, facilitation of communication, and restructuring of care processes to support the effective division of labor?
 - c. Mutual trust
 - i. Does an environment of mutual trust and support exist among the ICU team? Can breaches of trust be openly discussed and addressed between team members without a detrimental impact on professional or personal relationships?
 - ii. Does the hiring process include a focus on the personal and professional values that support an environment of mutual trust? Do members of the ICU team participate in the hiring process across traditional departmental siloes?
 - iii. Is the team effective at establishing and maintaining mutual trust with patients and families? Are effective communication skills used to explain the process of establishing goals, sharing information on progress, and incorporating effective negotiation and conflict resolution skills?
 - iv. Does the team regularly participate in non-patient care activities (e.g., social interaction) that allow team members to develop greater trust and know each other at many levels?
 - v. Is there adequate organizational support of the elements necessary to establish mutual trust among teams?
 - d. Effective communication
 - i. Has the team established a high priority for open, direct, clear, consistent, professional communication between team members?

- ii. Does communication take advantage of all potential modes and technologies of communication for efficiency and convenience?
- iii. Do members of the team use effective listening skills, recognizing that deep listening to the input of all team members, including patients and families, is an essential component of effective communication?
- iv. Are signs of tension and unspoken conflict in the communication process regularly recognized and addressed to improve team communication skills and effectiveness?
- v. Does effective communication occur across the team regardless of traditional hierarchical structures in health care?
- vi. Are the organizational elements for effective communication available to the team?
- e. Measurable processes and outcomes
 - i. Has the team identified and implemented reliable, timely, and ongoing measures of team performance?
 - ii. Are these measures focused on both process/outcomes of care provision and team function or effectiveness?
 - iii. Are measures of patient and family satisfaction included in the assessment process?
 - iv. Are measures of team member satisfaction included in the team assessment?
 - v. Does the team regularly report its measures of success and failure, both internally to the team and to others in the organization?
 - vi. Are performance data regularly used for process improvement with respect to both patient care and team function?
 - vii. Does the team use any standardized tools to assess team function and quality?
 - viii. Are organizational resources and commitment adequate to permit teams to adequately measure quality of patient care and team function?

F. Other Standards

- 1. The Joint Commission
 - a. Medication management chapter
 - i. High-alert, hazardous medication standards
 - ii. Look-alike/sound-alike medications
 - iii. Monitoring of medication response
 - iv. Adverse drug event detection, evaluation, and reporting
 - b. National Patient Safety Goals
 - i. Two-factor patient identification
 - ii. Medication reconciliation
 - iii. Safe medication use and labeling
 - iv. Anticoagulation management and education
- 2. Centers for Medicare & Medicaid Services (CMS) conditions for participation (42 CFR 482)
 - a. Quality assurance and performance improvement programs (§482.21)
 - i. Medical errors
 - ii. Adverse events
 - b. Preparation and administration of medications (§482.23)
 - c. Medical records requirements (§482.24)
 - d. Pharmaceutical services (§482.25)
 - i. Policies and procedures to minimize drug errors
 - ii. Adverse drug reaction and medication error detection and reporting
 - iii. Drug information standards

VI. TRAINING OF CRITICAL CARE PHARMACISTS

A. Positions and Policy

1. ACCP position

- a. ACCP clarified its position concerning qualifications of clinical pharmacists providing direct patient care in a 2013 Board of Regents commentary (Pharmacotherapy 2013;33:888-91): Clinical pharmacists providing direct patient care “should possess the education, training, and experience necessary to function effectively, efficiently, and responsibly in this role. Therefore, ACCP believes that clinical pharmacists engaged in direct patient care should be board certified (or board eligible if a Board of Pharmacy Specialties [BPS] certification does not exist in their area of practice) and have established a valid collaborative drug therapy management (CDTM) agreement or have been formally granted clinical privileges by the medical staff or credentialing system within the health care environment in which they practice.”
- b. Board certification
 - i. ACCP considers BPS certification the cornerstone of eligibility for direct patient care.
 - ii. Eligibility
 - (a) Graduate of an accredited school of pharmacy
 - (b) Pharmacy licensure
 - (c) Postgraduate residency training in area of specialization or 3–4 years of relevant experience with at least 50% of time practicing in the specialty area
 - iii. ACCP has expressed that postgraduate residency training is the preferred training pathway for clinical pharmacists providing direct patient care in previous position statements and a white paper.

2. ASHP policy

- a. Policy 0701: “By the year 2020, the completion of an ASHP-accredited postgraduate-year-one residency should be a requirement for all new college of pharmacy graduates who will be providing direct patient care.”
- b. ASHP has no policy directly related to the provision of direct patient care in a specialty practice area.

B. Potential Workforce Demands

1. Hospital data

- a. 5723 hospitals in the United States – 920,829 staffed beds (2012 American Hospital Association survey data; www.aha.org/research/rc/stat-studies/fast-facts.shtml)
- b. Around 71,400 adult and pediatric ICU beds (2007 survey data) – Excludes 20,500 neonatal ICU beds (www.sccm.org/Communications/Pages/CriticalCareStats.aspx)

2. Critical care pharmacists

- a. No accurate database to indicate the number of pharmacists spending 50% or more of time in critical care
- b. Direct patient care by pharmacist provided in 62.2% of ICUs in the United States in 2006, essentially unchanged from 20 years earlier. This represents primarily fundamental-level services (Ann Pharmacother 2006;40:612-8).
- c. A review of ACCP, SCCM, ASHP, and American Pharmacists Association (APhA) membership records identified 2928 individual pharmacists indicating specialization in critical care at the time of the petition for recognition of critical care as a specialty (https://www.accp.com/docs/positions/petitions/Final_CRITICAL_CARE_PETITION_For_BPS_Post.pdf).
- d. A survey sent to those 2928 pharmacists yielded 504 responses (https://www.accp.com/docs/positions/petitions/Final_CRITICAL_CARE_PETITION_For_BPS_Post.pdf).

- i. Out of the responses, 476 reported that they practiced in critical care (94%).
 - ii. Of those 476, 91% responded that their practice met the definition of critical care pharmacy as a specialty.
 - iii. Among the respondents, 74% indicated they spent at least 50% of their time practicing in the ICU.
 - iv. More than 80% of respondents completed residency or fellowship training in critical care.
 - e. A survey of employers of ICU pharmacists yielded 204 responses (https://www.accp.com/docs/positions/petitions/Final_CRITICAL_CARE_PETITION_For_BPS_Post.pdf).
 - i. Collectively employed 1034 full-time equivalent (FTE) critical care pharmacists
 - ii. Recruited 256 critical care pharmacists during the previous 3 years
 - iii. Estimated a need to hire 234–243 critical care pharmacists in the next 3 years
 - iv. Of the respondents, 99.5% estimated the demand for critical care pharmacists to grow or remain stable at their site during the next 5 years.
 - f. Critical Care Societies Collaborative (CCSC) – <http://ccsconline.org/workforce>
 - i. Collaborative effort of several stakeholder organizations in critical care to define the workforce shortage in critical care and advocate for federal action to address the problem
 - ii. Most of this work has focused on intensivist and ICU nurse shortages, but there is also recognition of shortages of other professionals, including critical care pharmacists.
 - g. Current and objective quantification of critical care pharmacist shortage or demand is unavailable.
- C. Training Recommendations and Capacity
- 1. Minimum requirements for all levels of ICU service (I–III)
 - a. Graduate of Accreditation Council for Pharmacy Education (ACPE)-accredited school or college of pharmacy
 - b. Licensure and registration by a state board of pharmacy
 - 2. Conventional or preferred postgraduate training
 - a. PGY1 pharmacy practice residency based in a hospital
 - b. PGY2 critical care residency or fellowship
 - 3. Nontraditional alternative paths: There is no widely accepted or clearly defined alternative pathway to specialty experience and competence in critical care pharmacy. Some potential pathways and components of a self-directed training program are outlined in the text that follows. The extent and variety of experiences needed may be determined by the practice setting, level of care to be provided, baseline knowledge, availability and willingness of qualified mentors, and other personal and professional skills of the individual. Although many potential paths are defined later, those that provide continued, practical experience during a prolonged period in a supervised or mentored environment are considered of greatest value in developing competency in the ICU setting.
 - a. Mentored or supervised clinical practice experience without residency
 - i. Clinical practice experience must be hands-on and team based under supervision.
 - ii. Mentors may be PGY2- or fellowship-trained critical care pharmacists, clinical pharmacists with equivalent experience, critical care faculty from affiliated schools of pharmacy, intensivist physicians, and/or other critical care professionals.
 - iii. Several mentors may best meet the variety of needs of the mentee pharmacist.
 - iv. Reinforced by frequent reading and analysis of the critical care primary and secondary literature, journal club participation, and frequent critical discussions of the clinical implications of the primary literature
 - v. Normally, expect at least 3–4 years of mentored/supervised experience to gain competency for independent clinical practice (optimal services) in level I and II ICUs. Shorter periods may be adequate to provide lower levels of service to level II and III ICUs.

- b. PGY1 with supervised/mentored ICU clinical practice experience
 - i. Mentored clinical experiences similar to those described earlier
 - ii. PGY1 with critical care experiences during residency may be adequate to provide fundamental and desirable services to level II and III ICUs.
 - iii. Normally, expect 2–3 years of mentored/supervised experience to gain competency for independent clinical practice (optimal services) in level I and II ICUs.
- c. Critical care traineeship (www.ashpfoundation.org/criticalcare)
 - i. Offered through the ASHP Foundation
 - ii. Four-month distance education component – Independent reading, web-based education, and teleconference case studies
 - iii. Two-week on-site experiential training
 - iv. Post-experiential training activities
 - v. Is not a comprehensive training program but can be a valuable component of a training program for nontraditional-path clinical pharmacists
- d. Other potential components of a nonconventional training program: Actual program structure will vary depending on the available resources, practice environment, baseline knowledge and skills of the pharmacist, and institutional support.
 - i. Graduate degree (e.g., master's degree)
 - ii. Continuing education (CE) programming – Live, web based, print
 - iii. Attendance at national and regional critical care meetings – CE, networking, research presentations
 - iv. Fundamental Critical Care Support course completion (http://www.sccm.org/Fundamentals/FCCS/Pages/default.aspx?gclid=CLmGxuXTzs8CFYgvgQodw_kKOg)
 - v. ACLS, advanced trauma life support (ATLS), and/or pediatric advanced life support (PALS) training and certification
 - vi. Regular participation in the SCCM Clinical Pharmacy and Pharmacology Section national journal club
 - vii. SCCM Clinical Pharmacy and Pharmacology Section mentor program – Long-distance mentoring program
 - viii. Self-arranged experiential rotations at peer institutions under the supervision of a qualified critical care pharmacist
 - ix. Visiting professor or scholar programs to bring specialized expertise to the clinical site for on-site experiential training and didactic teaching
 - x. Policy, guideline, and protocol development for critical care pharmacotherapy–related issues under the supervision of qualified peers
 - xi. Critical care pharmacy service or program development, implementation, and outcome measurement under the supervision of qualified peers
- 4. PGY2 residency and fellowship programs
 - a. First critical care pharmacy residency described: 1981 (The Ohio State University)
 - b. ASHP critical care pharmacy residency standards published in 1990
 - c. 116 ASHP-accredited critical care residencies in 2014; increased from eight in 2001 and from 39 in 2005
 - d. Most PGY2 critical residents somewhat or very satisfied (91% and 76%, respectively) with their program and mentorship according to 2012 survey
 - e. Critical care pharmacy research training: Long history of fellowship training; however, the ACCP fellowship directory lists four fellowship programs with a primary or secondary focus on critical care.

- D. Mentoring and Critical Care Pharmacy Training (Am J Pharm Educ 2013;77:1-7; Am J Pharm Educ 2003;67:1-7)
1. Mentor-protégé relationship
 - a. Symbiotic, nurturing relationship between two adults
 - b. Assist each other in meeting shared career objectives
 - c. Attributes of a successful mentor-protégé relationship (see Box 1)
 - d. Mentor typically 15–20 years older than protégé, predominantly male (still true in 2016?)
 2. Mentor should fulfill five functions:
 - a. Teaching – New knowledge, skills, and attitudes
 - b. Sponsoring – Helps protégé reach career goals, assists in networking, vouches for abilities, offers protection from threats
 - c. Encouraging – Affirming, challenging, inspiring
 - d. Counseling – Listening, probing, advising during difficult challenges
 - e. Befriending – Acceptance, understanding, and trust
 3. Phases of the mentor-protégé relationship:
 - a. Initiation phase
 - i. Weeks to months in duration
 - ii. Begin work together
 - iii. Mentor coaches protégé, and protégé may provide technical assistance.
 - b. Cultivation phase
 - i. 2–5 years in duration
 - ii. Both individuals realize personal and professional benefits.
 - iii. Deeply intimate and personal bonds are formed.
 - c. Separation phase
 - i. Typically months in duration
 - ii. Protégé no longer requires guidance and begins to seek more autonomy.
 - iii. Mentor may think they have been deserted, whereas protégé may believe they are being held back.
 - iv. Resentment or hostility may lead to end of relationship.
 - d. Transformation phase
 - i. Years in duration (lifelong)
 - ii. Peer relationship evolves.
 - iii. Mutual sense of gratitude and appreciation
 4. Voluntary versus arranged relationships
 - a. Increasingly, organizations are establishing mentoring programs with assigned mentors.
 - b. Successful mentoring relationships are voluntary and based on mutual respect.
 - c. Successful and powerful people are not necessarily good mentors.
 - d. The factors that lead to mentor-protégé relationships are unclear and may be difficult to create through assignment of mentors.
 - e. Factors that contribute to successful mentorship:
 - i. Common interests
 - ii. Common purpose
 - iii. Desire on the part of the mentor to participate
 - iv. Mentor and protégé must be able to spend time together.
 - v. Persistent and regular interaction between mentor and protégé
 - f. Formal mentoring programs can be successful, but less so than voluntary relationships.

5. Mentoring and critical care training
 - a. Beyond formal residency/fellowship programs, mentor-protégé relationships are essential to the formal development of critical care pharmacists.
 - b. Developing critical care pharmacists should seek out mentors with similar interests and purpose who can help them fill gaps in their knowledge, skills, and attitudes relative to critical care practice.
 - c. Over time, critical care pharmacists may have several mentor-protégé relationships to meet evolving educational and experiential needs.
 - d. Experienced and successful critical care pharmacists should volunteer to mentor junior pharmacists, residents, and students and take their roles as mentors seriously by being kind, helpful, supportive, and encouraging.
 - e. SCCM Clinical Pharmacy and Pharmacology Section mentoring services: Practice, education, administration, scholarship

VII. CONTINUING PROFESSIONAL DEVELOPMENT (<https://www.acpe-accredit.org/ceproviders/CPD.asp>; Resident Survival Guide. Lenexa, KS: ACCP, 2011:123-37; Am J Health Syst Pharm 2004;61:2069-76)

- A. General Considerations
 1. Lifelong learning by health care professionals is both a necessity and an obligation to several stakeholders.
 2. CPD is a multifaceted, self-directed, holistic, outcomes-focused approach to lifelong learning.
 3. CPD is a career-long iterative process with continuous cycles, rather than a start and a finish.
 4. Sustained career growth and success are more dependent on CPD than on early career education and training.
 5. CPD should be closely integrated into daily practice and the work environment for success and sustainability.
- B. Stakeholders in CPD: Stakeholders may have a role in contributing to lifelong learning, benefiting from the sustained competency of the clinical pharmacist, or both.
 1. Pharmacist-learner (self)
 - a. Most at stake
 - b. Primarily responsible for developing a self-directed, structured approach to learning and assessment
 - c. Must develop an approach that is flexible, integrated, and capable of being sustained throughout decades of practice
 - d. Must be prepared to commit personal time to CPD
 2. Employer
 - a. Has both an obligation to and an expectation of the clinical pharmacist relative to CPD
 - b. Provision of resources
 - i. Travel funding
 - ii. Access to electronic databases and literature
 - iii. Environment that promotes sharing and learning (clinical conferences, journal club, open discussion and debate among colleagues, etc.)
 - iv. Protected time to pursue educational opportunities
 - c. Establish a credentialing and privileging process that incorporates CPD expectations.
 - d. Aligning personal development goals with institutional priorities is mutually beneficial and may increase employer support.
 - e. Employer benefits from sustained and expanded competencies of clinical pharmacist and should incorporate into hiring, retention, and promotion decisions

3. Colleagues
 - a. Contribute to lifelong learning of the clinical pharmacist
 - i. Case-based discussion and debate on daily rounds
 - ii. Drug-related questions
 - iii. Interdisciplinary teaching rounds
 - iv. Clinical conferences, journal clubs
 - v. Inclusion in collaborative scholarly activities
 - b. Benefit from lifelong learning of the clinical pharmacist
 - i. Greater quality and sophistication of contributions to team-based care of critically ill patients
 - ii. Educational offerings by the clinical pharmacist
 - iii. Collaboration around scholarly activities
 - iv. ICU-related treatment guidelines and protocols developed by or in collaboration with the clinical pharmacist
 4. Students, residents, and fellows
 - a. Contribute to lifelong learning of the clinical pharmacist
 - i. Assisting in identifying gaps in their own knowledge
 - ii. Creating incentive to maintain competency through CPD
 - iii. Regularly challenging applicability and relevance of professional knowledge and skills
 - b. Benefit from current, relevant knowledge and skills being incorporated into:
 - i. Teaching
 - ii. Role modeling/coaching
 - iii. Mentoring
 - c. CPD is a lifelong obligation of pharmacists who accept responsibility for training future clinical pharmacists.
 - d. The best trainees seek out the most competent teachers, preceptors, and mentors.
 5. Patients
 - a. Greatest beneficiary of clinical pharmacist CPD
 - b. Providing the best possible care to ICU patients should be the biggest motivator for the clinical pharmacist to pursue CPD.
 - c. Well-informed patients will seek out the most competent and capable health care professionals.
- C. CPD Process: The CPD process is structured around four essential steps. A potential fifth step is documentation of the process, but that should be an integral part of each step, not a separate process.
1. Reflection
 - a. Self-assessment process
 - b. Evaluation and feedback from others
 - i. Coworkers
 - ii. Colleagues
 - iii. Employer
 - iv. Patients
 - c. Personal SWOT (strengths, weaknesses, opportunities, and threats)
 - i. Assessment of internal strengths and weaknesses related to knowledge, skills, experiences, and behaviors
 - ii. Assessment of external environmental factors for opportunities and threats
 - iii. Goal is to identify learning needs and opportunities that exist to address those needs.
 - d. Reflection should be both scheduled and episodic.
 - i. Annual performance evaluation/self-evaluation (scheduled)
 - ii. Some set or chosen anniversary date (scheduled)

- iii. After the care of a complex or difficult patient (episodic)
 - iv. After an interaction with a challenging student or resident (episodic)
 - e. Result of reflection is to identify two or three specific, well-defined, and achievable learning needs.
 - 2. Plan
 - a. Develop a personal development plan (PDP) to address the needs and opportunities identified during reflection.
 - b. Includes learning objectives that are specific, measurable, achievable, relevant, and timed (SMART)
 - c. Identifies resources needed to address the PDP
 - d. Evaluates the availability and access to needed resources and modifies plan accordingly
 - e. The PDP should be regularly reassessed and adjusted as needed.
 - 3. Act
 - a. Develop an action plan to implement the PDP.
 - b. The action plan will need to incorporate a variety of learning strategies and methods (see text that follows).
 - c. Incorporating the action plan into the daily practice activities is key to success and sustainability. CPD should not be considered an additional burden.
 - 4. Evaluate
 - a. Evaluate the effectiveness of the action plan for achieving the learning objectives of the PDP.
 - i. Did the activities provide adequate content, depth, and hands-on experiences to truly address the learning objectives and meet the needs identified during reflection?
 - ii. Did the activities stay focused on the learning objectives, and were timelines adhered to adequately?
 - iii. Were all competencies adequately addressed?
 - iv. How did the CPD activities affect the pharmacist-learner and possibly the patient (often very challenging to measure)?
 - b. Evaluation is expected to lead to the next round of reflection and restart the continuous and iterative process of CPD.
 - 5. Portfolio
 - a. Process of documenting the CPD progression
 - b. Although the format may be standardized by employer, regulatory authorities, CE providers, or others, the content should be individualized to reflect the needs, actions, and assessments of the pharmacist-learner.
 - c. Is a dynamic, living document that reflects the continuous, iterative nature of CPD
 - d. Examples of CPD portfolio formats/templates:
 - i. https://www.acpe-accredit.org/pdf/CPD_Portfolio.pdf
 - ii. www.ncbop.org/CE/CPDLearningPortfolio.pdf
 - iii. www.ocpinfo.com/practice-education/qa-program/learning-portfolio/
- D. CPD Learning Strategies and Methods
- 1. CPE
 - a. CPD is not a replacement for CPE, but CPE should be one component of a PDP.
 - b. ICU pharmacists should focus on CPE programming that meets their defined educational needs and incorporates several different techniques that will help meet the full range of competencies needed for clinical practice in the ICU.
 - c. Accreditation standards maintain minimum quality assurance of CPE activities.
 - d. CPE credits are the most widely used “currency” by regulatory bodies, accrediting agencies, and other organizations as a proxy for professional competency, and this is unlikely to change in the near or intermediate term.

- e. Traditional didactic lecture-style CPE activities have several limitations toward achieving CPD learning objectives.
 - i. Often non-curricular
 - ii. Limited influence on changing practice
 - iii. Educational outcomes may not align with the individual's needs.
 - iv. Content is sponsor or speaker driven.
 - v. Opportunity for bias (or perception of bias), depending on source of support
 - vi. CE efforts are often fragmented across professions (not interdisciplinary).
 - f. CPE providers are expanding the diversity of educational methodologies and techniques to include interaction, experiential learning, simulation, discussion and debate, and role-playing, among others.
 - g. Limited evidence suggests that live CE over print, multimedia format, and a series of programs on a curricular theme is the most effective CE method.
2. Short courses or seminars
- a. Certificate or credentialing programs
 - i. ACLS
 - ii. ATLS
 - iii. PALS
 - b. Structured curricular programs
 - i. ACCP Academies
 - ii. Fundamental Critical Care Support (FCCS) course
3. Membership and participation in national organizations
- a. ACCP; Critical Care PRN
 - b. SCCM; Clinical Pharmacy and Pharmacology Section
 - c. ASHP
 - d. Several specialty organizations related to critical care (American College of Chest Physicians, American Trauma Society, Neurocritical Care Society, etc.)
4. Primary and secondary literature
- a. Reading, analyzing, and applying the relevant literature should be central to any strategy of professional development.
 - b. No gold standard strategy for staying current with the literature
 - c. Many “foraging” strategies will need to be considered and used.
 - i. Review table of contents of high-impact journals in critical care (e-mail or rich site summary [RSS] push technology) (e.g., *Critical Care Medicine*, *Intensive Care Medicine*, *Chest*, *American Journal of Respiratory and Critical Care Medicine*, *Journal of Trauma and Acute Care Surgery*, *Journal of Critical Care*).
 - ii. Topic alerts (e-mail or RSS) for critical care articles from high-impact multispecialty journals (e.g., *New England Journal of Medicine*, *Annals of Internal Medicine*, *JAMA*, *The BMJ*, *Lancet*)
 - iii. Scan high-impact pharmacy specialty journals for critical care articles (e.g., *Pharmacotherapy*, *Annals of Pharmacotherapy*, *American Journal of Health-System Pharmacy*).
 - iv. Use of saved search strategies with automatic e-mail alerts on a scheduled interval (e.g., PubMed, PubCrawler, Ovid Medline)
 - v. Subscribe to a medical information alert service with high and transparent standards for validity, relevance, and contextual interpretation of the data (e.g., Essential Evidence Plus, FPIN [Family Physicians Inquiries Network] Clinical Inquiries, BMJ Clinical Evidence, Cochrane for Clinicians).
 - vi. Scan review journals relevant to critical care (e.g., *Critical Care Clinics*).
 - vii. Identify high-quality, relevant, and contemporary clinical practice guidelines for critical care therapeutics (e.g., National Guideline Clearinghouse, PubMed Clinical Queries, MD Consult).

- viii. Use up-to-date systematic reviews (e.g., *Cochrane Database of Systematic Reviews*, *Agency for Healthcare Research and Quality [AHRQ] Evidence-Based Practice Center Evidence-Based Reports*).
- ix. Selective use of other resources (e.g., evidence-based summaries such as Bandolier, Clinical Evidence), critically appraised topics, point-of-care review services (e.g., UpToDate, Medscape), and meta-search engines (e.g., Trip database)
- d. The tools and resources available for staying current with the literature is a rapidly evolving, dynamic market. The individual pharmacist will need to stay current to maximize use of the literature and will need to adapt his or her strategy over time.
- 5. Discussion and debate with colleagues, mentors, and other content experts
 - a. Therapeutic dilemmas
 - b. Complex cases
 - c. Primary literature
 - d. Guidelines
- 6. Journal clubs/clinical conferences
- 7. Interdisciplinary, patient care rounds – Daily interactive discussions of diagnostics, disease states, therapeutics, monitoring, technology in the ICU, ethics, communication with patients and families, etc.
- 8. Guideline and protocol development for the ICU
 - a. Translation of evidence to best practices
 - b. Benchmarking with peer institutions
 - c. Consensus building
 - d. Project management – Implementation and measurement of outcomes
- 9. Point-of-care learning
 - a. Refers to day-to-day learning opportunities
 - b. Uncommon disease state or unexpected adverse drug reaction prompts reading and learning.
 - c. Complex drug information questions from colleagues

VIII. CORE KNOWLEDGE BASE AREAS FOR PHARMACISTS CARING FOR CRITICALLY ILL PATIENTS (2012 BOARD OF PHARMACY SPECIALTIES CRITICAL CARE CONTENT OUTLINE)

- A. Pulmonary
- B. Cardiovascular
- C. Neurology and Neurologic Injuries
- D. Psychiatry
- E. Renal
- F. Hepatogastrointestinal
- G. Immunology
- H. Endocrine

- I. Hematology
- J. Infectious Diseases
- K. Toxicology
- L. Surgery

IX. DISSEMINATION OF CRITICAL CARE KNOWLEDGE

- A. Reasons to Disseminate Knowledge
 - 1. Recognition by peers
 - 2. Promotion and tenure
 - 3. Ethical obligation of research
 - 4. Grantsmanship success
 - 5. Giving back to the discipline – Critical care pharmacy is a new and evolving specialty.
 - 6. Travel support
- B. Venues for Disseminating Knowledge
 - 1. Peer-reviewed publications (see text that follows for greater detail)
 - a. Traditional, print journals
 - b. Open-access (electronic) journals
 - 2. Non-peer-reviewed publications
 - a. Textbook chapter
 - b. Commentary/editorial
 - c. Newsletter
 - d. Guideline
 - e. Compendia
 - f. CE material
 - 3. Abstract (see text that follows for greater detail)
 - a. Poster
 - b. Platform
 - c. Regional, national, international meetings
 - d. Virtual poster sessions
 - 4. Presentation
 - a. CE
 - i. Live/lecture – Local, regional, national, international venues
 - ii. Webinar
 - iii. Recorded/archived
 - b. Seminar or conference
- C. Publication and Peer-Review Process
 - 1. Categories of publications (will vary by journal)
 - a. Original research
 - b. Systematic review (e.g., meta-analysis)

- c. Expert review
- d. Brief reports (e.g., preliminary or pilot data)
- e. Case reports
- f. Practice or educational insights (typically must include assessment of outcomes)
- 2. Selecting a target journal
 - a. Quality and importance of the publication
 - i. First-tier journals – Highly important, innovative, and/or high quality
 - ii. Second- and third-tier journals – To be considered when paper unlikely to be accepted in, or rejected by, first-tier journal
 - b. Target audience and scope of the journal relative to content of publication – Looking for good match on both
 - c. Seek input from coauthors, peers, colleagues concerning appropriate journal to target
- 3. Preparing the manuscript
 - a. Comply with journal requirements.
 - i. Historically published with first issue of each volume
 - ii. Today, easiest to access online
 - iii. Manuscript format
 - iv. Margins, font, type size
 - v. Abstract format
 - vi. Word limits
 - vii. Reference style and limits
 - viii. Figures and tables
 - b. Succinct, focused, non-repetitive – Economy of words
 - c. Common weaknesses to avoid (original research) – In manuscript preparation, not underlying research
 - i. Abstract does not match body of manuscript
 - ii. Introduction fails to sell the importance and relevance of the objective(s)
 - iii. Poorly worded or unclear study objective(s)
 - iv. Methods without results; results without methods
 - v. Unnecessary duplication of results in tables and body of manuscript
 - vi. Rambling, unfocused discussion
 - vii. Failure to adequately address weaknesses of the study (all studies have them)
 - viii. Conclusions that reach beyond the data
 - ix. Several tables that can be consolidated
 - x. Unneeded figures (usually, simplistic presentations of data that can be presented parenthetically)
 - xi. Failure to cite the literature correctly or according to journal's requirements
 - xii. Exceeding word count limits – Both in abstract and in manuscript
- 4. Using citation manager software (EndNote, Reference Manager, RefWorks, etc.)
 - a. May contain templates consistent with many biomedical journal requirements
 - b. Actively cite the literature while writing
 - c. Automatically re-sort the references during revisions
 - d. Direct download of citations during literature searches
 - e. Can include PDF files and your notes in citation file
 - f. Develop libraries of commonly used citations
 - g. Overall, can ease the writing and formatting process for publication
- 5. Submitting the manuscript
 - a. Greatly simplified by web-based submission
 - b. Follow download instructions carefully.

- c. Cover letter
 - i. Communication to the editor
 - ii. Declare category of publication (though now part of submission template).
 - iii. Indicate corresponding author (also part of template).
 - iv. Some journals encourage a brief explanation of why paper is being submitted to the journal – Relevance, importance, target audience. However, this is declining.
- d. Copyright release
 - i. Electronic methods are increasingly used.
 - ii. Each author must sign/submit.
 - iii. Provide assurance that part or all of content has not been previously published and is not currently under consideration by another publisher. Usually excludes abstracts.
- 6. Conflicts of interest: All authors must provide conflict-of-interest statements.
- 7. Review and revision process
 - a. Editorial review
 - i. The editor or a member of the editorial board may review initially.
 - ii. Looking for relevance to journal, general quality of the manuscript, composition, and readability
 - iii. Failure to get past the editor's desk results in rejection
 - b. Peer or scientific review
 - i. Sent to peers with content expertise for review and critique
 - ii. Typically, sent to two to five reviewers (varies by journal and internal criteria)
 - iii. Most journals request a review to be returned in 10–30 days.
 - iv. Reviewers are asked to focus on the quality of the research or content and importance (including relevance to the journal's audience), not copyediting details.
 - v. Typical recommendation categories are as follows: Accept, minor revision, major revision, or reject.
 - vi. Reviewers provide detailed comments and critique to be shared with the authors, and, often, comments to the editor that are not shared with the authors.
 - c. Editor response
 - i. The editor (or designee) uses reviewer input to formulate a response to the authors.
 - ii. If minor or major revision is requested, details of the required revisions are provided, often including the reviewers' specific comments. The editor often adds requests for revision.
 - iii. A timeline for response is included. If manuscript is not resubmitted by deadline, opportunity to publish is usually surrendered.
 - iv. A rejection decision is usually final.
 - d. Revision process
 - i. The authors need to respond to each request. The authors need not agree with each request, but each must be responded to and defended if not revised as advised.
 - ii. Common format is a letter to the editor restating each request, with the response to the request immediately following.
 - iii. A manuscript incorporating all revisions is submitted with the letter. Some journals request a "track changes" version of the manuscript to ease the rereview process.
 - iv. All authors must review the revisions and indicate their agreement with all changes.
 - v. Revised manuscripts are often returned to the original peer reviewers for a second review, especially with major revisions. That may result in another round of revision and review.
- 8. After acceptance
 - a. At some point (timelines vary by journal), the corresponding author will receive the galley proof. This is a copyedited, typeset version of the paper that will look like the final publication.
 - b. The galley proof will come with comments that must be addressed.

- c. Deadline for galley submission may be as short as 48 hours.
 - d. The galley proof must be read very carefully and compared with the manuscript to ensure that copyediting changes do not affect the meaning, tables are formatted as intended, figures and legends are correct, and references are in the correct order and format (there are often errors with references – better with electronic confirmation).
 - e. Ideally, all authors should review the galley proof; however, that may not be practical. All authors should approve a review by the corresponding author.
- 9. Timelines (highly variable by journal)
 - a. Important competitive metric for biomedical journals
 - b. From submission to response – Can be 2–4 months
 - c. Reply to decision – Can be 1 week to 3 months (depends on whether rereview occurs)
 - d. Decision to publication – Can be an additional 3–6 months
 - e. Sometimes an important consideration when selecting a journal – Manuscript can be tied up for long periods.
 - f. Open-access and e-journals have a speed advantage – May have fees.
- D. Abstracts and Scientific Presentations
 - 1. Selecting a meeting
 - a. Quality and relevance of presentation
 - b. Prestige of the meeting relative to authors' career goals
 - c. Membership and desire to support an organization
 - d. Availability of travel funding
 - e. Priorities of key coauthors
 - f. Location of the meeting (unfortunate, but true ...)
 - g. Encore presentations permitted
 - 2. Developing the abstract
 - a. Succinct and effective
 - i. Greatest impact in the least space – No unnecessary words
 - ii. Use of identifiable abbreviations, but not to excess
 - iii. If allowed, use of tables to present results (many disallow)
 - b. Title must be brief, be on point, and capture the reader.
 - c. Clearly stated purpose/objective (minimize introductory material). May need to limit to primary objective.
 - d. Methods and analysis are concise but of adequate detail to permit review.
 - e. Results may need to be limited to the primary end point.
 - f. Conclusion is a single brief sentence directly tied to the objective(s).
 - g. Must meet word count limit (tricks and tips depend on organization)
 - h. Revise, revise, revise with input from all authors – Eliminate unnecessary words and content.
 - i. Some organizations may permit students or residents to submit abstracts without data or with partial data.
 - 3. Abstract submission
 - a. Greatly simplified by electronic submission
 - b. Must meet deadline – Most websites shut down after deadline.
 - c. Must carefully follow online instructions
 - d. Word limit usually controlled by software – Difficult to cheat
 - e. If platform presentations are an option, usually need to indicate consideration for platform, if that is the goal

4. Platform versus poster
 - a. Platform slots are intended for presentations that have high-quality content and that are relevant and effective.
 - b. Usually based on reviewer scores
 - c. Many organizations may accept a platform submission as a poster presentation if it was not scored high enough to be accepted as a platform; others may just reject it.
 - d. Authors must be realistic concerning the quality of their abstract when considering submission for a platform, given the meeting, audience, and likely competing research.
5. Review process
 - a. Typically reviewed by three to five reviewers
 - b. Review uses relatively limited scoring criteria, given the brevity of an abstract, combined with a recommendation of accept or reject.
 - c. Reviews are compiled into an overall score, and recommendation is provided to the authors.
 - d. There is no opportunity or time for revision and resubmission. Decisions are final.
 - e. Reviewer comments may or may not be shared with the authors.
 - f. Platform versus poster decisions may also be an outcome of the review process.
 - g. Review process may also be used for determining abstracts to be considered for awards.
6. Poster presentation
 - a. Format (size and/or style) is often specified by the organization.
 - b. Many tips and tricks are available for developing effective posters. Some key issues are:
 - i. Avoid wordy posters – Nobody wants to read them.
 - ii. Use tables, figures, and concise bullet lists as much as possible.
 - iii. Use a font size that can easily be read from about 5–6 feet (e.g., 24 point or greater).
 - iv. Ease of readability is more important than aesthetics – Consider dark letters on a white background.
 - v. Use a logical flow from left to right and from the introduction to the conclusions.
 - vi. Unless required, do not reprint an abstract on a poster – It is unnecessary and uses valuable space.
 - vii. Most institutions have requirements to use logos – Comply with the requirements or potentially run into last-minute challenges with printing.
 - viii. Large-print formats have eased the production and transport of posters; however, review proofs carefully for content changes before printing.
 - ix. Commercial printers who will ship to the meeting site are a great alternative if last-minute challenges develop.
 - c. If there are walk-rounds, be fully prepared to present the key points of your poster in about 5 minutes to allow time for questions. It is important to confirm the time allotment set by each organization because this may vary.
 - d. Consider having small, legible versions of the poster at the poster session for those who want a copy to review. In addition, have business cards available.
 - e. Plan to have at least one author stay for the duration of the poster session.
 - f. Virtual poster sessions are very similar in submission, review, and acceptance process. Presentations are virtual and may involve the abstract only or a more detailed “poster,” with interactive sessions scheduled with either random viewers or scheduled peer reviewers.
7. Platform presentation
 - a. Considered an honor of recognition for high-quality, innovative, or impactful work
 - b. Presentation is usually limited to 10 minutes, with 5–10 minutes left for questions.
 - c. Typical format is a brief slide presentation focused on the most important aspects of the work. Time does not allow a detailed description of all aspects of the project.

- d. May involve peer review/judging if awards are involved
 - e. Feedback in verbal or written format is often provided to the presenter.
 - f. May also require a poster presentation during one of the poster sessions (varies by organization)
 - g. Repeated practice with coauthors, peers, and colleagues, followed by critique and revision, is highly recommended.
- E. Participation in the Peer-Review Process (Eos 2011;92:233-40; PLoS Comput Biol 2006;2:e110)
- 1. Reasons to participate
 - a. Professional obligation
 - i. Authors “take” from the process, so they should “give back.”
 - ii. Contribute expertise to improving the biomedical literature
 - b. Professional service to an organization or journal
 - c. Recognition, tenure, and promotion – Professional service
 - d. Some enjoy reviewing the “raw” product of the biomedical literature.
 - e. Educational opportunity for trainees
 - 2. Reasons to decline invitation to participate
 - a. Conflict of interest
 - i. Former trainee is author
 - ii. Collaborator or coworker is author
 - iii. Financial conflict of interest with the subject
 - b. Lack of expertise in the subject matter
 - c. Lack of time to meet the deadline because of other commitments
 - 3. Getting on the list of potential reviewers
 - a. Publishing in the journal
 - b. Being recommended by a peer to the editor
 - c. Being a recognized expert (nationally, internationally) in a relevant field
 - d. Publishing in the field in peer journals
 - e. Volunteering through the journal’s website or a general call for reviewers – Not an option for all journals
 - 4. Review process
 - a. Invitation
 - i. Normally sent by e-mail with a response link
 - ii. Includes an abstract of the paper and often identifies the authors and institution
 - iii. Deadline for submission of review is provided so that reviewer can gauge availability of time.
 - iv. Usually a short timeline to respond to invitation
 - v. If decline, most journals ask for recommendation of a peer to review (building their reviewer database)
 - vi. Once accepted, online access to content is provided (manuscript, review form, instructions to reviewers, etc.).
 - b. Tips for the review
 - i. Biomedical literature review skills are beyond the scope of this chapter.
 - ii. Review is expected to focus on scientific quality and importance of the paper.
 - iii. Grammar, sentence structure, and word choices are normally better handled by the copyeditors because of their greater expertise, unless it is critical to the scientific meaning of the paper.
 - iv. Connect the dots to find common errors (original research and systematic reviews).
 - (a) Objective/purpose and conclusions must match.
 - (b) Methods must be directly related to the objective/purpose.

- (c) Methods must be valid, widely accepted, and/or state of the art, including statistical handling of the data.
 - (d) Widely accepted guidelines according to study design should be complied with (e.g., CONSORT, STROBE, PRISMA, STARD).
 - (e) Every method described must have results reported.
 - (f) Every result reported has to be tied to a method description.
 - (g) Conclusions must be limited to and supported by the study results.
 - (h) A fair and complete discussion of study weaknesses must be presented.
- c. Recommendation to editor
 - i. Reason for rejection
 - (a) Fatal flaw – No amount of rewriting or reanalysis of the data will make it worthy of publication – Poor-quality research or serious errors in methods
 - (b) Extent of revision required is so extensive that it is equivalent to starting over
 - (c) Valid research that is not important, either because of lack of relevance to the target journal or because manuscript is reporting a well-known finding with no new information
 - (d) Republication of all or an extensive portion of the content (may be justifiable [e.g., portions of the methods section when it is a legitimate secondary publication of a previously published study])
 - (e) Serious ethical violations
 - ii. Revision (minor or major revision)
 - (a) Usually for publications believed to have adequate quality and importance, but there are weaknesses that need to be corrected or addressed
 - (b) Major revisions usually require a second review – The journal may ask whether you will serve as a continuing reviewer, or it may be assumed.
 - (c) Minor revisions may not require rereview; depends on reasons for revision
 - (d) Most journals will share the recommendation to the authors, together with the other reviewers' comments to author – Can be very instructive for future reviews
 - iii. Accept (without revision)
 - (a) Unusual with first submission and review
 - (b) Is a truly exceptional manuscript
- d. Submission of the review
 - i. Electronic submission according to the journal
 - ii. Format is often dictated by the journal.
 - iii. Meet the deadline – Delayed reviews prolong the timeline and create workflow challenges for the journal.
 - iv. Comments to the authors
 - (a) Should be clear, concise, and factual. Should not be abrasive or a personal attack.
 - (b) Comments should be clearly referenced to the location in the manuscript (e.g., line number, page/paragraph/sentence).
 - (c) Are usually anonymous, but some journals provide option to be identified
 - (d) For manuscripts with a fatal flaw, comments can be limited to that flaw.
 - v. Comments to the editor
 - (a) Should not require extensive comments beyond those to the authors
 - (b) Is an opportunity to further explain the rationale for the recommendation or ethical concerns
 - (c) Are attributed to the reviewer, but not shared with the authors
 - vi. Miscellaneous
 - (a) Journal may ask whether you believe an editorial is needed, and a proposed author
 - (b) There may be a question about concerns with ethics, animal treatment, or human subjects' protection.

5. Rereview process
 - a. Response content
 - i. Cover letter detailing response to comments/requests of editor and reviewers
 - ii. Revised manuscript (with or without “track changes”)
 - b. Review process
 - i. Should restrict comments to responses in first review. Finding an entirely new set of criticisms to original content is considered “not playing fair.”
 - ii. Confirm that the revisions have not materially altered the meaning of other parts of the manuscript.
 - iii. If the authors have argued not to make a recommended revision, evaluate the validity of the response.
 - iv. Recommendations are the same options as for the primary review.
 - v. If major revisions are still needed, the editor may decide to reject, or it may undergo another round of reply and review.
 - vi. Deadline for the review is often shorter than for the primary review.

Table 1. Critical Care Pharmacy Services

Critical Care Pharmacist Activities		
Fundamental	Desirable	Optimal
• Dedicates time to ICU patients with few commitments outside the ICU • Prospectively reviews all medication orders for appropriateness • Prospectively reviews all nutritional orders in collaboration with clinical dietitians • Leads process improvement to identify, prevent, and manage ADEs • Uses the medical record for communication and documentation • Provides pharmacokinetic monitoring of targeted drugs • Provides drug information, including IV compatibilities, and maintains current tertiary drug references • Provides drug therapy education to ICU team members • Participates in ADE reporting, internal and external (e.g., the FDA), to the institution	• In addition to providing fundamental activities, the ICU pharmacist: • Regularly participates in multidisciplinary patient care rounds • Maintains knowledge of primary literature relevant to ICU therapeutics • Completes a comprehensive medication reconciliation for all ICU admissions, including identification and management of potential medication-related admissions • Provides formal nutritional consultation in collaboration with clinical dietitians • Maintains ACLS (or PALS) certification and participates in code team responses • Provides didactic education to health care students on ICU pharmacotherapeutic topics	• In addition to providing fundamental and desirable activities, the ICU pharmacist: • Assists physicians and other team members during family discussions concerning treatment options • Provides accredited educational programming for medical, nursing, and pharmacy professionals and students on ICU-related drug therapy topics • Participates in teaching ACLS • Develops residencies and fellowships in critical care pharmacy • Develops and delivers critical care training programs for pharmacists and pharmacy technicians

Table 1. Critical Care Pharmacy Services (*continued*)

Critical Care Pharmacist Activities		
Fundamental	Desirable	Optimal
• Documents clinical activities • Serves as a liaison to the ICU team as it pertains to drug use policies, procedures, and standards • Contributes to internal communications (e.g., newsletters, monographs) related to ICU drug use • Develops, implements, and maintains drug use policy related to the ICU • Collaborates with other ICU team members and hospital and departmental administration to meet regulatory and accreditation compliance standards • Serves as a consultant to hospital committees (e.g., P&T) on ICU drug therapy-related issues • Identifies and implements measures to ensure cost-effectiveness and cost containment for drug therapy in the ICU • Participates in quality assurance and quality improvement initiatives related to ICU pharmaceutical care • Has access to pharmacy information system that maintains medication profile with basic decision support tools (allergy checking, drug interactions, dosing, etc.) and interfaces with laboratory results reporting • Ensures that, if manual medication records, appropriate quality assurance standards are in place • Maintains unit-of-use drug distribution system • Ensures that large- and small-volume sterile products prepared by pharmacy • Maintains pharmacy-managed investigational drug service • Ensures that pharmacy is represented on the institutional review board or scientific review committee	• Participates in experiential education and training for pharmacy students, residents, and fellows as applicable • Coordinates the development and implementation of guidelines and protocols for ICU drug therapy • Documents the value of clinical pharmacist activities using accepted methods to quantify clinical significance and cost • Contributes to drug therapy research through coordination of clinical trials, study design, and data analysis • Contributes to the critical care pharmacy and medical literature • Provides non-patient care service on hospital committees and through the provision of educational in-services • Maintains computerized hospital information system that includes medication use system fundamental requirements and additional integrated functions • Maintains computerized medication administration records • Ensures that ICU satellite dispensing pharmacy is operational at least 40 hours/week	• Promotes and educates concerning the importance of critical care pharmacists as members of the ICU team to several audiences, including the lay public and other health care providers • Evaluates the impact of guidelines and protocols related to critical care drug therapy on patient outcomes • Incorporates pharmacoeconomic principles into the evaluation of pharmacy services and new drugs in the ICU • Proactively develops, prioritizes, and promotes new pharmacy programs or services in the ICU • Secures funding for research • Reports results of research and program analyses at regional and national meetings • Publishes in peer-reviewed pharmacy and medical literature • Has access to hospital information system that includes computerized physician order entry and interfaces with clinical information system • Ensures that ICU satellite pharmacy is operational 24/7 • Ensures that clinical pharmacy services are available 24/7

ACLS = advanced cardiac life support; ADE = adverse drug event; FDA = U.S. Food and Drug Administration; ICU = intensive care unit; IV = intravenous; PALS = pediatric advanced life support.

Box 1. Attributes of Successful Mentor-Protégé Relationships

Mentor Qualities
Strong interpersonal skills Technical competence/expertise Knowledge of organization and profession Status/prestige within the organization and profession Willingness to be responsible for someone else's growth and development Ability to share credit Patience
Protégé Qualities
Self-perceived growth needs A record of seeking/accepting challenging assignments Receptivity to feedback and coaching Willingness to assume responsibility for own growth and development Ability to perform in more than one skill area
Relationship Qualities
Voluntary Mutual benefits perceived and derived from the relationship No conflicts of interest/competition between mentor and protégé Not confined to professional or business interests

Adapted from: Haines ST. The mentor-protégé relationship. Am J Pharm Educ 2003;67:Article 82, p 2.

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Dissemination of Knowledge in Critical Care

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ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS**1. Answer: A**

The journal *Drug Intelligence and Clinical Pharmacy* (now *Annals of Pharmacotherapy*) was the first to publish a critical care therapeutics column in 1982, which was a landmark event relative to the evolution of critical care pharmacy (Answer A). Although the other journals listed—*Pharmacotherapy* (Answer B), *Chest* (Answer C), and *Heart and Lung* (Answer D)—publish critical care therapeutics articles, *Annals of Pharmacotherapy* was the first to incorporate a critical care therapeutics column into its publication.

2. Answer: C

In 2001, ACCM, which exists within the organizational framework of SCCM, formed the two task forces focused on models of critical care delivery, the definition of an intensivist, and the practice of critical care medicine within three different proposed models (Answer C). Neither the Institute of Medicine (Answer A) nor ACCP (Answer B) was involved in formulating the levels of critical care delivery. Although the Clinical Pharmacy and Pharmacology Section of SCCM (Answer D) may have contributed to this document, it is not mentioned in the publication.

3. Answer: D

In a 2008 study, mortality rates were higher in ICUs without clinical pharmacists than in ICUs with clinical pharmacists: 23.6% for nosocomial-acquired infections, 16.2% for community-acquired infections, and 4.8% for sepsis ($p \leq 0.008$) (Answer D). Although the impact of clinical pharmacists in affecting QTc-interval prolongation (Answer A), preventable adverse drug interactions (Answer B), and drug-drug interactions (Answer C) has been evaluated, differences in mortality have not been documented. Therefore, these answers are incorrect.

4. Answer: A

The core knowledge areas for pharmacists caring for critically ill patients include pulmonary, cardiovascular, neurology and neurologic injuries, psychiatry, renal, hepatogastrointestinal, immunology, endocrine, hematology, infectious diseases, toxicology, and surgery. Therefore, infectious diseases (Answer A) is correct. Oncology (Answer B), transplantation (Answer C), and obstetrics (Answer D) are not considered core knowledge areas and are therefore incorrect.

5. Answer: C

The landmark study documenting a decrease in preventable adverse drug reactions after the inclusion of pharmacists on interdisciplinary medical rounds was published in the *Journal of the American Medical Association* by Dr. Lucian Leape and colleagues (Answer C). This highly publicized article published in a mainstream medical journal by a physician remains one of the foundational studies documenting the association of critical care pharmacy services with favorable health care outcomes. The other mainstream medical journals listed, *New England Journal of Medicine* (Answer A), *Lancet* (Answer B), and *Annals of Internal Medicine* (Answer D), have not published similar articles on preventable adverse drug reactions after the inclusion of pharmacists on interdisciplinary medical rounds.

6. Answer: B

As stated, there were eight ASHP-accredited critical care pharmacy residencies in 2001. In 2014, ASHP notes 116 ASHP-accredited critical care pharmacy residencies. Assuming linear growth, the 108-residency increase over 13 years equals an increase of about eight residencies per year (Answer B is correct). Although this represents significant growth, more than 2200 pharmacists would be needed to provide critical care pharmacy services, assuming 30 patients/pharmacists in the more than 67,000 adult ICU beds in the United States as of 2009. Answer A (6 residencies/year), Answer C (10 residencies/year), and Answer D (12 residencies/year) are incorrect.

7. Answer: C

The preferred and recommended pathway to training in critical care pharmacy is a PGY1 pharmacy practice residency, followed by a PGY2 critical care residency. This is especially true for the provision of desirable-to-optimal pharmacy services in ICUs providing level I and II services. Critical care fellowship training is an option that would also be considered preferred; however, the intent is for a greater research and academic focus. The demands of the workplace often exceed the supply of PGY2-trained critical care pharmacists. And although many of the alternative pathways available to gaining experience, knowledge, and skills in critical care pharmacy have been successful, these are not considered preferred pathways, given the high degree of variability

and inconsistency of resources to support them, therefore options A, B and D are non-preferred alternative pathways and are incorrect.

8. Answer: A

According to the position paper prepared and published by ACCP and SCCM defining pharmacy practice elements for fundamental, desirable, and optimal services, the publication of research and program evaluations in the medicine and pharmacy literature is an expectation of the clinical pharmacist providing optimal services. The other elements listed as options B, C and D for this question are considered desirable, but they are not uniquely preferred to meet the definition of an optimal critical care pharmacy practice, and are therefore incorrect.

9. Answer: C

Even though the principles of team-based health care are all interdependent, effective communication is most tightly linked to mutual trust. Open and frank communication and the willingness to state your beliefs and challenge those of your teammates require a high level of mutual trust to keep the relationship and conversation professional and nonpersonal. Without mutual trust, communication can be more guarded, ineffective, and political. Options A, B and D are relevant principles of team-based healthcare, but not as tightly linked to effective communication, and are incorrect.

10. Answer: B

Although structured mentor-mentee programs can be successful, there is a greater probability of success with relationships that are voluntary and that evolve from mutual interests and a perceived opportunity to have a mutually beneficial relationship. Mentors must be willing to serve in this role, which can require a great deal of time and effort; they wish to work with mentees who are highly motivated with a track record of accepting challenges. Moreover, mentees must be responsive to feedback and teaching. Mentees seek out mentors with shared interests, a record of sharing their time and expertise, and the necessary prestige and position in the organization to promote and create opportunities for them. In an arranged relationship, it is less likely that all of these factors will come together to lead to a highly productive relationship. Mentoring relationships can exist both within and outside formal training programs like residencies and fellowships so option A is incorrect,

and clinical pharmacists will often have several mentors through the different stages of their career to address different and evolving needs as they mature in their practice and scholarly activities so option D is incorrect. Finally, although mentored training programs are a viable option for the nonconventional training of critical care pharmacists, they are not an exclusive pathway so option C is incorrect.

11. Answer: D

Continuing pharmacy education should be included as an important strategy in a CPD PDP, and therefore options A and B are incorrect. The self-directed learner should select CPE programs that are relevant to their PDP, incorporate active learning strategies, are preferably curricular based, and are free of commercial or other bias. Continuing professional development is not an alternative to CPE; rather, it is an individualized, self-directed, continuous, and iterative process intended to address specific learning objectives developed over time by the pharmacist-learner. Continuing pharmacy education is an important component of this process, but it should not be the only learning strategy. Both CPD and CPE can include multiple learning strategies, so option C is incorrect.

12. Answer: C

The recently published Standards of Practice for Clinical Pharmacy, which includes a standardized process of care endorsed by all major pharmacy practitioner organizations, is intended to be applicable to any practice environment, regardless of acuity or complexity. Like other professions (e.g., medicine, nursing, physical therapy), clinical pharmacy must define and apply standards of care to create consistent expectations by all stakeholders. It is often argued that clinical pharmacists in different complex or unique practice environments cannot possibly conform to a standard of care; however, a thoughtful review of the Standards of Practice for Clinical Pharmacy reveals that it can be easily incorporated into any practice environment, and therefore options A, B and D are incorrect.

13. Answer: A

Clinical pharmacists practicing in the ICU have long had a broad educational role that includes students and residents in their own profession, residents and students in other professions, and colleagues on the critical care

team, as well as coworkers in the pharmacy department, among the target audiences. Clinical pharmacists have used many different strategies and techniques to teach these diverse audiences across different learning environments. Although there are exceptions, the frequent or regular inclusion of patients and families in their educational activities is a more recent development. Many factors have led to this change, including a greater focus on patient- and family-centered care, greater inclusion of patients and families as members of the team, increased demand for inclusion by patients and families, inclusion of patient satisfaction scores in pay-for-performance metrics (including pain control and understanding of medications), and greater patient awareness and interaction in the ICU with changes in sedation goals. It is anticipated that clinical pharmacists in the ICU will increasingly be directly involved in patient and family discussions and education. Options B, C and D all represent traditional audiences for clinical pharmacist educational efforts and are therefore incorrect.

14. Answer: B

In the context of CPD, episodic opportunities for reflection refer to spontaneous, unscheduled events that contribute to the self-assessment of learning and training needs that can be incorporated into the overall PDP. Scheduled reflection usually involves a predictable cycle like performance evaluations, annual self-evaluations, peer feedback as part of annual assessment, or a decision to schedule reflection around some set anniversary (e.g., hire dates, birthdays, end of academic year), and therefore options A, C and D are incorrect. Examples of opportunity for episodic reflection may include the challenges of managing a very difficult case, post-event debriefings for code responses, experiences with a difficult student or resident, or a request to develop a treatment guideline that is outside the clinician's usual area of expertise.

15. Answer: B

A methodological flaw that results in the collection and reporting of incorrect data would be considered a "fatal flaw" that no amount of rewriting or reanalysis could correct. Poor writing can be corrected with revision by the authors or during copyediting, but if the study is well conducted and has value, this would not necessarily be a reason to recommend rejection so option A is incorrect. Disagreements concerning statistical analysis are

not uncommon; however, the authors may have a valid explanation or be able to revise the statistical analysis if it is not a major departure from the original intent of the study meaning option C is incorrect. It is also not uncommon for the abstract to disagree in some way with the body of the manuscript, and there is an opportunity to correct that during revisions so option D is also incorrect.

TOXICOLOGY

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Learning Objectives

1. Describe the epidemiology for acute poisonings in the United States.
2. Distinguish the common clinical toxidromes associated with acute poisonings.
3. Describe the general management of a patient with an acute overdose.
4. Assess the gastric decontamination strategies for an acute overdose.
5. Examine the options for the management of selected toxins.
6. Assess a patient with clinical acute overdose, and develop a patient care plan according to current evidence.
7. Identify the adverse effects and monitoring of the patient who is poisoned.

Abbreviations in This Chapter

ABC	Airway, breathing, and circulation
ED	Emergency department
HIET	Hyperinsulinemic euglycemic therapy
ICU	Intensive care unit
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant

Self-Assessment Questions

Answers and explanations to these questions can be found at the end of this chapter.

1. A 38-year-old woman with type 2 diabetes is admitted for confusion and altered mental status. She has an active prescription for glipizide 10 mg by mouth twice daily, but she cannot respond to further questioning. Her vital signs are as follows: blood pressure (BP) 115/65 mm Hg, heart rate (HR) 68 beats/minute, respiratory rate (RR) 15 breaths/minute, and temperature 98.6°F (37°C). Her point-of-care glucose concentration is 45 mg/dL, and she is given 50 mL of 50% dextrose in water intravenously twice. Her follow-up point-of-care glucose concentration is 50 mg/dL after the first dose and 57 mg/dL after the second dose, with no improvement in symptoms. Which is the most appropriate intervention at this time?
 - A. Dextrose
 - B. Glucagon
 - C. Octreotide
 - D. Sodium bicarbonate
2. A 56-year-old man is admitted to the intensive care unit (ICU) after a β -blocker overdose. After administering 2 L of 0.9% sodium chloride and 3 g of calcium gluconate, his vital signs are as follows: BP 70/40 mm Hg, HR 52 beats/minute, and RR 22 breaths/minute. Which therapy is most appropriate at this time?
 - A. Glucagon 5 mg
 - B. Atropine 1 mg
 - C. Insulin 0.1 unit/kg
 - D. Dopamine 2 mcg/kg/minute
3. A 76-year-old woman is admitted to the emergency department (ED) with the chief concern of decreased mental status. Her vital signs are as follows: BP 118/72 mm Hg, HR 57 beats/minute, and RR 17 breaths/minute. She is experiencing nausea, but her physical examination is otherwise normal. Her husband is concerned that she may not be taking her medications properly. Given her presentation, which common toxidrome is most likely in the patient?
 - A. Anticholinergic
 - B. Cholinergic
 - C. Opioid
 - D. Sympathomimetic
4. A 38-year-old woman is admitted to the ICU after a suspected overdose of risperidone. She was initially hypotensive, but she was stabilized after the administration of two 500-mL boluses of lactated Ringer solution. Her BP is now 118/77 mm Hg, HR 75 beats/minute, and RR 16 breaths/minute. A 12-lead electrocardiogram (ECG) shows QT prolongation (corrected QT interval [QTc] = 480 milliseconds), and her chemistry panel is significant for a bicarbonate of 24 mEq/L, potassium of 3.1 mEq/L, and magnesium of 1.8 mg/dL. Which intervention is most appropriate at this time?
 - A. Potassium chloride 20 mEq every hour for two doses
 - B. Activated charcoal 50 g
 - C. Magnesium sulfate 2 g
 - D. Lorazepam 2 mg

5. A 48-year-old man is admitted to the medical floor for community-acquired pneumonia. His medical history is significant for hypertension, hyperlipidemia, and chronic obstructive pulmonary disease (COPD), and he reports occasional alcohol use. He is initiated on levofloxacin 750 mg intravenously daily and nebulizer treatments with albuterol and ipratropium. Twenty-four hours after admission, he is increasingly more confused and has nausea and vomiting. His vital signs are stable: BP 115/68 mm Hg, HR 122 beats/minute, RR 21 breaths/minute, and temperature 99.7°F (37.6°C). The team is concerned about possible alcohol withdrawal and asks for recommendations for initial therapy. Which is the most appropriate treatment for this patient?
- A. Lorazepam 2 mg intravenous push every 4 hours as needed according to the patient's Clinical Institute Withdrawal Assessment for Alcohol Scale (CIWA) score
 - B. Phenobarbital 65 mg by mouth every 8 hours as needed according to the patient's CIWA score
 - C. Propofol continuous infusion
 - D. Clonidine 0.1 mg by mouth every 12 hours
6. A 57-year-old male patient on the medical floor is incorrectly administered a dose of methadone 40 mg by mouth that was written for the patient in the adjoining bed. Two hours later, the nurse finds him unresponsive with the following vital signs: BP 105/67 mm Hg, HR 61 beats/minute, RR 8 breaths/minute, and temperature 98.7°F (37.1°C). The nurse calls for the rapid response team, and, as the team pharmacist, you are asked for a recommendation. Which treatment is most appropriate at this time?
- A. Activated charcoal 50 g
 - B. Naloxone 0.04 mg intravenously
 - C. Whole bowel irrigation
 - D. 1 L of 0.9% sodium chloride
7. A 56-year-old female patient is admitted to the ED after an intentional overdose of 25 amlodipine 10-mg tablets. She is given activated charcoal 50 g, 2 L of 0.9% sodium chloride, and 3 g of calcium gluconate. Her current vital signs are as follows: BP 90/50 mm Hg, HR 107 beats/minute, RR 17 breaths/minute, and temperature 98.7°F (37.1°C). Serum chemistries are as follows: Na 141 mEq/L, K 2.5 mEq/L, Cl 101 mEq/L, HCO₃ 24 mEq/L, blood urea nitrogen (BUN) 19 mg/dL, serum creatinine (SCr) 0.9 mg/dL, and glucose 215 mg/dL. The ED physician wants to initiate hyperinsulinemic euglycemic therapy (HIET). Which is most appropriate to initiate first with respect to HIET?
- A. Give insulin 1 unit/kg.
 - B. Give 50 mL of 50% dextrose in water.
 - C. Warn the physician that full effects may take up to 30 minutes.
 - D. Give 20 mEq of potassium chloride intravenously every hour for four doses.
8. The patient in the previous question is not responding to HIET initiation. Her BP remains low at 70/40 mm Hg, and her HR is now 58 beats/minute. Which is most appropriate to initiate at this time?
- A. Continue HIET, and initiate norepinephrine.
 - B. Continue HIET, and increase the insulin infusion rate.
 - C. Continue HIET, and initiate epinephrine.
 - D. Discontinue HIET, and begin intravenous lipid therapy.

I. EPIDEMIOLOGY

- A. Population based: The American Association of Poison Control Centers releases an annual report based on all the cases submitted by the 55 regional poison centers to the National Poison Data System (Clin Toxicol 2015;53:962-1147).
1. In 2014, 2,165,142 human exposures were reported. Fatalities were reported in 1,835 cases (Table 1).
 2. The most common site of exposure was a residence (71.0%), followed by workplace (1.7%) and school (1.3%).
 3. Most of the reported cases (1,326,789) occurred in children, defined in the report as younger than 20 years. To add perspective, 1,168,321 reported cases were reported in children younger than 12 years.
 4. The most common reasons associated with these exposures were unintentional (79.4%), intentional (16.7%), and adverse reactions (2.5%). Of note, therapeutic errors accounted for 271,737 (12.6%) of all cases. The scenarios reported for therapeutic errors included inadvertent double dosing (29.2%), incorrect medication administered or taken (17.2%), incorrect dose (14.8%), doses administered too close in time (11.6%), and inadvertent exposure to another person's medication (8.4%).
 5. Routes of exposure included ingestion (80.0%), dermal (6.7%), inhalation/nasal (5.8%), and ocular (4.0%). Of the 1,173 exposure related fatalities, the majority were by ingestion (81.4%), followed by inhalation/nasal (10.1%) and parenteral (5.2%).
- B. Management based
1. Only 28.3% of exposures were managed in a health care facility, with 16.5% being managed in critical care units.
 2. Gastric decontamination was used in about half of all exposures (48.6%); however, antidotes were given in only 11.5% of the exposures.
 - a. The most common gastric decontamination strategy was the use of activated charcoal (2.1% of total exposures), followed by other emetic agents (0.62%), cathartics (0.37%), gastric lavage (0.09%), and whole bowel irrigation (0.08%).
 - b. Looking at trends in specific gastric decontamination strategies, ipecac use has declined from about 15% of all cases in 1985 to only 0.006% of all cases in 2014 and is no longer being produced. Use of activated charcoal has also declined, from a high of 7.7% of all cases in 1995 to only 2.1% of all cases in 2014.

Table 1. Top 5 Most Common Medication-Related Toxic Exposures in 2014

Most Common Medication-Related Exposures	% of Total Cases
All human exposures	
Analgesics	11.29
Sedatives/hypnotics/antipsychotics	5.85
Antidepressants	4.36
Antihistamines	4.01
Cardiovascular drugs	3.96
Adult exposures (> 20 yr of age)	
Analgesics	11.86
Sedatives/hypnotics/antipsychotics	10.43
Antidepressants	6.70
Cardiovascular drugs	6.08
Alcohols	4.55

Table 1. Top 5 Most Common Medication-Related Toxic Exposures in 2014 (*continued*)

Most Common Medication-Related Exposures	% of Total Cases
Pediatric exposures (< 5 yr of age)	
Analgesics	9.34
Vitamins	4.49
Antihistamines	4.27
Gastrointestinal preparations	2.65
Dietary Supplements/Herbals/Homeopathic	2.57

Information from: Mowry JB, Spyker DA, Brooks DE, et al. 2014 annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 32nd annual report. Clin Toxicol 2015;53:962-1147.

II. EMERGENCY EVALUATION AND MANAGEMENT

- A. The primary treatment strategy for managing a toxic exposure should focus on stabilizing the patient, with an emphasis on airway, breathing, and circulation (ABC). The most common factor contributing to death from a poisoning or drug overdose is the loss of the protective reflexes of the airway secondary to flaccid tongue, aspiration of gastric contents into the lungs, or respiratory compromise including arrest. Patients should be monitored for vital signs (HR, RR, temperature, and oxygen saturation) and changes in mental status. After stabilization, the DEFG approach can be considered:
 - D: Decontamination
 - E: Enhanced elimination
 - F: Focused antidote therapy
 - G: Get help from a poison control center or toxicologist
- B. Supportive care should be based on specific patient symptoms and may include the administration of intravenous fluids, supplemental oxygen, and advanced airway management. Other potential complications should be assessed, such as presence of rhabdomyolysis, rigidity, or dystonia. Additional tests, such as a 12-lead ECG, chest radiograph, or electroencephalogram may be required. In addition, essential laboratory tests should be conducted and assessed for the presence of an osmolar gap, anion gap acidosis, hyper/hypoglycemia, hyper/hyponatremia, hyper/hypokalemia, renal failure, and liver failure.
 1. Use of “coma cocktail” preparations is controversial and therefore not routinely recommended because they should not replace or substitute for a thorough analysis of the patient (JEMS 2002;27:54-60). Formulations vary, but they typically contain one or more of the following: dextrose, thiamine, and naloxone. The following text presents an overview of the common additives, a rationale for use, and potential controversies.
 - a. Dextrose 50%, 12.5–25 g (25–50 mL) intravenously is administered to treat hypoglycemia; it is recommended to perform point-of-care blood glucose testing to confirm before administration.
 - b. Thiamine 100 mg is administered intravenously to prevent Wernicke encephalopathy; often under-recognized, several doses are typically required to effectively treat.
 - c. Naloxone 0.04–2 mg is administered in a stepwise titration to reverse respiratory depression secondary to opiate overdose; however, this is recommended only in unconscious patients.
- C. Ingestions
 1. A thorough physical examination should be performed.
 2. A medication history and reconciliation should be done, including all prescription medications, over-the-counter agents, and herbal products.

3. The history of the ingestion should be determined, if possible, including the following elements (Ann Emerg Med 1999;33:735-56):
 - a. Timing and route of the exposure, the possible agents involved and their strengths and amounts, and the potential intent of the patient
 - b. History from the prehospital care providers, family members, or other patient advocates
 - c. Onset and progression of any symptoms
4. Some providers advocate for the use of toxidromes, which are a collection of symptoms that occur with particular classes of toxic agents. Toxidromes may help identify the toxic agent and assist in care by helping providers anticipate additional symptoms. Although they may be very useful in the care of an acute poisoning, they should be used with caution because some symptoms may overlap with other classes of toxins or may be absent altogether.
5. Common Toxidromes and Presentation (CHEST 2011;140:795-806) (Crit Care Clin 2012;28:180-198)
 - a. Anticholinergic
 - i. Mechanism of toxicity is through competitive antagonism of the effects of acetylcholine at peripheral muscarinic receptors and central receptors.
 - ii. Signs and symptoms include mydriasis, tachycardia, anhidrosis, dry mucous membranes, hypoactive bowel sounds, altered mental status, delirium, mumbling speech, hallucinations, urinary retention, flushing, and hyperthermia.
 - iii. Common drugs that have anticholinergic activity include antihistamines, antipsychotics, tricyclic antidepressants, and skeletal muscle relaxants.
 - b. Cholinergic
 - i. Mechanism of toxicity is inhibition of acetylcholinesterase causing accumulation of acetylcholine ultimately resulting in overstimulation of muscarinic and nicotinic receptors.
 - ii. Signs and symptoms include bradycardia, bronchospasm, bronchorrhea, central nervous system depression, confusion, diarrhea, diaphoresis, urination, emesis, lacrimation, miosis, salivation, confusion, tachycardia, hypertension, muscle weakness/twitching, and wet mucous membranes.
 - iii. Common drugs that have cholinergic activity include organophosphates, nerve agent exposure, and physostigmine.
 - c. Opioid
 - i. Mechanism of toxicity is stimulation of opioid receptors causing a decrease in autonomic activity.
 - ii. Signs and symptoms include sedation, miosis, decreased bowel sounds, decreased respirations, bradycardia, and hypotension.
 - iii. Common drugs that have opioid activity include heroin, morphine, codeine, synthetic opioids, and dextromethorphan (in large quantities).
 - d. Sympathomimetic
 - i. Mechanism of toxicity is through an increase in sympathetic tone through release of catecholamines, inhibition of reuptake, by direct receptor stimulation, and alterations in neurotransmitter metabolism.
 - ii. Signs and symptoms include agitation, delirium, myoclonus, mydriasis, tachycardia, hypertension, hyperthermia, and diaphoresis.
 - iii. Common drugs that have sympathomimetic activity include cocaine, methamphetamine, pseudoephedrine, and caffeine.

6. Drug screens are used in acute toxic ingestions, the most common of which is the qualitative urine screen. This method tests for the presence of a substance, but it cannot detect the amount of substance present. If a toxin is known, a quantitative drug screen may be used to confirm the exact amount present. Although urine drug screens may vary by institution, they may include amphetamines, barbiturates, benzodiazepines, cocaine, MDMA (ecstasy), methamphetamines, opiates, THC (marijuana), and tricyclic antidepressants (TCAs). Urine screens are not considered comprehensive; therefore, the presence of additional agents should be tested for (e.g., acetaminophen, salicylates).
 - a. A negative screen does not exclude the presence of a toxic substance, especially if the presumed agent is not present on the screen. Many agents are not identified by their designated screen; this is especially an issue with standard amphetamines, benzodiazepines, and opiate screens.
 - b. A positive test also does not necessarily confirm the diagnosis because another agent may be present but at concentrations below a detectable threshold. In addition, a positive test does not indicate that the patient is intoxicated on the particular substance (e.g., cocaine is positive for 3 days; however, its effects last only a few hours) or that the agent ingested is the exact agent that is screened (e.g., bupropion causes a positive amphetamine screen).

Patient Case

1. 1. A 53-year-old man (height 74 inches, weight 97 kg [215 lb]) arrives in the ED confused and disoriented. He cannot provide any information about his condition or medical history. Vital signs are as follows: BP 85/50 mm Hg, HR 120 beats/minute, RR 28 breaths/minute, and temperature 99.2°F (37.3°C). On physical examination, an unmarked pill bottle is found in his pocket. Two tablets remain, and a possible drug overdose is suspected. Which is most appropriate to do first for this patient?
 - A. Send a quantitative urine drug screen.
 - B. Stabilize the patient's ABC.
 - C. Order a coma cocktail.
 - D. Try to identify the tablets in a drug database.

III. GASTRIC DECONTAMINATION/ENHANCED ELIMINATION

- A. Many strategies for gastric decontamination are used to try to remove toxins or prevent further absorption. No particular strategy is preferred to another; each has certain advantages and disadvantages, and the risks and benefits must be considered before use. Consensus statements from the American Academy of Clinical Toxicology and the European Association of Poisons Centres and Clinical Toxicologists recommend against the routine use of any decontamination strategy but suggest that these strategies play a role in individualized care after a poison exposure. Table 2 lists the common dosing strategies for general decontamination and enhanced elimination.
- B. Ipecac
 1. Ipecac is no longer manufactured in the United States because of concerns for safety and ability to improve outcomes for patients who have been poisoned.
 2. Mechanism of action is to induce vomiting through irritation of the gastric mucosa and stimulation of the chemoreceptor trigger zone in the medulla.

3. It is no longer recommended because of its inability to improve patient outcomes and because of safety concerns.
4. Recent guidelines recommend ipecac (if available) to be given only under a specific recommendation from a poison control center, ED physician, or other qualified medical personnel when all the following conditions are met (Clin Toxicol 2013;51:134-9; Clin Toxicol 2005;43:1-10):
 - a. No specific contraindication exists for use.
 - b. There is a substantial risk of serious toxicity to the patient.
 - c. No alternatives are available or considered effective to reduce the toxin absorption.
 - d. A delay of more than 1 hour is expected before arrival to a medical facility.
 - e. Use of ipecac will not adversely affect a more definitive treatment option.

C. Gastric Lavage

1. Gastric lavage is performed by inserting a larger-bore catheter tube (36–40 French for adults and 24–28 French for children) with several holes at the distal end into the stomach. Aliquots of warmed tap water are then instilled until there is clearing of aspirated fluid.
2. The efficacy is highly variable and diminishes over time; therefore, it is optimal to perform within 60 minutes of ingestion.
3. Recent guidelines emphasize that gastric lavage has not been proved to decrease the severity of illness, improve recovery times, or improve outcomes (Clin Toxicol 2013;51:140-6).
4. Should be considered only for life-threatening ingestions when it can be safely performed within 30–60 minutes.
5. Even in life-threatening overdoses, it may not be beneficial. Gastric lavage should not be performed routinely, if at all, for treating the patient who is poisoned. In the rare situation when it might be appropriate, clinicians should consider treatment with activated charcoal or observation and supportive care in place of gastric lavage (Clin Toxicol 2013;51:140-6).
6. Contraindications for gastric lavage include patients with craniofacial abnormalities, concomitant head trauma, unprotected airway, and increased risk of and severity for aspiration and those at risk of gastrointestinal (GI) hemorrhage or perforation. Patients with decreased consciousness require oral or nasal intubation before the procedure.
7. Complications associated with gastric lavage include aspiration, laryngospasm, perforation of the esophagus or stomach, arrhythmias, fluid imbalance, hyponatremia, and small conjunctival hemorrhages.

D. Cathartics

1. Used to reduce the transit time of toxins and hence absorption, as well as in combination with charcoal to decrease constipating effects.
2. Cathartics have conflicting data regarding decreased transit time in the GI tract and have no data to support improved patient outcomes (J Toxicol Clin Toxicol 2004;42:243-53).
3. Cathartic use is not recommended; if used, it should be limited to a single dose.
4. Contraindications to cathartic use include absence of bowel sounds, recent GI surgery, intestinal perforation or obstruction, hypotension, electrolyte disturbances, and renal insufficiency (for magnesium-based cathartics).
5. Complications include nausea, dehydration, hypotension, and magnesium imbalances.

E. Activated Charcoal

1. Activated charcoal is an adsorbent that works by binding the toxin throughout the GI tract to reduce systemic absorption. Although activated charcoal binds most substances, Table 3 lists the agents for which activated charcoal is NOT recommended.
 - a. Acids and alkalis should be avoided because charcoal may cause vomiting, which can be damaging in these ingestions. The black color and thickness of the activated charcoal may also cause discoloration of the stomach lining and therefore interfere with endoscopy.
 - b. Alcohols bind poorly; therefore, large doses are needed, which are difficult to ingest.
 - c. Cyanide will bind, but not with as much activity as other substances. Because the toxic dose of cyanide is so small, normal doses of activated charcoal may be ineffective.
 - d. Hydrocarbons may lead to a significant risk of aspiration.
2. It is optimal to administer activated charcoal within 60 minutes of the toxin ingestion to maximize efficacy.
3. If significant nausea occurs, it is recommended to administer an antiemetic. When choosing an antiemetic, potential drug and symptom interactions should be considered as well.
4. Complications include aspiration, accidental administration into the lung, emesis, constipation, and gastric obstruction.
5. Contraindications include an unconscious state or an inability to otherwise protect the airway without endotracheal intubation and recent GI surgery.
6. Multidose activated charcoal is a method described to enhance the elimination of certain toxins. It is not more effective in reducing morbidity or mortality than single-dose charcoal, but it may be administered to enhance elimination in life-threatening ingestions caused by medications that undergo significant enterohepatic recirculation with active enterohepatic metabolites (J Toxicol Clin Toxicol 1999;37:731-51).

F. Whole Bowel Irrigation

1. Whole bowel irrigation is a strategy for cleansing the bowel to remove potential toxins by administering an osmotic polyethylene glycol solution.
2. Not recommended for routine use, but may be useful in potentially life-threatening ingestions of medications with long half-lives, sustained-release dosage forms, or enteric-coated formulations. Specifically useful for certain toxic substances not adsorbed by activated charcoal (e.g., lithium and iron). May also be beneficial for iron overdoses and for packers or stuffers of illicit substances. Concurrent administration of activated charcoal and whole bowel irrigation may decrease the efficacy of charcoal.
3. Complications of the polyethylene glycol electrolyte solutions include anaphylaxis, angioedema of the lips, aspiration, Mallory-Weiss tear, and esophageal perforation.
4. Contraindications include bowel obstruction, perforation, ileus, and in patients with recent bowel surgery. A kidney-ureter-bladder radiograph may be used to rule out these contraindications.

G. Urine Alkalinization

1. Urine alkalinization is a strategy to improve the elimination of toxins by increasing the urine pH to levels of 7.5 or greater with the administration of sodium bicarbonate or sodium acetate (J Toxicol Clin Toxicol 2004;42:1-26).
2. Specific substances that may benefit from this strategy include salicylates, phenobarbital, chlorpropamide, and other weak acids with intrinsic urinary clearance.
3. Contraindications include acute and chronic renal failure and preexisting heart failure owing to the volume of fluid required for this treatment strategy.
4. Complications include hypokalemia, hyponatremia, hypocalcemia, cerebral vasoconstriction, and coronary vasoconstriction.

5. To administer urine alkalization, it is recommended to check baseline blood chemistries, electrolyte values, and an arterial blood gas and to correct any fluid or electrolyte deficits (especially potassium because alkalemia will push potassium intracellularly). Hypokalemia will make it impossible to get the urine alkaline because of the K^+-H^+ exchange in the kidneys, which will excrete H^+ into urine if K^+ is low.
6. Guideline-recommended monitoring includes urine pH every 15–30 minutes (every 30–60 minutes is more accepted in clinical practice) until the goal pH level of 7.5–8.5 is achieved, followed by every hour; serum potassium concentrations, central venous pressure, and arterial blood gases should be measured hourly.

Table 2. Common Dosage Strategies for General Decontamination and Enhanced Elimination

Decontamination/ Elimination Strategy	Pediatric Dosing	Adult Dosing
Gastric lavage ^a	10-mL/kg aliquots, followed by return of an equal amount	200- to 300-mL aliquots, followed by return of an equal amount
Cathartics Magnesium citrate: Sorbitol:	4 mL/kg 4.3 mL/kg (35% solution)	240 mL 1–2 mL/kg (70% solution)
Activated charcoal Single dose Multidose	Up to 1 yr of age: 0.5–1 g/kg (usually 10–25 g) 1–12 years: 0.5–1 g/kg (usually 25–50 g) 0.5–1 g/kg (25–50 g), followed by 0.25–0.5 g/kg (10–25 g) every 4 hr	> 12 years and adults: 25–100 g (doses > 50 g may induce vomiting) ^b 50 g, followed by 25–50 g every 4 hr
Whole bowel irrigation ^c	9 mo to 6 yr: 500 mL/hr 6–12 yr: 1000 mL/hr	> 12 yr and adults: Goal is 2000 mL/hr (initiated at 500 mL/hr and doubled every 30 min)
Urine alkalization ^d	25–50 mEq intravenously for 1 hr	225 mEq intravenously for 1 hr

^aSterile water or 0.9% sodium chloride; may repeat until the return fluid is clear and absent of particulate matter.

^bUpper limit may vary depending on the capacity of the stomach.

^cPolyethylene glycol electrolyte lavage solutions; dose until the rectal effluent is clear or the desired effect has been achieved.

^dSodium bicarbonate solution; additional boluses can be given hourly (or begin a continuous infusion at this hourly rate) to maintain a urine pH of 7.5–8.5.

Table 3. Agents for Which Activated Charcoal Is NOT Recommended

Substance	Examples
Acids	Boric acid, mineral acids
Alcohols	Ethanol, ethylene glycol, methanol
Alkalis	Bleach, cleaning solutions, dishwasher detergents, lye
Carbamates	Insecticides, neostigmine, physostigmine
Cyanide	Cyanogen chloride, hydrogen cyanide, potassium cyanide, sodium cyanide
Hydrocarbons	Gasoline, kerosene, petroleum oils
Metals	Arsenic, iron, lead, lithium, mercury
Organic solvents	Acetic acid, acetone, ethylene glycol, glycerin, toluene
Organophosphates	Antihelminthic drugs (trichlorfon), insecticides (malathion, parathion), herbicides

IV. ACETAMINOPHEN

A. Background

1. Acetaminophen is consistently one of the most common toxic drug exposures.
2. Accounted for 50,396 exposures (as a single agent) and resulted in 65 deaths in 2014.
3. Acetaminophen ingestions of 4 g or greater may cause injury in select patients. In general, acute doses of 150 mg/kg or 7.5 g in adults and 200 mg/kg in children are considered toxic. It is recommended that doses exceeding this threshold be managed in a health care facility.
4. The mechanism of toxicity is caused by the active metabolite N-acetyl-p-benzoquinoneimine (NAPQI), which can lead to oxidant cell injury, hepatic failure, and death.
5. Around 90% of acetaminophen undergoes phase II conjugation to glucuronide and sulfate conjugates that are excreted in the urine. An additional 2% is excreted unchanged in the urine. The remaining amount (8%–10%) is converted by cytochrome P450 (CYP2E1) to NAPQI. NAPQI is normally converted by glutathione to cysteine conjugates, which are renally excreted. In an overdose, the sulfation and glucuronidation pathways become saturated, leading to glutathione depletion and a subsequent buildup of NAPQI (Clin Liver Dis 2013;17:587-607).

B. Clinical Presentation – Four clinical phases are associated with an acetaminophen toxicity (time intervals are estimated and may vary with individual patients).

1. Phase I occurs within the first 24 hours after ingestion. Patients may present with minimal or no signs of distress. Potential signs and symptoms include nausea, vomiting, diaphoresis, and anorexia.
2. Phase II occurs 24–48 hours after exposure and is marked by initial damage to the hepatocytes. Patients may present with right upper quadrant pain, increases in liver transaminases, elevated total bilirubin concentrations, and prolonged prothrombin time.
3. Phase III occurs 72–96 hours after initial exposure and is the peak of the hepatotoxic effects. Patients may present with lactic acidosis, acute renal failure, acute pancreatitis, and fulminant hepatic failure, as evidenced by jaundice, extensive coagulopathies, hypoglycemia, and hepatic encephalopathy.
4. Phase IV occurs about 1 week after exposure and marks the recovery phase if the patient survives phase III.

C. Treatment

1. The goal of treatment is to prevent the development of hepatic toxicity and reduce mortality.
2. Gastric decontamination with a single dose of activated charcoal can be considered if the patient presents within the first hour after exposure, is not vomiting, and has no alterations in mental status.
3. Antidote therapy is recommended with acetylcysteine. The mechanism of action for acetylcysteine is to increase the synthesis and bioavailability of glutathione, substituting for glutathione by binding to the reduced sulfur group of NAPQI, and supplying a substrate for sulfation, thereby increasing nontoxic metabolism.
4. Guidelines suggest that acetylcysteine treatment be administered to patients within the first 8 hours of exposure if they can be stratified as being at possible or probable risk of hepatotoxicity by the Rumack-Matthew nomogram (Figure 1). If patients cannot be stratified because of unknown time of ingestion, they should receive acetylcysteine if any of the following conditions apply: increased alanine aminotransferase (ALT) concentration, serum acetaminophen concentrations greater than 20 mcg/mL, or history of chronic ingestions exceeding 4 g/day with an elevated serum ALT concentration (Ann Emerg Med 2007;50:292-313).
 - a. This includes patients presenting more than 24 hours postingestion with evidence of hepatotoxicity.
 - b. Limitations to use of the Rumack-Matthew nomogram include the following (Ann Emerg Med 2007;50:292-313):
 - i. Presentation more than 24 hours postingestion
 - ii. An unknown or unreliable history of ingestion

- iii. Overdoses with extended-release formulations
 - iv. Chronic or repeated supratherapeutic ingestions
 - v. Patients with preexisting hepatic disease, chronic alcohol use, or concurrent medications metabolized by the CYP system
5. Intravenous acetylcysteine is advantageous because of its decreased overall administration time (21 hours vs. 72 hours for oral) and minimal GI adverse effects. If the commercially available intravenous acetylcysteine formulation is not available and cannot be obtained in a timely fashion, poison control centers can be contacted for instructions on compounding the inhalational acetylcysteine formulation for intravenous use. It is not recommended to use this strategy except for emergencies.
 6. Oral acetylcysteine is dosed for 18 total doses; doses may be repeated if emesis occurs within 1 hour of a dose. To improve palatability, doses may be diluted in juice or carbonated beverages in a covered cup with a straw. Antiemetics may be administered if significant nausea or vomiting occurs. Table 4 discusses the dosing strategies for oral and intravenous administration of acetylcysteine.
 7. Although treatment guidelines recommend 18 total doses of acetylcysteine administered throughout 72 hours for oral acetylcysteine therapy and 21 hours of the intravenous infusion of acetylcysteine, many poison control centers recommend early discontinuation (or prolonged therapy) if the following conditions are met (Ann Emerg Med 2007;50:280-1):
 - a. Serum acetaminophen concentrations are undetectable or less than 10 mcg/mL.
 - b. ALT concentrations are normal (60 IU/L or less) or improving. Some clinicians also advocate an international normalized ratio (INR) of 1.3 or less.
 - c. The patient is clinically improved.
 8. Adverse effects (intravenous): Anaphylactoid reactions (rash, urticarial, pruritus), hyponatremia, hypervolemia, seizures (pediatric patients with unadjusted volume)
 9. Adverse effects (oral): Nausea, vomiting, anaphylactoid reactions (rare)
 10. Patients experiencing mild anaphylactoid reactions (rash, pruritus, flushing) can be effectively treated with diphenhydramine, and acetylcysteine therapy can be resumed.
 11. Medication errors may occur because of the complex dosing regimens (Ann Pharmacother 2008;42:766-70). Common errors include delays in therapy, incorrect dosages, and incorrect infusion rates.
- D. Monitoring
1. Patients should be monitored for improvement in vital signs and mental status.
 2. The following laboratory values should be monitored periodically for improvement as well as for potential worsening.
 - a. ALT, aspartate aminotransferase (AST), total bilirubin, and prothrombin time
 - b. BUN and SCr
 - c. Serum electrolytes
 - d. Fulminant hepatic failure: Serum bicarbonate, serum lactate, arterial blood gas, serum glucose, and ammonia concentrations

Table 4. Acetylcysteine Dosage

Route	Dose
Oral	Loading dose: 140 mg/kg Maintenance doses: 70 mg/kg every 4 hr for a total of 17 doses (72 hr)
Intravenous	Loading dose: 150 mg/kg (max 15 g ^a) in 200 mL of 5% dextrose in water infused for 60 min Maintenance dose: 50 mg/kg (max 5 g ^a) in 500 mL of 5% dextrose in water infused for 4 hr followed by 100 mg/kg (max 10 g ^a) in 1000 mL of 5% dextrose in water infused for 16 hr Patients weighing < 40 kg require reduced volume administration

^aAcetadote has not been well studied in patients weighing more than 100 kg; dose limits are recommended by the manufacturer.

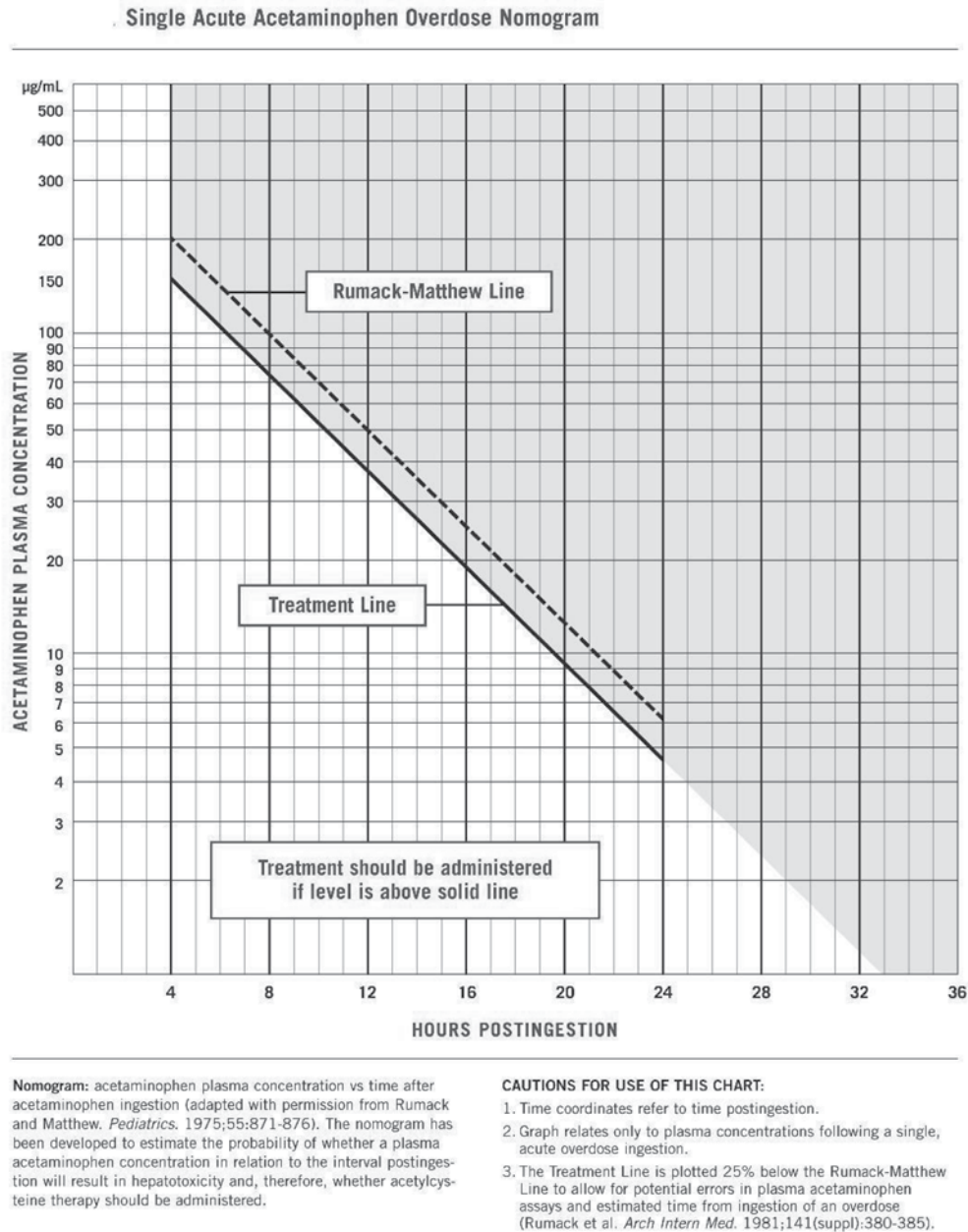


Figure 1. Rumack-Matthew nomogram.

Reprinted from: Tylenol for Healthcare Professionals. Guidelines for the Management of Acetaminophen Overdose. McNeil Consumer & Specialty Pharmaceuticals. Available at www.tylenolprofessional.com/guidelines-and-studies.html. Accessed October 21, 2016.

Patient Case

Questions 2 and 3 pertain to the following case.

A 42-year-old woman (height 66 inches, weight 79.2 kg [176 lb]) presents to the ED with the chief concern of flu-like symptoms. Her symptoms include headache, congestion, severe nausea and vomiting, abdominal pain, and some confusion. She has been taking acetaminophen 500-mg caplets as needed for her symptoms, but she just ran out of the bottle she purchased yesterday. On presentation, she is alert and oriented. Her vital signs are as follows: BP 135/90 mm Hg, HR 83 beats/minute, RR 18 breaths/minute, and temperature 101.8°F (38.8°C). An acetaminophen concentration on admission was 100 mcg/mL, AST 560 IU/L, and ALT 310 IU/L. The physician wants to begin general management.

2. Which general management strategy is most indicated for this patient?
 - A. 10% magnesium citrate 240 mL per tube once
 - B. Continued stabilization of the patient and good supportive care
 - C. Gastric lavage
 - D. Charcoal 50 g once
3. Which is the most appropriate treatment for her acetaminophen toxicity?
 - A. Give acetylcysteine 11,200 mg oral bolus, followed by 5600 mg orally every 4 hours for 17 doses.
 - B. Give acetylcysteine 11,200 mg intravenous bolus, followed by 5600 mg intravenously every 4 hours for 12 doses.
 - C. Give acetylcysteine 12,000 mg intravenously over 1 hour, followed by 4000 mg intravenously over 4 hours; then 8000 mg intravenously over 16 hours.
 - D. Acetylcysteine therapy is not indicated in this patient.

V. SALICYLATES**A. Background**

1. Salicylates as a single agent (not in combination with other agents) accounted for 9,825 overdoses and 13 deaths in 2014. These numbers, which include overdoses of both adult and pediatric formulations of acetylsalicylic acid, are often underreported because these products are not typically recognized as a potential cause.
2. However, because of the development of child-resistant containers, aspirin overdose causing accidental death in children has reduced drastically.

B. Clinical Presentation

1. The mechanism of toxicity for salicylates is through the interference with aerobic metabolism owing to the uncoupling of mitochondrial oxidative phosphorylation, leading to increases in anaerobic metabolism, which causes a significant lactic acidosis (Emerg Med Clin North Am 2007;25:333-46). This also leads to hypoglycemia because of glycogen depletion, gluconeogenesis, and catabolism of proteins and free fatty acids. Salicylates also directly stimulate the respiratory center, leading to hyperventilation and respiratory alkalosis. Secondary complications from hyperventilation include dehydration and compensatory metabolic acidosis.

2. Salicylates are readily absorbed in the stomach and small intestine and are then conjugated with glycine in the liver to the active component, salicylic acid. In overdoses, the liver cannot metabolize the excess drug, and most is then excreted unchanged by the kidneys (Postgrad Med 2007;121:162-8).
3. The most common clinical symptoms associated with a salicylate overdose are hyperventilation (respiratory alkalosis), tinnitus, and GI irritation. Symptoms may vary depending on the serum salicylate concentration; however, these may be low to normal early in the presentation (Postgrad Med 2007;121:162-8):
 - a. Serum concentration less than 30 mg/dL: Asymptomatic
 - b. Serum concentration 15–30 mg/dL: Therapeutic concentrations
 - c. Serum concentration 30–50 mg/dL: Hyperventilation, nausea, vomiting, tinnitus, dizziness
 - d. Serum concentration 50–70 mg/dL: Tachypnea, fever, sweating, dehydration, listlessness
 - e. Serum concentration greater than 70 mg/dL: Coma, seizures, hallucinations, stupor, cerebral edema, dysrhythmias, hypotension, oliguria, renal failure
 - f. Acute salicylate toxicity is typically associated more with the GI symptoms; chronic toxicity is more associated with the central nervous system (CNS)-type symptoms.
 - g. Absorption may be delayed up to 36 hours because of gastric pylorospasm, bezoar formation (precipitate concretions because of poor solubility), or enteric-coated formulations; therefore, these ranges should be used with caution because they may not correlate with actual symptoms (Am J Emerg Med 2010;28:383-4).

C. Treatment

1. There is no antidote for salicylate poisoning; the goals of therapy are to limit the additional absorption of salicylates and to provide supportive care.
2. Maintain a patent airway and assist ventilation, if necessary. Ensure adequate ventilation to prevent respiratory acidosis; however, do not mechanically ventilate patients because this will interfere with the patient's ability to appropriately compensate and maintain pH.
3. Gastric decontamination with a single dose of activated charcoal is recommended for acute ingestions and if the patient is alert with the absence of vomiting.
4. Administer intravenous crystalloid fluids to maintain BP.
5. Administer intravenous glucose for hypoglycemia or significant neurologic symptoms.
6. Urine alkalinization is recommended to enhance renal elimination and increase the glomerular filtration rate.
 - a. Administration strategies that have been described in the literature:
 - i. Administer 250 mL of sodium bicarbonate 8.4% over 1 hour; then administer additional 50-mL boluses as needed to maintain a goal urine pH range of 7.5–8.5.
 - ii. Administer 150 mL of sodium bicarbonate 8.4% in 1 L of 5% dextrose in water at 2–3 mL/kg/hour to maintain a urine output of 1–2 mL/kg/hour. Do not allow the serum pH to fall below 7.4.
 - b. Oral bicarbonate is not recommended because it may enhance salicylate absorption.
 - c. Discontinue therapy once the serum salicylate concentrations are less than 30 mg/dL or there is a resolution of clinical symptoms.
7. Replace serum potassium concentrations, if necessary.
8. Consider hemodialysis for any of the following (Postgrad Med 2007;121:162-8):
 - a. Acute renal insufficiency
 - b. End-organ damage (severe pulmonary edema, seizures, rhabdomyolysis)
 - c. Altered mental status
 - d. Deterioration of clinical status
 - e. Severe acid-base disturbances
 - f. If hemodialysis is not effective, extracorporeal treatment may be considered.

D. Monitoring

1. Patients should be monitored for up to 24 hours because of the possibility of delayed or impaired absorption.
2. Monitor RR, and support as needed; caution is advised if intubation is required because of a requirement for an increased minute ventilation (Am J Emerg Med 2010;28:383-4).
3. During urine alkalization, monitor for signs and symptoms of fluid overload, hypernatremia, hypokalemia, and worsening alkalemia.

Patient Case

4. A 62-year-old man presents to the ED with the chief concern of nausea, tachypnea, and flu-like symptoms. He is alert and oriented and can communicate that his symptoms have been worsening for the past 2 days. He has been taking a combination cold product, which he thinks has helped. His medical history is significant for a stroke, for which he takes aspirin 325 mg by mouth daily, and hypertension, for which he takes amlodipine 5 mg by mouth daily. His vital signs are as follows: BP 135/82 mm Hg, HR 78 beats/minute, RR 29 breaths/minute, and temperature 100.2°F (37.9°C). Arterial blood gas results are as follows: pH 7.52, P_{CO_2} 25, and HCO_3 20 mEq/L. A salicylate concentration is sent, which is 25 mg/dL. Which treatment management strategy is most indicated for this patient?
 - A. Sodium chloride infusion
 - B. Urgent endotracheal intubation
 - C. Sodium bicarbonate infusion
 - D. Hemodialysis

VI. OPIOIDS**A. Background**

1. Opioids as a single agent (not in combination with other agents) accounted for 19,688 overdoses and 58 deaths in 2014 because of non-combination opioid products. The Centers for Disease Control and Prevention reports that almost 15,000 deaths are caused by prescription opioid painkillers annually.
2. The most common agents associated with a toxicologic event were tramadol, oxycodone, methadone, morphine, and buprenorphine.
3. The most common agents associated with a toxicologic death were methadone, oxycodone, fentanyl, morphine, and tramadol.
4. Opioids act at the mu, delta, and kappa opioid receptors, although mu is responsible for most of the opioids' clinical effects.

B. Clinical Presentation

1. The most common clinical symptoms associated with opioid overdose are respiratory depression (defined as fewer than 12 breaths/minute), coma, miosis, and hypoactive bowel sounds.
2. Additional findings may include stupor, hepatotoxicity, acute renal failure, rhabdomyolysis, compartment syndrome, hypothermia, and seizures (N Engl J Med 2012;367:146-55).

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3. Diagnostic workup (Pharmacotherapy: A Pathophysiologic Approach, 9e. New York: McGraw-Hill, 2014):
 - a. 12-lead ECG to test for QT prolongation – Methadone may cause QT prolongation and potentially torsades de pointes.
 - b. Arterial blood gas to monitor for respiratory acidosis
 - c. Standard chemistry panel for electrolyte and glucose abnormalities – Creatinine kinase (CK), BUN, and SCr for signs of rhabdomyolysis
 - d. Pulse oximetry
 - C. Treatment
 1. Stabilize the airway, provide supplemental bag-valve mask respirations if needed, and administer supplemental oxygen. Establishment of an airway, if needed, by endotracheal intubation.
 2. Administer intravenous crystalloid fluids to maintain BP.
 3. Gastric decontamination with a single dose of activated charcoal may be considered only if the patient presents within the first hour after exposure and is awake with an intact airway. Whole bowel irrigation can be considered for extended-release formulations or for packers or stuffers of illicit substances (including ingestion of fentanyl patches).
 4. Antidote therapy (N Engl J Med 2012;367:146-55):
 - a. Naloxone is a competitive antagonist at the opioid receptor.
 - b. The intravenous route is preferred, but naloxone is also effective through the endotracheal, intramuscular, intranasal, inhalational, intraosseous, or intrapulmonary route.
 - c. Onset of action of intravenous naloxone is 2 minutes, with a duration of 30–120 minutes.
 - d. Dosing may be affected by the specific opioid agent and dose, affinity for the mu-receptor, and patient weight.
 - e. Initial dose is 0.04 mg in adult patients and 0.1 mg/kg in pediatric patients; if no response, the dose is increased every 2–3 minutes to 0.5 mg, 2 mg, 4 mg, and 10 mg, followed by 15 mg.
 - f. It is recommended that a continuous infusion be initiated at a dose of two-thirds the effective bolus dose per hour (0.04–4 mg/hour) for patients requiring subsequent naloxone doses to sustain effect (Ann Emerg Med 1986;15:566-70).
 - g. Intranasal administration appears to be safe and effective when the intravenous route is not available. The dose is administered by attaching a 2 mg/2 mL naloxone prefilled syringe to an atomizer and spraying an equal portion (1 mL) of the contents into each nostril.
 - h. Adverse effects are rare and may be more related to a return of sympathetic response to opioid withdrawal.
 - i. If no effect is seen at the higher naloxone doses, consider other causes such as secondary or alternative agents.
 - D. Monitoring – Observe respiratory status and vital signs for a minimum of 4 hours after the last dose of naloxone or discontinuation of the continuous infusion. Closely monitor for signs and symptoms of opioid withdrawal syndrome, such as anxiety, piloerection, heightened sensation to pain, abdominal cramps, diarrhea, and insomnia.
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VII. ALCOHOLS (METHANOL AND ETHYLENE GLYCOL)

A. Background

1. Alcohol poisonings (methanol and ethylene glycol) are not as common as poisonings with other substances, accounting for 2.7% of all cases in 2014 (National Poison Data System), but they can be serious and potentially fatal.
2. Methanol is commonly found in products such as windshield washer fluid, antifreeze, brake and carburetor fluids, and cooking products.
3. Ethylene glycol is commonly found in products such as antifreeze, de-icing solutions, refrigerants, and brake fluids.
4. Toxicity of both agents is caused by the breakdown to toxic metabolites by alcohol dehydrogenase and aldehyde dehydrogenase.
 - a. Methanol is converted to formaldehyde and then to formic acid, which results in an anion gap acidosis and ocular toxicity.
 - b. Ethylene glycol is converted to glycoaldehyde and then to glycolic acid, followed by glyoxylic acid, and, eventually, oxalic acid. Glycolic acid results in an anion gap acidosis and CNS toxicity. Oxalic acid results in CNS toxicity and renal toxicity because of the formation of calcium oxalate crystals.

B. Clinical Presentation

1. Common symptoms include inebriation, altered mental status, nausea, vomiting, hematemesis, nystagmus, and depressed reflexes. In rare cases of ethylene glycol toxicity, patients may present with tetany caused by hypocalcemia.
2. Early in therapy, an osmolar gap will be present, but this will diminish as the parent compound is metabolized.
 - a. As the osmolar gap declines, the anion gap will rise, resulting in a significant metabolic acidosis.
 - b. Calculations:
 - i. Osmolar gap:
 $(\text{sodium} \times 2) + (\text{glucose}/18) + (\text{BUN}/2.8)$
 - ii. Osmolar gap with ethanol ingestion:
 $(\text{sodium} \times 2) + (\text{glucose}/18) + (\text{BUN}/2.8) + (\text{ethanol}/4.6)$
 - iii. Osmolar gap with methanol ingestion:
 $(\text{sodium} \times 2) + (\text{glucose}/18) + (\text{BUN}/2.8) + (\text{methanol}/3.2)$
 - iv. Osmolar gap with ethylene glycol ingestion:
 $(\text{sodium} \times 2) + (\text{glucose}/18) + (\text{BUN}/2.8) + (\text{ethylene glycol}/6.2)$
 - v. Anion gap:
 $\text{Na} - (\text{Cl} + \text{HCO}_3)$
3. Methanol and ethylene glycol serum concentrations may be monitored to determine severity and to guide therapy in conjunction with an anion gap metabolic acidosis. Often, the ability to obtain these serum concentrations is not readily available and may take several hours to perform; therefore, therapy should not be delayed.

C. Treatment

1. Treatment is focused on blocking the toxic alcohol metabolism and allowing it to be excreted unchanged in the urine.
2. Gastric decontamination is not recommended.
3. Fomepizole is the preferred antidote because of its predictable response, ease of dosing, and lack of contraindications to use.
 - a. Mechanism of action is competitive inhibition of alcohol dehydrogenase.

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- b. Dosing is a 15-mg/kg intravenous bolus; then 10 mg/kg every 12 hours for four doses; then 15 mg/kg every 12 hours until methanol/ethylene glycol concentrations are less than 20 mg/dL.
 - c. Oral administration is effective and may be considered if intravenous access cannot be established (Clin Toxicol 2008;46:181-6).
 - d. After 48 hours, fomepizole induces its own metabolism, requiring dosage increases.
 - e. Therapy is discontinued when methanol/ethylene glycol concentrations are less than 20 mg/dL. If the patient is still symptomatic with a normal pH, further workup is warranted, and hemodialysis may be indicated.
 - f. Hemodialysis increases the clearance of fomepizole; therefore, doses must be administered every 4 hours during hemodialysis.
 - g. Adverse effects may include headache, nausea, dizziness, abdominal pain, hypotension, and bradycardia.
- 4. Ethanol may be administered by diluting 95% alcohol for intravenous, oral, or per-tube administration.
 - a. Mechanism of action is competitive inhibition of alcohol dehydrogenase.
 - b. Alcohol dehydrogenase has a higher affinity for ethanol.
 - c. Intravenous alcohol preparations are no longer commercially available and must be compounded.
 - d. Initial dosing is 600–700 mg (7.6–8.9 mL/kg) of a 10% solution, followed by an infusion of 66 mg/kg/hour (0.83 mL/kg/hour). The infusion dose may be initiated at 154 mg/kg/hour (1.96 mL/kg/hour) in chronic drinkers. The goal is to maintain a serum ethanol concentration of 100 mg/dL (0.1%) until symptoms have diminished and methanol or ethylene glycol serum concentrations are undetectable. (Ann Emerg Med 2009;53:439-50).
 - e. Disadvantages include frequent monitoring and ICU admission in some institutions.
 - f. Adverse effects include CNS depression, nausea, vomiting, abdominal pain, polyuria, and hypoglycemia (especially in children).
 - 5. Hemodialysis should be considered if the clinical condition deteriorates, as evidenced by:
 - a. Methanol/ethylene glycol concentration greater than 50 mg/dL
 - b. Significant metabolic acidosis
 - c. Development of acute renal failure or visual disturbances (methanol)
 - d. Development of significant electrolyte abnormalities
 - 6. Additional therapies
 - a. Pyridoxine and thiamine
 - i. Serve as cofactors in the metabolism of the toxic metabolites of ethylene glycol to nontoxic metabolites.
 - ii. Pyridoxine promotes the metabolism of glyoxylate to glycine.
 - iii. Thiamine promotes the metabolism of glycolic acid to a nontoxic metabolite; also used to prevent or treat Wernicke-Korsakoff syndrome.
 - b. Folinic acid
 - i. Serves as a cofactor in the metabolism of the toxic metabolites of methanol to nontoxic metabolites. May reduce formate accumulation and reduce the development of metabolic acidosis ingestion (Crit Care Clin 2012;28:661-771).
 - ii. Folic acid may be used if folinic acid is unavailable.
 - c. Dextrose
 - i. Recommended to check a point-of-care level blood glucose concentration before administration (Crit Care Clin 2012;28: 661-771)
 - ii. Administer 50 mL of 50% dextrose in water if blood glucose is 70 mg/dL or less or if testing is unavailable.
 - d. Magnesium – Recommended to administer 1–2 g intravenously for hypomagnesemia (more common in chronic alcohol use)
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- e. Antiseizure medications
 - i. Benzodiazepines are the preferred agent to treat seizures.
 - ii. Other options include phenobarbital, propofol, and phenytoin.
- D. Monitoring
 - 1. Patient should be closely monitored for resolution of clinical symptoms and return of baseline mental status.
 - 2. Monitor serum electrolytes and blood glucose periodically.
 - 3. Arterial blood gases with a goal of pH greater than 7.2
 - 4. Methanol/ethylene glycol concentrations with a goal of less than 20 mg/dL

Patient Cases

- 5. A 35-year-old man is admitted to the ED appearing inebriated. He is alert but oriented only to person. His vital signs are BP 122/80 mm Hg, HR 82 beats/minute, and RR 25 breaths/minute. His serum ethanol concentration is 20 mg/dL, and his ethylene glycol concentration is 100 mg/dL. Which is the most appropriate therapy at this time?
 - A. Fomepizole
 - B. Ethanol infusion
 - C. Thiamine
 - D. Activated charcoal
- 6. A patient with methanol intoxication is initiated on fomepizole treatment together with hemodialysis. After the 15-mg/kg bolus dose is given, which would be best for adjusting the maintenance fomepizole doses during dialysis?
 - A. 10 mg/kg every 12 hours
 - B. 20 mg/kg every 12 hours
 - C. 10 mg/kg every 4 hours
 - D. 20 mg/kg every 4 hours

VIII. ALCOHOL WITHDRAWAL

- A. Background
 - 1. Alcohol withdrawal is a relatively common consequence of hospital admission.
 - 2. The strongest risk factor is a history of alcohol withdrawal.
- B. Clinical Presentation
 - 1. Withdrawal symptoms typically occur within 8 hours after blood alcohol concentrations decrease, peak at 72 hours, and are markedly reduced at 5–7 days (N Engl J Med 2014;371:2109-13).
 - 2. Common symptoms include tremors, diaphoresis, nausea, vomiting, and abnormal vital signs, including hypertension, tachycardia, hyperthermia, and tachypnea (Am J Emerg Med 2013;31:734-42).
 - 3. Additional symptoms categorized as moderate to severe withdrawal include:
 - a. Alcoholic hallucinations – Auditory, visual, or tactile; may last up to 6 days

- b. Alcohol withdrawal seizures (tonic-clonic) – Occur within 72 hours
- c. Delirium tremens – Severe and potentially life-threatening symptom that may develop within 72 hours. Includes autonomic hyperactivity, confusion, delirium, psychosis, hallucinations, and seizures.

C. Treatment

1. The goal of therapy is to keep the patient safe, alleviate and prevent the progression of symptoms, and treat comorbidities (Crit Care Med 2010;38(suppl):S494-S501). Agents for the treatment of alcohol withdrawal are listed in Table 5.
2. Benzodiazepines are the primary agents used in treatment. Binds to the γ -aminobutyric acid (GABAA) receptor, resulting in hyperpolarization and membrane stabilization.
 - a. Lorazepam and diazepam are preferred because of their more predictable effects.
 - b. Chlordiazepoxide is not recommended in the acute setting.
 - c. Symptom-triggered therapy is preferred because it reduces benzodiazepine use, duration of mechanical ventilation, and duration of ICU stay.
 - d. Scheduled treatment may be necessary if symptoms are severe or difficult to control.
3. Ethanol – Use of ethanol to control alcohol withdrawal is controversial and is not routinely recommended.
4. Phenobarbital
 - a. Barbiturate with sedative, hypnotic, and antiseizure activity. Increases the binding of GABA to GABAA receptor and prolonging the chloride channel opening. Potential advantage over benzodiazepines in alcohol withdrawal because it does not require GABA to be effective (GABA may be depleted).
 - b. Typically considered a second-line agent if benzodiazepines fail to adequately control symptoms.
 - c. May increase the efficacy of benzodiazepines when used in combination by increasing the binding to the GABAA receptor.
5. Clonidine: α_2 -receptor agonist that helps control the catecholamine surge associated with withdrawal that is responsible for elevations in BP and HR
6. Baclofen: Selective GABAB receptor agonist that reduces the signs and symptoms of alcohol withdrawal
7. Propofol
 - a. General anesthetic acting through GABAA receptor agonism and N-methyl-D-aspartate (NMDA) receptor antagonism; chronic alcohol use is associated with an up-regulation of NMDA.
 - b. Useful for controlling delirium and preventing seizures
8. Dexmedetomidine
 - a. α_2 -Receptor agonist, which may help control BP and HR
 - b. May reduce overall benzodiazepine requirements
 - c. Recommended when clonidine cannot be administered and as adjunct therapy
9. Supportive care: Alcohol-dependent patients are often nutritionally deficient and at risk of Wernicke encephalopathy and hypomagnesemia. Multivitamin, folic acid, thiamine, and magnesium should be administered to nutrient-deficient patients.

D. Monitoring

1. Clinical Institute Withdrawal Assessment for Alcohol Scale (revised version) (CIWA-Ar) to determine the severity of symptoms and treatment
2. Vital signs every 2–4 hours
3. Electroencephalogram for sustained seizure-related activity

Table 5. Agents for Treatment of Alcohol Withdrawal

Agent	Suggested Starting Dose	Suggested Interval/Infusion Dose Range
Diazepam	5–20 mg PO/IV	Every 6–8 hr
Lorazepam	2–4 mg PO/IV	Every 4–6 hr
Phenobarbital	65–130 mg	Every 15–20 min until symptoms are controlled
Clonidine	0.1–0.3 mg	Every 8–12 hr
Baclofen	10 mg	Every 8–12 hr
Propofol	10–20 mcg/kg/min	20–70 mcg/kg/min
Dexmedetomidine	0.1–0.3 mcg/kg/hr	0.5–1 mcg/kg/hr
Multivitamin	10 mL IV or 1 tablet	Once daily for 2–3 days
Thiamine	100–500 mg	Once daily for 2–3 days
Folic acid	1–5 mg	Once daily for 2–3 days
Magnesium	1–4 g	Replacement based on serum concentrations

IV = intravenously; PO = orally or per tube.

IX. β -BLOCKERS AND CALCIUM CHANNEL BLOCKERS

A. Background

- Cardiovascular agents accounted for a little more than 100,000 toxic exposures in 2014 and were the second leading cause of death.
- Two of the most common cardiovascular agents involved in single-agent toxic exposures were β -blockers (10,459 cases and 14 deaths in 2014) and calcium channel blockers (5001 cases and 20 deaths in 2014).

B. Clinical Presentation

- β -Blocker overdoses are characterized by hypotension, bradycardia, and prolonged atrioventricular conduction.
- Calcium channel blocker overdoses by the non-dihydropyridine agents are characterized by hypotension, prolonged atrioventricular conduction, bradycardia, lethargy, hyperglycemia, and depressed consciousness. The dihydropyridine agents act peripherally and are primarily associated with vasodilation, hypotension, and reflex tachycardia.

C. Treatment

- Consider gastric lavage or activated charcoal if patients present within 1–2 hours of overdose. Whole bowel irrigation is recommended for delayed presentation or for sustained- or extended-release formulations.
- Maintenance of hemodynamic stability
 - Goal of therapy is a mean arterial pressure greater than 65 mm Hg or systolic blood pressure (SBP) greater than 90 mm Hg.
 - Administer isotonic fluids (0.9% sodium chloride or lactated Ringer solution) at 20–30 mL/kg (preferred) or colloidal solutions (e.g., albumin 5% 250 mL).
- Administer intravenous calcium chloride or calcium gluconate.
 - Calcium chloride 1–2 g (central line is preferred; however, bolus doses may be administered in a peripheral line if needed)
 - Calcium gluconate 3–6 g. Repeat dose may be given every 15–30 minutes; may also consider continuous infusion at 0.3–0.7 mEq/kg/hour.

4. Consider sodium bicarbonate for QRS widening, severe acidosis, or dysrhythmia: 1– 2 mEq/kg bolus; may consider a continuous infusion if symptoms persist.
5. Treat symptomatic bradycardia:
 - a. Atropine 0.5 mg intravenously; if no response, continue to the following options:
 - b. Glucagon 5–10 mg (100 mcg/kg) intravenous push for 1 minute. If HR and symptom response is achieved from the bolus, may consider a continuous intravenous infusion initiated at the same rate as the bolus dose that achieved response.
 - i. Stimulates adenylate cyclase, which increases intracellular cAMP (cyclic adenosine monophosphate), leading to increased inotropy, chronotropy, and cardiac conduction
 - ii. Adverse effects include nausea, vomiting, and hyperglycemia.
 - iii. Use with caution with decreased mental status because of possible aspiration or airway obstruction (also causes lower esophageal sphincter relaxation).
 - iv. Not recommended as a preferred treatment option because of limited efficacy and cost
 - c. Norepinephrine continuous infusion initiated at 2–5 mcg/minute (0.1 mcg/kg/minute) and titrated to response
 - d. Dopamine continuous infusion at 5–10 mcg/kg/minute and titrated to response (maximum of 20 mcg/kg/minute)
 - e. Phenylephrine continuous infusion at 20–40 mcg/kg/minute and titrated to response
 - f. Epinephrine continuous infusion at 1 mcg/minute (0.01–0.1 mcg/kg/minute) and titrated to response
 - g. Transcutaneous or transvenous pacing or intra-aortic balloon pumps
6. Hyperinsulinemic euglycemic therapy (HIET)
 - a. Mechanism of action:
 - i. Insulin increases the plasma concentrations of ionized calcium, improves the hyperglycemic acidotic state, improves the myocardial use of carbohydrates, and exerts an independent inotropic effect (Am J Crit Care Med 2007;16:498-503).
 - ii. Dextrose prevents the development of hypoglycemia after insulin administration.
 - iii. Potassium prevents the development of hypokalemia after insulin administration.
 - iv. Onset of action is as soon as 5 minutes; however, it may take up to 30 minutes for full effects to be seen.
 - b. HIET administration (Clin Toxicol 2011;49:277-83; Am J Health Syst Pharm 2006;63:1828-35):
 - i. If baseline glucose is less than 200 mg/dL, administer 50 mL of 50% dextrose in water – May consider an infusion of 10%–20% dextrose to maintain a serum glucose concentration greater than 100 mg/dL
 - ii. If baseline potassium is less than 2.5 mEq/L, administer an initial 40 mEq of potassium chloride intravenously – Hypokalemia is uncommon; however, it is recommended to replace potassium if serum concentrations fall below 2.8 mEq/L during treatment.
 - iii. Bolus 1 unit/kg of regular insulin intravenously, followed by a continuous intravenous infusion at 0.5–1 unit/kg/hour; increase rate every 10 minutes to a maximum of 10 units/kg/hour.
 - c. Adverse effects: Hypoglycemia, hypomagnesemia, and hypokalemia
 - d. Monitoring:
 - i. Vital signs every 15–60 minutes with a goal mean arterial pressure greater than 65 mm Hg and an HR greater than 50 beats/minute
 - ii. Serum glucose every 15 minutes; then every 30–60 minutes once stable to target serum concentrations greater than 100 mg/dL
 - iii. Serum potassium every hour during the insulin infusion; then every 6 hours to maintain concentrations above 2.8 mEq/L

7. Intravenous lipid emulsion (J Emerg Med 2015;48:387-97)
 - a. Mechanism of action is not well known; however, it is thought to be owing to a combination of binding lipid-soluble agents and the provision of free fatty acids that increase cardiac energy and intracellular calcium.
 - b. Improves HR and reduces mortality as an individual treatment or in combination with other therapies.
 - c. Evidence is limited to animal models and human case reports, and its role in therapy is controversial.
 - d. Administration:
 - i. Bolus of 1.5 mL/kg of 20% lipid emulsion (Intralipid) for 1–5 minutes (typical dose is usually 100 mL)
 - ii. May repeat up to two times for persistent cardiovascular collapse
 - iii. Intravenous infusion of 0.25–0.5 mL/kg/minute for 60 minutes (typical dose is 18 mL/minute)
 - iv. Continue for up to 10 minutes after cardiovascular recovery.
 - v. Adverse effects may include pancreatitis, jaundice, coagulopathies, interference with laboratory results, and fat embolism.
 - vi. Drug interactions are not well known.

Patient Case

Questions 7 and 8 pertain to the following case.

A 52-year-old man is admitted to the ED with concerns about dizziness and headache. His vital signs are as follows: temperature 98.9°F (37.2°C), BP 87/50 mm Hg, and HR 58 beats/minute. His wife reports that he has a history of hypertension and that he was recently given a diagnosis of being in the early stages of Alzheimer disease. She has brought his medications with her; the 1-month supply was refilled 2 days ago: a bottle of diltiazem CD 120 mg/day (7 tablets remaining) and a bottle of donepezil 5 mg once daily (28 tablets remaining).

7. Which decontamination strategy would provide the most benefit?
 - A. Charcoal 25 g every hour until his BP improves
 - B. Ipecac 30 mL, followed by 240 mL of water
 - C. Polyethylene glycol-electrolyte solution 1500 mL/hour until the rectal effluent is clear
 - D. Magnesium citrate 240 mL, followed by 240 mL of water
8. Which antidote would be best to administer first?
 - A. Calcium chloride 1 g intravenously for 1 minute
 - B. Glucagon 5 mg intravenously for 1 minute
 - C. Atropine 1 mg intravenously for 1 minute
 - D. Epinephrine 1 mg intravenously for 1 minute

X. DIGOXIN

A. Background

1. The cardiac glycosides accounted for 1,432 single-agent toxic exposures and 38 deaths in 2014.
2. Mechanism of action is inhibition of the sodium-potassium adenosine triphosphatase pump and suppression of the atrioventricular node.
3. Because of its narrow therapeutic index, toxicity has been reported in as many as 35% of patients receiving digoxin (Postgrad Med 1993;69:337-9).
 - a. The normal therapeutic range is 0.8–2.1 ng/mL.
 - b. Toxicity may be related to an acute ingestion or may be an issue with chronic dosing or renal dysfunction.
4. Risk factors for digoxin toxicity include renal failure, advanced age, ischemic heart disease, left ventricular dysfunction, electrolyte imbalances (hypokalemia, hypomagnesemia, hypercalcemia), and hypothyroidism (Postgrad Med 1993;69:337-9).

B. Clinical Presentation

1. Cardiac effects associated with digoxin toxicity include heart block, tachyarrhythmias, and bradyarrhythmias. More specific examples include fascicular tachycardia, ventricular bigeminy, and ventricular tachycardia (Am J Cardiol 1992;69:108G-119G).
2. Noncardiac effects associated with digoxin toxicity include nausea and vomiting, lethargy, headaches, confusion, and visual disturbances.

C. Treatment

1. Consider decontamination strategies if patients present within 2 hours of overdose.
 - a. Multidose activated charcoal is beneficial because of the enterohepatic recirculation of digoxin. Load 50–100 g; then 10 g/hour, 10–20 g every 2 hours, or 40 g every 4 hours (Postgrad Med 1993;69:337-9).
 - b. Colestipol or cholestyramine is an effective drug-binding alternative to charcoal, but it may not be useful in acute toxicity (Am J Cardiol 1992;69:108G-119G).
 - c. Hemodialysis is not considered effective.
2. Correct serum electrolyte abnormalities.
 - a. Correct serum potassium concentration to a goal of 3.5–4 mEq/L.
 - b. Correct serum magnesium concentration to a goal of 1.5–2.2 mg/dL.
 - c. Correct serum calcium concentration to a goal of 8.5–10.5 mg/dL.
3. Treat symptomatic bradyarrhythmias with atropine 0.5 mg.
4. Digoxin immune antigen-binding fragments (Fab)
 - a. Antibodies that bind to digoxin molecules that are then renally excreted
 - b. Indications for use in acute intoxications (Crit Care Clin 2012;28:527-35):
 - i. Life-threatening arrhythmias: systole, ventricular fibrillation or tachycardia, complete heart block, symptomatic bradycardia
 - ii. Evidence of end-organ damage (e.g., renal failure, altered mental status)
 - iii. Hyperkalemia (greater than 5–5.5 mEq/L)
 - c. Products:
 - i. Digibind (Digoxin Immune Fab): 38 mg per vial
 - ii. DigiFab (Digoxin Immune Fab): 40 mg per vial
 - d. Dosing:
 - i. If amount is unknown: 10–20 vials for acute toxicity or 6 vials for chronic toxicity

- ii. If the amount of digoxin ingested is known:
Dose (vials) = total body load ($0.8 \times \text{mg of digoxin ingested}$)/0.5
 - iii. If digoxin concentration is known:
Dose (vials) = [serum digoxin concentration (ng/mL) $\times$ weight (kg)]/100
 - iv. May consider lower doses of 1 or 2 vials (40–80 mg) for acute ingestions with repeat doses if necessary
 - e. Adverse effects include heart failure exacerbation, atrial fibrillation, orthostatic hypotension, hypokalemia, and phlebitis.
- D. Monitoring
- 1. Monitor vital signs every 30–60 minutes initially. Goal HR of greater than 60 beats/minute and asymptomatic
 - 2. Monitor serum potassium concentrations hourly for at least the first 6 hours.
 - 3. Additional serum digoxin concentrations are not recommended after the administration of Fab. A rapid rise in serum concentrations is expected because of the mechanism of the Fab-digoxin complex. Repeat serum digoxin concentrations may be checked 24 hours after the initial treatment if Fab is not administered.

XI. ANTIDEPRESSANTS

A. Background

- 1. Antidepressants accounted for more than 110,000 toxic exposures and 32 deaths in 2014.
- 2. The most common agents involved in toxic exposures were the selective serotonin reuptake inhibitors (SSRIs) and the tricyclic antidepressants (TCAs).
- 3. SSRIs block the reuptake of serotonin at the presynaptic neuron.
- 4. Patients with SSRI overdoses are often asymptomatic with self-limiting effects (Emerg Med Clin North Am 2007;25:477-97). The most common adverse effects may include drowsiness, tremor, altered mental status, nausea and vomiting, tachycardia, hypotension, seizures, and QRS- or QT-interval prolongation.
- 5. TCAs exert many effects, including blocking the reuptake of norepinephrine and serotonin at the presynaptic neuron, blocking muscarinic cholinergic receptors, blocking antihistamine effect, blocking the sodium channel, and, to a lesser degree, blocking α -adrenergic receptors.
- 6. Individuals with TCA overdoses may present with the following adverse effects (Emerg Med Clin North Am 1994;12:533-47):
 - a. Cardiovascular: Hypo- or hypertension, tachy- or bradycardia, increased QRS or QT interval, atrioventricular-conduction block, complete heart block
 - b. Respiratory: Hypoventilation, crackles, hypoxia
 - c. Neurologic: Delirium, lethargy, seizures, coma
 - d. Other: Hyperthermia, dry mucous membranes, urinary retention, blurred vision

B. Treatment

- 1. There are no specific antidotes for antidepressant overdoses; general supportive care is recommended, with a focus on ABC.
- 2. Gastric decontamination is not typically recommended; however, single-dose activated charcoal may be administered within the first hour of exposure (Emerg Med Clin North Am 2000;18:637-54).

3. Administer crystalloid or colloid fluids to maintain BP and HR, with the goal of an SBP greater than 90 mm Hg and a HR greater than 60 beats/minute.
 - a. Norepinephrine or epinephrine may be used if fluid resuscitation alone is unsuccessful.
 - b. Dopamine may not be an effective agent because endogenous norepinephrine stores are depleted in an overdose.
4. Sodium channel blockade
 - a. Alkalinization of blood to a pH of 7.45–7.55 is recommended for the TCAs to resolve metabolic acidosis and improve cardiac symptoms. Requires frequent monitoring of arterial pH (varies by effect, but as often as every 15–30 minutes).
 - b. Administer sodium bicarbonate
 - i. Recommended bolus dose of 1 mEq/kg (minimum: 50 mEq)
 - ii. May repeat bolus every 15 minutes until ECG stabilized or arterial pH goal achieved.
 - iii. May consider a continuous infusion of hypertonic saline.
 - c. Proposed indications for sodium bicarbonate include the following (Chest 2008;133:1006-13):
 - i. QRS greater than 100–120 milliseconds
 - ii. Wide complex tachycardia
 - iii. Cardiac arrest
 - iv. Right bundle-branch block
 - v. Refractory hypotension
 - d. Replace serum electrolytes if QT prolongation
 - e. Seizures should be managed with benzodiazepines. Phenobarbital may be considered if the patient is refractory to benzodiazepines and has a stable BP.
 - f. Intravenous fat emulsion
 - i. Many case reports for use in amitriptyline and SSRI overdose
 - ii. Administration:
 - (a) Bolus of 1.5 mL/kg of 20% lipid emulsion (Intralipid) for 1–5 minutes (typical dose is usually 100 mL)
 - (b) May repeat up to two times for persistent cardiovascular collapse
 - (c) Intravenous infusion of 0.25–0.5 mL/kg/minute for 60 minutes (typical dose is 18 mL/minute)
 - (d) Continue for up to 10 minutes after cardiovascular recovery.
- C. Monitoring – Patients should be monitored for clinical improvement for at least 6–8 hours and for a minimum of 24 hours for more severe adverse effects or with citalopram or escitalopram (because of the longer half-lives of these agents).
 - a. Monitor for cardiac toxicity with a 12-lead ECG, CK-MB, troponins, BP, and HR.
 - b. Monitor for signs and symptoms of respiratory depression with RR and pulse oximetry.
- D. Serotonin Syndrome
 1. Excessive serotonin concentrations lead to overstimulation of serotonin-1A and serotonin-2A receptors in the central and peripheral nervous systems (Emerg Med Clin North Am 2007;25:477-97).
 2. Adverse effects include altered mental status, autonomic instability (hyperthermia, tachycardia, hypertension, arrhythmias), and neuromuscular changes (hyperreflexia, increased rigidity).
 3. Diagnosis is made according to clinical findings; many clinicians support the use of the Hunter Serotonin Toxicity Criteria (QJM 2003;96:635-42). By this method, patients likely have serotonin toxicity if they have taken a serotonergic agent and one of the following criteria are present:
 - a. Spontaneous clonus
 - b. Inducible clonus PLUS agitation or diaphoresis

- c. Ocular clonus PLUS agitation or diaphoresis
 - d. Tremor PLUS hyperreflexia
 - e. Hypertonia PLUS temperature above 100.4°F (38°C) PLUS ocular clonus or inducible clonus
4. Treatment should focus on supportive care with intravenous fluids; symptoms typically resolve within 24–48 hours.
- a. Discontinue the offending agent.
 - b. Benzodiazepines should be administered as first line for agitation and muscle rigidity.
 - c. Cyproheptadine is a histamine-1 receptor antagonist and nonspecific serotonin receptor antagonist. A single dose of 8–12 mg by mouth should be administered for agitation and muscle rigidity as an adjunct to benzodiazepines. A second dose may be administered in 6–8 hours if symptoms persist.
 - d. If condition worsens, may require intubation with continuous infusion benzodiazepines
 - e. Although not well studied, case reports have shown the efficacy of dexmedetomidine at doses of 0.05–0.8 mcg/kg/hour (in pediatric patients).

Patient Case

9. A 21-year-old man is admitted to the ED after taking 30 citalopram 20-mg tablets about 2 hours ago. His vital signs are as follows: BP 125/85 mm Hg, HR 77 beats/minute, RR 15 breaths/minute, and temperature 98.7°F (37.1°C). Which is the best intervention for this patient?
- A. Administer lorazepam 2 mg intravenously to prevent seizure activity.
 - B. Closely monitor the patient for the development of any toxic effects.
 - C. Recommend a cooling blanket to prevent serotonin syndrome–related hyperthermia.
 - D. Order a 12-lead ECG to monitor for cardiac conduction disturbances.

XII. ATYPICAL ANTIPSYCHOTICS**A. Background**

- 1. The atypical antipsychotic agents accounted for about 40,500 toxic exposures and 15 deaths in 2014.
- 2. These agents are classified primarily as having D2-dopaminergic receptor and serotonin-2A receptor antagonism. Additional effects include antagonism of the α_1 - and histamine-1 receptors.
- 3. Adverse effects associated with the atypical antipsychotics are typically self-limiting.
 - a. More severe adverse effects may include CNS depression, tachycardia, hypotension, and QT prolongation.
 - b. Less severe adverse effects include dizziness, drowsiness, miosis, blurred vision, urinary retention, and CNS excitation.

B. Treatment

- 1. There are no specific antidotes for the atypical antipsychotics; general supportive care is recommended, focusing on ABC.
- 2. Gastric decontamination is not typically recommended; however, single-dose activated charcoal may be administered within the first hour of exposure if no contraindications exist (J Emerg Med 2012;43:906-13).

3. Administer crystalloid to maintain BP with a goal of an SBP greater than 90 mm Hg and an HR greater than 60 beats/minute.
 - a. Consider vasopressors if fluid resuscitation is inadequate.
 - b. Because of the α -receptor antagonist activity of these agents, norepinephrine or phenylephrine is preferred if vasopressors are needed.
 4. Administer sodium bicarbonate if QRS prolongation (quetiapine overdose only)
 5. Replace serum electrolytes, especially magnesium and potassium, if QT prolongation. Magnesium replacement is recommended for membrane stabilization in patients with a QTc greater than 500 milliseconds and normal serum magnesium concentrations.
 6. Seizure activity should be managed with benzodiazepines, barbiturates, or propofol.
 7. Lipid emulsion therapy may be effective because of the high lipophilicity of these agents and may be considered if more traditional treatment means do not improve the cardiovascular complications of decreased HR and/or BP (J Emerg Med 2012;43:906-13). Administer an intravenous bolus dose of 1.5 mL/kg of 20% intralipid for 2–3 minutes, followed by a continuous intravenous infusion of 15 mL/kg for 60 minutes, if necessary.
- C. Monitoring: Patients should be monitored for clinical improvement for at least 8–12 hours.
1. Monitor for cardiac toxicity with a 12-lead ECG, CK-MB, and troponins.
 2. Monitor for respiratory depression with RR and pulse oximetry.

XIII. LITHIUM

- A. Background
1. Lithium was associated with almost 7000 toxic exposures and seven deaths in 2014.
 2. Mechanism of action is through an influence on serotonin and norepinephrine reuptake, inhibition of the phosphatidylinositol cycle, and inhibition of the post-synaptic D2 receptor.
 3. Adverse effects associated with lithium include:
 - a. Acute overdose:
 - i. GI: Nausea, vomiting, diarrhea
 - ii. CNS: Confusion, tremor, myoclonus, seizures, coma
 - iii. Cardiovascular: T-wave inversion, ventricular arrhythmias
 - b. Chronic adverse effects:
 - i. Endocrine: Hypothyroidism, myxedema coma
 - ii. Nephrogenic diabetes insipidus
- B. Treatment
1. There are no specific antidotes for lithium; general supportive care is recommended, focusing on ABC.
 2. Gastric decontamination is not typically recommended in toxic acute ingestions. Single-dose activated charcoal is not effective for lithium overdoses; whole bowel irrigation may be beneficial.
 3. Administer crystalloid to maintain BP, with a goal of an SBP greater than 90 mm Hg. Consider vasopressors if fluid resuscitation is not adequate.
 4. Replace serum electrolytes, especially magnesium and potassium, if QT prolongation.
 5. Seizure activity should be managed with benzodiazepines, barbiturates, or propofol.
 6. Lithium overdoses are primarily managed with hemodialysis or continuous replacement therapy.
 - a. Saline infusions may be administered if there are no contraindications to fluid therapy (goal is a serum sodium concentration of 140–145 mEq/L). Lithium clearance is reduced in hyponatremia.

- b. Intermittent hemodialysis may require several sessions to fully remove lithium concentrations because of the rebound of lithium concentrations that occurs after dialysis sessions.
 - c. Suggested indications for the use of hemodialysis include (Chest 2005;133:1006-13):
 - i. Severe toxicity (severe altered mental status or seizures)
 - ii. Renal failure (cannot eliminate lithium)
 - iii. Lithium concentrations greater than 2.5 mmol/L in chronic exposures
 - iv. Lithium concentrations greater than 4 mmol/L in acute exposures
- C. Monitoring – Patients should be monitored for clinical improvement for at least 8–12 hours.
- 1. Monitor for cardiac toxicity with a 12-lead ECG, CK-MB, and troponins.
 - 2. Monitor for respiratory depression with RR and pulse oximetry.
 - 3. Monitor renal function with urine output, BUN, and SCr.
 - 4. Monitor baseline lithium concentrations and then every 6 hours after until concentrations have decreased to less than 1.5 mmol/L (normal 0.6–1.2 mmol/L).

Patient Case

10. A 24-year-old woman is brought to the ED by her roommate. She has been in a normal state of health, but the roommate is concerned because she “seems really out of it.” According to the roommate, the patient had an appointment with the physician today, and she had been given a prescription to refill olanzapine 5 mg by mouth daily, but the bottle is empty. On physical examination, she is alert and oriented person, place and time but she dozes off several times. Her vital signs are stable, and a 12-lead ECG shows sinus tachycardia. Which intervention is most appropriate for this patient?
- A. Lactated Ringer solution 500 mL
 - B. 8.4% sodium bicarbonate 50 mL
 - C. Lorazepam 2 mg
 - D. Clinical monitoring for 6 hours

XIV. ORAL HYPOGLYCEMICS

- A. Background
- 1. Oral hypoglycemics accounted for about 38,651 single-agent exposures and 14 deaths in 2014.
 - 2. The most common oral hypoglycemic involved in toxic exposures was metformin, followed by the sulfonylureas and the thiazolidinediones.
 - 3. The most serious adverse effects were reported with the sulfonylureas; however, most fatalities were associated with metformin.
- B. Clinical Presentation
- 1. Clinical signs and symptoms include hypoglycemia (not with metformin), nausea, vomiting, dizziness, tachycardia, and diaphoresis.
 - 2. More severe adverse effects include seizures, palpitations, tachyarrhythmias, electrolyte abnormalities, and metabolic (lactic) acidosis.

C. Treatment

1. Stabilization of the ABC
2. Identifying the causative agent is important because specific treatment will vary by the agent involved.
3. Consider gastric decontamination with single-dose activated charcoal if patients present within 1 hour of overdose.
4. Observe clinically asymptomatic patients for a minimum of 8 hours (Am J Health Syst Pharm 2006;63:929-38).
5. For symptomatic patients or blood glucose less than 60 mg/dL, treat with glucose:
 - a. Conscious patients: Administer 8 oz of an oral carbohydrate (such as juice, non-diet sodas, or milk) or oral glucose tablets or gels.
 - b. Unconscious patients: Administer intravenous dextrose, 0.5–1 g/kg
 - c. Repeat doses may be required; consider a continuous infusion of dextrose if needed. Glucose concentrations should be monitored often (every 15–60 minutes) until stable.
 - d. Use caution to avoid overcorrection of serum glucose.
6. Octreotide
 - a. Mechanism of action is a somatostatin analog that inhibits the secretion of insulin.
 - b. Primarily studied in sulfonylurea overdose, but considered a treatment option for all oral hypoglycemic toxic exposures
 - c. Administer 50 mcg subcutaneous or intravenous, followed by three 50 mcg doses every 6 hours. Intravenous dextrose infusion should be slowly tapered off.
 - d. Adverse effects include headache, dizziness, nausea, abdominal pain, and sinus bradycardia.
7. Glucagon
 - a. Mechanism of action is stimulation of gluconeogenesis.
 - b. May trigger additional insulin secretion, leading to a secondary hypoglycemia
 - c. May provide a benefit in prehospital settings when oral or intravenous options are not available, but is not routinely recommended
 - d. Not recommended in pediatric patients, in malnourished patients, or for sulfonylurea toxic exposures
8. Sodium bicarbonate
 - a. Indicated for severe metformin-associated lactic acidosis
 - b. 1–2 mEq/kg or 50–200 mEq of 8.4% sodium bicarbonate intravenously
9. Hemodialysis or continuous renal replacement therapy may be necessary to enhance metformin clearance in severe cases.

D. Monitoring

1. Regular assessment of vital signs and mental status (Emerg Med J 2006;23:565-7)
2. Measure capillary blood glucose at a minimum of every hour for 24 hours with a goal of greater than 70 mg/dL.
3. Measure BP hourly, especially after octreotide administration.

Patient Case

11. As the pharmacist in the ICU satellite, you receive a call from a distressed nurse about a patient in the cardiac step-down unit. The patient was found unconscious, and, on investigation, it was discovered that he had received a glyburide 20-mg tablet 1 hour earlier that was meant for another patient. The patient has stable vital signs, but his point-of-care blood glucose concentration is 37 mg/dL. Which intervention is most appropriate at this time?
- A. 8 oz of milk by mouth
 - B. 50 mL of 50% dextrose in water intravenously
 - C. Octreotide 100 mcg subcutaneously
 - D. Glucagon 1 mg intramuscularly

XV. DRUGS OF ABUSE**A. Background**

1. Miscellaneous stimulants and street drugs accounted for about 68,500 toxic exposures and 119 deaths in 2014.
2. The most common drugs of abuse involved in toxic exposures were amphetamines, marijuana (and derivatives), cocaine, methamphetamines, and heroin.
3. Total numbers are difficult to determine because few of these agents can be detected with current techniques.

B. Amphetamines/Methamphetamines/MDMA (ecstasy)

1. Mechanism of action/toxicity: stimulation of the CNS, peripheral release of catecholamines, inhibition of catecholamine reuptake, inhibition of monoamine oxidase (Intensive Care Med 2004;30:1526-36)
2. Clinical presentation (Intensive Care Med 2004;30:1526-36)
 - a. Common: Confusion, tremor, anxiety, agitation, irritability, mydriasis, tachyarrhythmias
 - b. Severe: Hepatocellular necrosis, acute hepatitis, myocardial ischemia, hypertension, cerebral hemorrhage, seizures, hyponatremia
3. Treatment
 - a. Mostly supportive care with intravenous fluid administration and airway maintenance
 - b. Gastric lavage or activated charcoal if within 1 hour of ingestion
 - c. BP control with nitroglycerin, nitroprusside, or nicardipine. Avoid the use of β -receptor blocking agents because of unopposed α -receptor activity leading to an increase in BP.
 - d. Benzodiazepines for agitation, titrated to effect. Haloperidol or phenothiazines may be considered for use (with caution) in patients with primary psychiatric disorders or dopamine-mediated movement disorders.
 - e. Cooling therapy if temperature elevated
 - f. Monitor for serotonin syndrome.

C. Synthetic Cannabinoids: K2/Spice

1. Mechanism of action/toxicity: stimulation of the cannabinoid-1 (CB1) and cannabinoid-2 (CB2) receptors (Pharmacotherapy 2015;35:189-97)
 - a. CB1 receptors modulate glutamate and GABA and are found both peripherally and centrally.
 - b. CB2 receptors are located in immune tissue and the CNS and modulate pain and emesis.
2. Clinical presentation (J Pharm Pract 2015;28:50-65)
 - a. Predominantly euphoria or excited delirium
 - b. Common adverse effects include:
 - i. Psychiatric: Agitation, anxiety, hallucinations, paranoia, catatonia
 - ii. Neurologic: Cognitive impairment, ataxia, dizziness, headache, seizures
 - iii. Cardiovascular: Tachycardia, palpitations, hypertension
 - iv. GI: Nausea, vomiting
 - v. Renal: Acute kidney injury, rhabdomyolysis
3. Treatment
 - a. Mostly supportive care with intravenous fluid administration
 - b. Benzodiazepines for agitation or seizure activity. Antipsychotics for agitation may be considered for use (with caution) in patients with primary psychiatric disorders or dopamine-mediated movement disorders.

D. Cocaine

1. Mechanism of action/toxicity (Intensive Care Med 2004;30:1526-36):
 - a. Potent sympathetic nervous system stimulant
 - b. Inhibits the presynaptic reuptake of epinephrine and norepinephrine; also stimulates norepinephrine release
 - c. Acts as a reuptake inhibitor of dopamine, norepinephrine, and serotonin
2. Clinical presentation (Intensive Care Med 2004;30:1526-36)
 - a. Predominantly euphoria or excited delirium
 - b. Common/severe adverse effects include:
 - i. Psychiatric: Agitation, anxiety, psychosis, delirium
 - ii. Neurologic: Stroke, subarachnoid or intracranial hemorrhage, seizures
 - iii. Cardiovascular: Tachycardia, hypertension, palpitations, arrhythmias, heart failure, aortic dissection
 - iv. GI: Gastric ulcers, gastric perforation, bowel ischemia
 - v. Respiratory: Status asthmaticus, pulmonary hypertension, pulmonary edema, alveolar hemorrhage
 - vi. Renal: Acute kidney injury, rhabdomyolysis
3. Treatment
 - a. Mostly supportive care with intravenous fluid administration
 - b. Gastric decontamination is typically not recommended. Activated charcoal may provide benefit if given within 1 hour of oral ingestion.
 - c. Benzodiazepines are administered for agitation or seizure activity and titrated to relaxation. Because of their ability to block the CNS stimulant effect of cocaine, benzodiazepines are also an effective treatment for hypertension and tachycardia.
 - d. BP control with nitroglycerin, nitroprusside, or nicardipine. Avoid the use of β -receptor blocking agents because of unopposed α -receptor activity leading to an increase in BP.

E. Synthetic Cathinones: Bath Salts

1. Mechanism of action/toxicity: increases presynaptic concentrations of serotonin, dopamine, and norepinephrine by stimulating release and antagonizing monoamine reuptake (Pharmacotherapy 2014;34:745-757)
2. Clinical presentation (J Pharm Pract 2015;28:50-65):
 - a. Predominantly euphoria, increased energy, and alertness
 - b. Common adverse effects include:
 - i. Psychiatric: Agitation, aggression, anxiety, hallucinations, paranoia
 - ii. Neurologic: Amnesia, confusion, insomnia, seizures, dizziness, headache
 - iii. Cardiovascular: Angina, hypertension, tachycardia, palpitations
 - iv. GI: Abdominal pain, nausea, vomiting, anorexia, hepatic failure
 - v. Renal: Acute kidney injury, increased SCr
3. Treatment
 - a. Mostly supportive care with intravenous fluid administration
 - b. Benzodiazepines or antipsychotics for agitation or anxiety
 - i. Haloperidol is an alternative option, but it should be monitored for worsening hyperthermia.
 - ii. Consider propofol or dexmedetomidine for severe symptoms.
 - c. Antiemetics for severe nausea and vomiting
 - d. Monitor for serotonin syndrome.

F. Piperazines

1. Mechanism of action/toxicity: enhances neurotransmitter release and reuptake inhibition of dopamine, serotonin, and norepinephrine release (Emerg Med Clin North Am 2014;32:1-28)
2. Clinical presentation (J Pharm Pract 2015;28:50-65):
 - a. Predominantly euphoria and increased energy
 - b. Common adverse effects include:
 - i. Psychiatric: Agitation, anxiety, hallucinations, psychosis, depressed mood or mood swings, paranoia
 - ii. Neurologic: Confusion, insomnia, tremor, seizures, dizziness, headache
 - iii. Cardiovascular: Angina, hypertension, tachycardia, palpitations, QT prolongation
 - iv. GI: Abdominal pain, nausea, vomiting
 - v. Renal: Urinary retention
3. Treatment
 - a. Mostly supportive care with intravenous fluid administration
 - b. Benzodiazepines for agitation or seizures
 - c. Avoid antipsychotics because of worsening hyperthermia, extrapyramidal effects, and hypotension or arrhythmias.
 - d. Treat hypertension with parenteral antihypertensives or clonidine.
 - e. Hyperthermia treatment if above 104°F (40°C)
 - f. Monitor for serotonin syndrome.

G. Ketamine

1. Mechanism of action/toxicity (Lancet 2005;365:2137-45):
 - a. Noncompetitive NMDA receptor antagonist (blocks glutamate and aspartate)
 - b. Mild to moderate blockade of catecholamine reuptake

2. Clinical presentation:
 - a. Predominantly hallucinations and vivid dreams
 - b. Common adverse effects include:
 - i. Psychiatric: Impaired memory, cognitive dysfunction, severe agitation
 - ii. Cardiovascular: Hypertension, tachycardia, cardiac arrhythmias
 - iii. Respiratory: Laryngospasm, apnea, respiratory depression
 - iv. GI: Anorexia, nausea, vomiting
 - v. Genitourinary: Cystitis, irritable bladder, urethritis
3. Treatment
 - a. Mostly supportive care with intravenous fluid administration
 - i. Monitor for rhabdomyolysis
 - ii. Aspiration precautions are recommended in comatose patients
 - iii. Urinalysis and serum chemistries if symptomatic for cystitis
 - b. Activated charcoal may provide benefit if given within 1 hour of oral ingestion. Additional doses every 4 hours may be considered.
 - c. Benzodiazepines are recommended for agitation or seizures.
 - d. Haloperidol may be used if benzodiazepines are not effective. Monitor closely because of the potential of lowering the seizure threshold and worsening of dystonia, hypotension, neuroleptic malignant syndrome, and/or myoglobinuria.

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ANSWERS AND EXPLANATION TO PATIENT CASES

1. Answer: B

The most important first step in all drug overdose cases is to try to stabilize the patient's ABC. This may involve the use of supplemental oxygen or advanced airway management, establishment of intravenous access, and administration of intravenous fluids. Once the patient is stable, the process of identifying the suspected toxin can begin. This may include thoroughly examining the patient, speaking with family or first responders, and communicating with the patient's physicians and pharmacies. Blood and urine samples may be sent for quantitative or qualitative toxicologic assays. A coma cocktail may provide some benefit, but a clear cause should be established before considering its use.

2. Answer: B

The patient has symptoms of an acute acetaminophen overdose, and stabilizing the patient, together with providing good supportive care, is indicated until a determination for additional therapy can be made. Typical decontamination strategies may provide benefit, but they do not definitively improve patient outcome. Magnesium citrate (and cathartics as a whole) is not considered an effective decontamination strategy. Gastric lavage is of most benefit within the first 60 minutes of exposure, and the potential adverse effects outweigh any potential benefit. Similarly, single-dose charcoal requires more rapid administration.

3. Answer: C

The patient is considered at high risk of developing hepatic damage from acetaminophen and requires therapy with intravenous acetylcysteine. The dose of intravenous acetylcysteine is as follows (doses are calculated using actual body weight): loading dose: 150 mg/kg in 200 mL of 5% dextrose in water for 60 minutes; maintenance dose: 50 mg/kg in 500 mL of 5% dextrose in water for 4 hours, followed by 100 mg/kg in 1000 mL of 5% dextrose in water for 16 hours. Oral dosing of acetylcysteine is not a viable option because of the patient's severe nausea and vomiting.

4. Answer: C

This patient has an acute salicylate overdose. Although his serum salicylate concentrations are in the therapeutic range, he has symptoms consistent with salicylate toxicity, as evidenced by his nausea, tachycardia, and

respiratory alkalosis. He is currently stable, but his serum salicylate concentrations may continue to rise; therefore, enhanced elimination with serum bicarbonate is the best option. His vital signs, which are stable, should be monitored for changes; however, although he is not experiencing signs of significant dehydration, he would benefit from the fluid administration of sodium bicarbonate. Sodium chloride would be more beneficial if his vital signs were more unstable. His RR, which is elevated, should be monitored; however, he is alert and able to communicate and therefore does not need intubation at this time. He is also not indicated for hemodialysis because of his moderate symptoms, but this could be considered if his condition deteriorates.

5. Answer: A

The most appropriate therapy for an ethylene glycol intoxication is fomepizole. An ethanol infusion is a possible treatment option, but it is not preferred because of the difficulties in dosing and adverse effects. Thiamine is a cofactor in the metabolism of ethylene glycol, but it would not be preferred to administer thiamine before fomepizole. Activated charcoal is not an option for gastric decontamination because it is not effective for alcohols.

6. Answer: C

After the initial bolus of fomepizole, 10 mg/kg should be administered every 12 hours. Because of the increased clearance of fomepizole during hemodialysis, the frequency is changed to every 4 hours during dialysis. When dialysis is completed, the dose returns to 10 mg/kg administered every 12 hours; and once the patient has been on 48 hours of therapy, dosing increases to 15 mg/kg because of self-induction. There is no indication for a dose increase.

7. Answer: C

The best treatment option for this patient is whole bowel irrigation because of the extended-release formulation of diltiazem. Activated charcoal may provide some benefit, but, similar to ipecac, the time interval is not known, and diltiazem does not undergo enterohepatic recirculation. Ipecac is not recommended because it may impede treatment with more effective treatment options and because it is no longer manufactured in the United States. A cathartic would not be useful in this situation;

guidelines recommend its use only in combination with other decontamination strategies, not as a single agent.

8. Answer: A

There are several potential antidotes for a calcium channel blocker overdose. Calcium is the most effective, and it should be given by bolus, followed by continuous infusion if needed. Glucagon is not an effective antidote and is therefore not an option for this patient. Atropine is effective for symptomatic bradycardia caused by the calcium channel blocker, but the dose should be 0.5 mg. Epinephrine is an alternative to glucagon, but it requires administration by continuous infusion.

solution fails to raise the blood glucose above 70 mg/dL for two consecutive readings. Glucagon is a potential option for treatment, but because the patient has intravenous access, the intramuscular route would not be preferred.

9. Answer: D

Most of the SSRIs are relatively safe, and many patients will present as asymptomatic after an overdose. However, there is a potential for a patient to develop serious adverse effects, such as serotonin syndrome, seizures, and cardiac toxicity. Although this patient is stable and has no specific concerns, it is recommended to check a 12-lead ECG to measure for QT-interval prolongation and treat with sodium bicarbonate, if necessary. A benzodiazepine should be administered if muscle rigidity develops, but it should not be used as a prophylactic measure. It is recommended that the patient be observed for at least 6–8 hours. Measures should be performed to reduce hyperthermia if a serotonergic syndrome develops, but this should be treated with measures to reduce muscle activity (i.e., sedation or chemical paralysis), not by applying measures to enhance surface cooling.

10. Answer: D

Although the patient appears to have taken an overdose of olanzapine, she is experiencing only mild symptoms. The best intervention would be to monitor her for 6 hours for the progression of her symptoms or development of additional complications. Intravenous fluids would be appropriate if the patient has dehydration or hypotension. Sodium bicarbonate is indicated for QRS prolongation and is not warranted at this time. Olanzapine does not cause seizures; therefore, lorazepam would not be indicated.

11. Answer: B

The most appropriate intervention at this time is to give the patient intravenous dextrose. Oral glucose is a viable option, but it cannot be administered to an unconscious patient without oral access. Octreotide should be reserved for use if the administration of a glucose

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS**1. Answer: C**

The best option for this patient right now is to administer octreotide 50–100 mcg subcutaneously. The patient has not responded to two doses of intravenous dextrose, as evidenced by point-of-care glucose concentrations less than 70 mg/dL; therefore, additional doses of dextrose are not indicated. Although glucagon is also a potential option, it is not recommended for sulfonylurea exposures. Sodium bicarbonate is indicated only for metformin-induced metabolic acidosis.

2. Answer: A

Any of the options listed in this question are possible treatments for a patient with a β -blocker overdose who is not responding to the administration of intravenous fluids and calcium. The optimal choice ultimately involves efficacy and appropriate dosing. Glucagon is an option, and it should be dosed at 5–10 mg initially. Atropine is an option for the patient's bradycardia, but the initial recommended dose is 0.5 mg. Hyperinsulinemic euglycemic therapy may be preferred in this setting; however, the correct bolus dose is 1 unit/kg. Dopamine is an option for the treatment of hypotension and bradycardia, but the correct dose would be the initiation of an infusion at 5–10 mcg/kg/minute titrated to effect.

3. Answer: B

Given the patient's presentation and the common toxidromes, the most likely scenario is a cholinergic agent. The patient is experiencing bradycardia with a normal BP and RR, has a decrease in mental status, and is experiencing nausea. Although not an absolute, anticholinergics and sympathomimetics are more commonly associated with tachycardia. Similarly, opioids are typically associated with a decrease in respirations.

4. Answer: A

The patient is experiencing QT prolongation after an atypical antipsychotic overdose. It is important to stabilize the patient by administering sodium bicarbonate and electrolyte replacement. Her potassium concentration is low, requiring replacement. Because the time interval of the overdose is not known, there is limited benefit for activated charcoal. Although her magnesium concentration is normal, it should be monitored; however, her

magnesium concentration does not require replacement at this time because her QTc is less than 500 milliseconds. Lorazepam is not indicated for prophylaxis of seizure activity.

5. Answer: A

This patient has the clinical signs and symptoms of alcohol withdrawal. Management should focus on the patient's safety and controlling his symptoms, and treatment should be administered using a symptom-triggered therapy strategy. The primary agents used to control symptoms are the benzodiazepines, and lorazepam is a good option. Barbiturates such as phenobarbital are typically reserved for patients who do not respond to benzodiazepine therapy because of benzodiazepine's long elimination half-life and stronger sedative effects. Propofol should be avoided in non-intubated patients. Clonidine is a potential option, especially because this patient has borderline hypertension, but oral dosing may be difficult with his level of confusion.

6. Answer: B

The patient is experiencing an unintended opioid overdose, as evidenced by the decreased RR and decreased consciousness. Administration of the antidote, naloxone, is the best option. Because 2 hours have passed since the methadone dose was given, there is limited usefulness for activated charcoal at this time, and it would not be advisable to administer it to an unconscious patient without an established airway. Whole bowel irrigation is also not useful in this situation because it is too late to prevent drug absorption together with the airway safety concern. Administration of intravenous fluids would be beneficial to improve BP but should not be administered in this case before naloxone.

7. Answer: D

The patient is not responding to the initiation of intravenous fluids and calcium gluconate, so HIET is warranted. Because of the patient's low serum potassium concentrations, it is critical to replace this before administering insulin. The patient's glucose concentration is greater than 200 mg/dL, so additional glucose need not be given at this time. Full effects may take up to 30 minutes to be seen, but this should not prevent the initiation of HIET.

8. Answer: B

The patient is not responding to the initiation of intravenous fluids, calcium, and HIET. The most appropriate option at this time would be to increase the rate of the insulin infusion. The initial infusion rate is 0.5–1 unit/kg/hour and is titrated every 15–20 minutes until hemodynamically stable. The next option would be to initiate a vasopressor agent. From the choices listed, the best first option is norepinephrine initiated at 4 mcg/minute and titrated to the desired effect. Epinephrine is also a possible option, but it would be recommended if the patient were not responding to increasing doses of norepinephrine. Intravenous lipid emulsion is a potential therapy, but it is typically administered in a patient with severe decompensation caused by a lipophilic medication who is not responding to fluids or vasopressors.

CARDIOVASCULAR CRITICAL CARE

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Learning Objectives

1. Interpret a patient's hemodynamic status accounting for cardiovascular anatomy, inherent physiologic function, and circulation, and recommend appropriate corresponding pharmacotherapeutic regimens.
2. Evaluate patients, and devise a treatment strategy for patients with cardiogenic shock, considering pharmacodynamic response to vasopressors/inotropes.
3. Evaluate and interpret the contributing effects of various cardiovascular disease states associated with cardiogenic shock.
4. Recommend appropriate pharmacotherapeutic regimens in cardiovascular diseases in critically ill patients, including, but not limited to, cardiogenic shock, coronary artery disease, heart failure, valvular disease, and cardiac surgery perioperative management.
5. Recognize the options for and roles of mechanical circulatory support and heart transplantation as advanced therapies for heart failure and/or cardiogenic shock.

Abbreviations in This Chapter

ABG	Arterial blood gas
ACE	Angiotensin-converting enzyme
ACS	Acute coronary syndrome(s)
AF	Atrial fibrillation
ARB	Angiotensin receptor blocker
AV	Atrioventricular
BNP	Brain natriuretic peptide
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CVP	Central venous pressure
ECHO	Echocardiography/echocardiogram
ECMO	Extracorporeal membrane oxygenation
HOCM	Hypertrophic obstructive cardiomyopathy
ICU	Intensive care unit
LV	Left ventricle/ventricular
LVAD	Left ventricular assist device
LVEF	Left ventricular ejection fraction
MAP	Mean arterial pressure
MCS	Mechanical circulatory support
MI	Myocardial infarction
NSTEMI	Non-ST-segment elevation myocardial infarction

PCI	Percutaneous coronary intervention
PVR	Pulmonary vascular resistance
RV	Right ventricle/ventricular
SA	Sinoatrial
STEMI	ST-segment elevation myocardial infarction
SVR	Systemic vascular resistance
VAD	Ventricular assist device
VT	Ventricular tachycardia

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

Questions 1–8 pertain to the following case.

A 58-year-old man (height 71 inches, weight 106 kg) was transferred to the intensive care unit (ICU) from an outlying hospital after 24 hours of progressively worsening chest pain and shortness of breath. He arrives on 6 L of oxygen by high-flow nasal cannula, with a heparin infusion at 16 units/kg/hour and dopamine infusion at 15 mcg/kg/minute. Notes show that he was bradycardic (heart rate of 50–58 beats/minute) and hypotensive (78/49–86/55 mm Hg) on presentation to the outlying hospital. His 12-lead electrocardiogram (ECG) at the outlying hospital showed ST-segment elevation in leads II, III, and aVF. Given his chest pain and ECG findings, aspirin 324 mg (chewed and swallowed), clopidogrel 600 mg, and morphine 4 mg intravenously once were administered before transfer. Notes also show that β -blockers and nitroglycerin were held because of bradycardia and hypotension.

His past medical history is significant for nonadherence, hypertension, diabetes mellitus, dyslipidemia, and heart failure with preserved ejection fraction (HFpEF), with a last-reported left ventricular ejection fraction (LVEF) of 65% 1 year ago. The patient reports that he currently takes no medications at home.

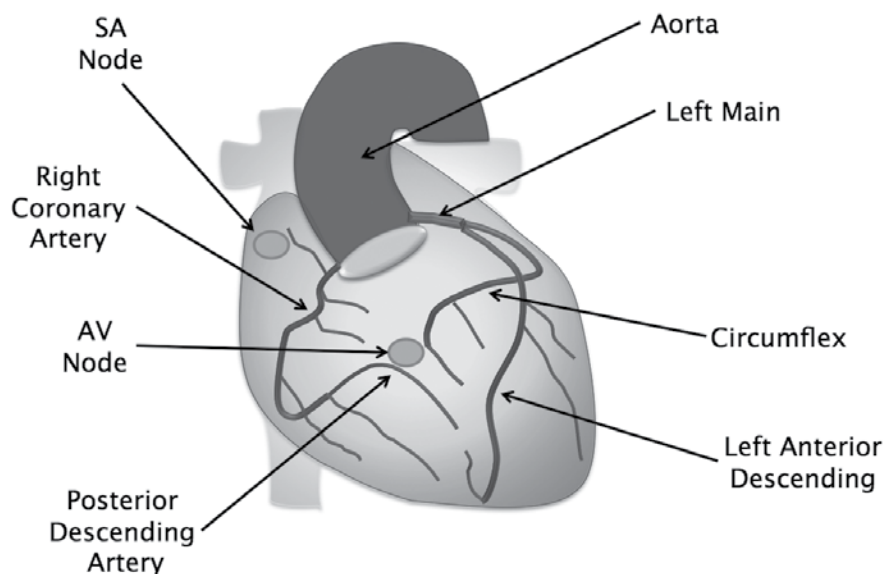
- Vital signs on transfer: blood pressure 87/52 mm Hg, heart rate 110 beats/minute, respiratory rate 19 breaths/minute, temperature 99.7°F (37.6°C)
- The team's physical assessment indicates ongoing distress, radiating chest pain 7/10, evidence of rales, absence of any cardiac murmurs, and presence of a right radial arterial line.
- A preexisting urinary catheter with 20 mL of urine in the reservoir is also present (the patient reports that his most recent void was yesterday morning). According to outlying hospital records, only 30 mL of urine was reported before time of transfer.

- His chest radiography reveals evidence of diffuse patchy opacities; however, the report indicates that an infiltrate cannot be ruled out.
 - His serum chemistry panel results are as follows: sodium 132 mEq/L, potassium 4.2 mEq/L, chloride 102 mEq/L, carbon dioxide 22 mEq/L, blood urea nitrogen (BUN) 34 mg/dL, serum creatinine (SCr) 1.9 mg/dL, and glucose 163 mg/dL.
 - Results of the complete blood cell count (CBC) are as follows: white blood cell count (WBC) 11.3×10^3 cells/mm³, hemoglobin 10.9 g/dL, hematocrit 31.1%, and platelet count 213,000/mm³.
 - Additional laboratory values include troponin-T 3.9 ng/mL, aspartate aminotransferase (AST) 14 IU/L, alanine aminotransferase (ALT) 46 IU/L, hemoglobin A1C (A1C) 8.3%, and brain natriuretic peptide (BNP) of 1423 pg/mL.
1. Which is the most likely cause of this patient's admission and transfer?
 - A. Septic shock caused by suspected pneumonia with subsequent myocardial depression and demand ischemia
 - B. Cardiogenic shock caused by acute on chronic decompensated systolic heart failure
 - C. Cardiogenic shock caused by a suspected inferior ST-segment elevation myocardial infarction (STEMI)
 - D. Cardiogenic shock caused by a suspected non-ST-segment elevation myocardial infarction (NSTEMI) affecting the lateral wall
 2. Given this patient's presentation, which coronary artery is most likely to be the culprit lesion?
 - A. Left main coronary artery
 - B. Left anterior descending artery
 - C. Left circumflex coronary artery
 - D. Right coronary artery
 3. The interventional cardiologist who is evaluating the patient for potential revascularization asks the ICU team to place a central venous catheter. Which changes/interventions regarding this patient's hemodynamic support would be best to recommend?
 - A. Increase dopamine to achieve a mean arterial pressure (MAP) greater than 65 mm Hg.
 - B. Convert the patient to norepinephrine, and titrate the dose to achieve a MAP greater than 65 mm Hg while weaning off dopamine.
 - C. Initiate milrinone at 0.375 mcg/kg/minute, and continue dopamine at 15 mcg/kg/minute.
 - D. Administer 1000 mL of normal saline as a bolus because of low urine output.
 4. The patient has been taken to the cardiac catheterization laboratory, and a "code blue" is called overhead for immediate emergency response to this patient's procedural area. On arrival, chest compressions have just been paused for defibrillation, and a single dose of epinephrine has been administered. The interventional team indicates that, when attempting visualization of the right coronary artery, the patient went into ventricular tachycardia (VT). The patient's telemetry monitor now shows sinus tachycardia with noted ectopy—heart rate 113 beats/minute and blood pressure 84/52 mm Hg. The cardiologist asks for recommendations for an antiarrhythmic because he is concerned about a VT recurrence, given the bigeminy on telemetry. Which agent would be best to recommend?
 - A. Lidocaine 100 mg intravenous push for 2–3 minutes, followed by an infusion at 1 mg/minute
 - B. Amiodarone 300 mg intravenous push for less than 1 minute
 - C. Metoprolol 10 mg intravenous push for 1–2 minutes
 - D. Diltiazem 20 mg intravenous push for 2 minutes, followed by a continuous infusion at 5 mg/hour and titrated to maintain a heart rate less than 110 beats/minute
 5. The patient returns to the ICU after his left heart catheterization, which was performed through the femoral artery. In addition to his acute decompensation, which major procedural complication is of greatest concern during the next 12 hours?
 - A. Bleeding (particularly retroperitoneal bleeding)
 - B. Dissection/rupture
 - C. Stent thrombosis
 - D. Papillary muscle rupture

6. The patient returns to the ICU with a pulmonary artery catheter in place and is currently receiving dopamine at 12 mcg/kg/minute and norepinephrine at 0.08 mcg/kg/minute with heart rate 108 beats/minute, blood pressure 82/51 mm Hg, cardiac index 2.0, central venous pressure (CVP) 26 mm Hg, and pulmonary artery pressure 49/21 mm Hg. The physician is concerned about right ventricular dysfunction in the setting of shock and approaches you for a recommendation to increase blood pressure (BP). Ideally, the physician would prefer to wean dopamine and minimize further increases in pulmonary vascular resistance (PVR) because of the presence of pulmonary hypertension. Which strategy would be best to recommend?
- A. Keep the current infusions, and reevaluate later.
 - B. Initiate phenylephrine at 1 mcg/kg/minute, and wean the dopamine off if MAP is greater than 65 mm Hg.
 - C. Initiate vasopressin at 0.04 unit/minute, and wean the dopamine off if MAP is greater than 65 mm Hg.
 - D. Administer a 1-L bolus of normal saline, and wean the dopamine off if MAP is greater than 65 mm Hg.
7. Hours later, this patient goes into atrial fibrillation (AF) with a heart rate of 126 beats/minute; however, the patient's blood pressure remains 86/56 mm Hg according to the regimen selected in the previous question. Which agent would you most likely administer to manage the patient's AF?
- A. Amiodarone 150 mg intravenous push, followed by a continuous infusion at 1 mg/minute
 - B. Amiodarone 150 mg intravenous infusion for 10 minutes, followed by a continuous infusion at 1 mg/minute
 - C. Metoprolol 5 mg intravenous push once, followed by 5 mg intravenous push every 6 hours
 - D. Diltiazem 20 mg intravenous push, followed by a continuous infusion at 5 mg/hour and titrated to maintain a heart rate of less than 110 beats/minute
8. Which medication-related quality metric would not require documentation of contraindications based on this patient's clinical presentation (acute MI with preserved LVEF)?
- A. Aspirin contraindication
 - B. Statin contraindication
 - C. β -Blocker contraindication
 - D. Angiotensin-converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB) contraindication

I. CARDIOVASCULAR FUNDAMENTALS OVERVIEW

- A. The myocardium has five functions and distinctive properties:
1. Chronotropy: Ability to generate an electrical impulse at an intrinsic rate
 2. Dromotropy: The speed and ability to facilitate electrical impulse conduction
 3. Inotropy: Ability to contract in relation to a given preload, afterload, and heart rate
 4. Bathmotropy: Demonstration of an intrinsic excitatory threshold
 5. Lusitropy: Relaxation of the myocardium, independent from termination of contraction
 6. Other related terms:
 - a. Preload: Volume of blood (represented in most cases by a pressure) in a ventricular cavity at the end of diastole immediately before contraction, imparting stretch on a resting myocardial sarcomere
 - b. Afterload: The pressure that a *ventricle* must overcome to generate cardiac output. The greater the afterload (vascular resistance or impedance), the greater the amount of energy and force required to enable ejection of blood from a ventricle and vice versa
- B. Coronary Artery Circulation
1. Myocardial perfusion occurs through the coronary arteries during diastole.
 2. Coronary artery anatomy and perfusion are not the same in everyone.
 3. ECG abnormalities, hemodynamic assessment, and patient symptoms may assist with coronary artery disease (CAD) localization.
 4. Circulatory dominance:
 - a. Right dominant: Posterior descending artery and atrioventricular (AV) nodal artery arise from the right coronary artery (85% of the population).
 - b. Left dominant: Posterior descending artery arises from the circumflex artery (8% of the population).
 - c. Codominant: Posterior descending artery arises from branches of the circumflex and the right coronary artery (7% of the population).
 - d. Other notable variations: The sinoatrial (SA) node may have variation in the vessels that supply it; it is most commonly perfused by the right coronary artery (about 70%), circumflex (about 25%), and right coronary artery and circumflex (about 5%).

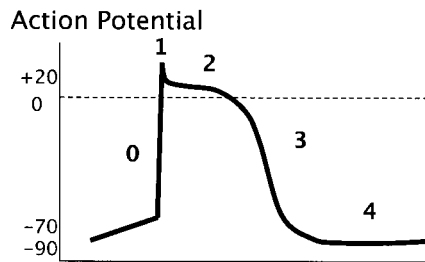


Developed by Erik Abel, PharmD, BCPS

Figure 1. Coronary artery circulation.

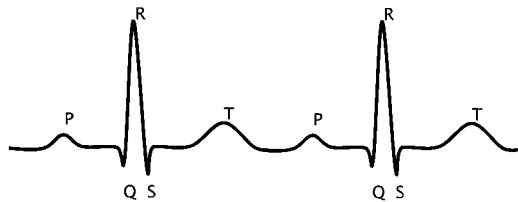
C. Anatomy in Relation to the ECG

1. A single lead of an ECG tracing is a summative representation of the action potentials occurring from a single cell, facilitating myocardial conduction, contraction, and relaxation.
2. A 12-lead ECG can provide a geographic representation of conduction within the myocardial tissue. Conduction abnormalities within specified leads may indicate perfusion defects in some clinical scenarios (i.e., acute coronary syndromes [ACS]).



Phase	Electrolyte movement	Conduction change
0	Na ⁺ influx into cell	Depolarization
1	Pre-refractory Ca ²⁺ and Cl ⁻ into cell	Effective Refractory Period
2	Ca ²⁺ into cell and K ⁺ out of cell	
3	K ⁺ out of cell	Repolarization
4	Resting Membrane Potential	

Electrocardiogram (ECG)



ECG point	Representation
P	Sinoatrial (SA) node impulse generation
PR interval	Duration for conduction to occur from the SA node through the AV node, bundle of His, bundle branches and Purkinje fibers
QRS	Concurrent atrial repolarization and ventricular depolarization
ST segment	Ventricular refractory period
T	Ventricular repolarization
QT interval	Duration for atrial and ventricular repolarization
RR interval	Duration between ventricular depolarizations (represents heart rate)
U	No listed or commonly visualized; may be more prominent in hypothermia or in severe electrolyte depletions

12 — Lead Electrocardiogram (ECG)

Limb leads				Precordial Leads			
I	Anterolateral (Circumflex)	aVR		V1	Anteroseptal (LAD)	V4	Anterapical (Distal LAD)
II	Inferior (RCA)	aVL	Anterolateral (Circumflex)	V2	Anteroseptal (LAD) Posterior (RCA)	V5	Anterolateral (Circumflex)
III	Inferior (RCA)	aVF	Inferior (RCA)	V3	Anterapical (Distal LAD) Posterior (RCA)	V6	Anterolateral (Circumflex)

adapted from ACLS instructor book

Figure 2. Anatomy in relation to the ECG.

II. HEMODYNAMIC MANAGEMENT AND THE HEART

A. Hemodynamic Assessment Relies on the Clinician's Interpretation to:

1. Understand cardiovascular circulation (Figure 3) and pathophysiology contributing to the hemodynamic variables in isolation and in the context of other changes and conditions.
2. Account for hemodynamic trends in view of end-organ function and use surrogates of oxygen delivery.
3. Understand the roles of hemodynamic tools, limitations in use, and interpretation of the devices/technology.
4. Identify appropriate therapeutic targets (Figure 4), and apply the pharmacologic/pharmacodynamic principles (Table 1) to initiate, modify, or discontinue therapy depending on clinical response.

Table 1. Pharmacologic Support in Cardiovascular Critical Illness (Br J Pharmacol 2012;165:2015-33; J Am Coll Cardiol 2014;63:2069-78; Pathophysiology of Heart Disease 2011:xiv; Circulation 2008;118:1047-56; Critical Care Medicine 2014:xix; J Pharm Pract 2011;24:44-60)

Vasopressors	Dopa	α_1	β_1	β_2	Other Mechanism	HR	CVP	CO	SVR	PVR
Dopamine ^a	+++++	+++	++++	++		↑	↔	↑	↔ or ↑	↔ or ↑
Epinephrine ^a		++++	++++	+++		↑	↔ or ↑	↑	↑	↑
Norepinephrine ^a		+++++	+++	++		↑	↑	↑ or ↓	↑	↑
Phenylephrine		+++++				↔ or ↓	↑	↔ or ↓	↑	↑
Vasopressin	N/A “ α_1 -like effects”				V ₁ and V ₂ agonism	↔ or ↓	↑	↔ or ↓	↑	↔ or ↓
Inotropes										
Dobutamine		+	++++	++		↑	↔ or ↓	↑	↔ or ↓	↔ or ↓
Isoproterenol			+++++	+++++		↑	↔ or ↓	↑	↔ or ↓	↔ or ↓
Milrinone ^b	N/A “B ₁ and β_2 -like effects”				PDE ₃ inhibition	↑	↓	↑	↓	↓
Vasodilators										
Nitroglycerin					cGMP	↔ or ↑	↓	↔ or ↑	↔ or ↓	↔ or ↓
Nitroprusside					cGMP	↔ or ↑	↓	↔ or ↑	↓	↓
Nesiritide					cGMP	↔ or ↑	↓	↔ or ↑	↓	↓
Nitric oxide (inhaled)					cGMP	N/A	↔	↔ or ↑	↔	↓
Epoprostenol (inhaled)					cAMP	N/A	↔	↔ or ↑	↔	↓

^aHigh doses associated with increasing α_1 activity.

^bNormal half-life is 2.5 hours, but drug is eliminated renally. Loading dose rarely used in routine management because of hypotension.

^cAMP = cyclic adenosine monophosphate; cGMP = cyclic guanosine monophosphate; CVP = central venous pressure; N/A = not applicable; PDE₃ = phosphodiesterase type 3; PVR = pulmonary vascular resistance; SVR = systemic vascular resistance.

B. Advantages and Disadvantages of Invasive Hemodynamic Monitoring for Assessing Cardiac Output and/or Volume Status

1. Hemodynamic monitoring techniques facilitate diagnosis
2. Therapy guided by clinical assessment and a pulmonary artery (PA) catheter compared with clinical assessment alone for heart failure did not result in differences in overall mortality or hospitalizations. However, more anticipated adverse events (i.e., infection, bleeding) were seen with PA catheter-guided care (JAMA 2005;294:1625-33).
3. Diligent use and skilled interpretation of these technologies, together with patient assessment, can be used to guide therapeutic interventions.
4. See comparisons of invasive and minimally invasive hemodynamic monitoring devices (Table 2 in the Shock and Resuscitation chapter).

C. Pharmacologic Support in Cardiovascular Critical Illness (see Table 1)

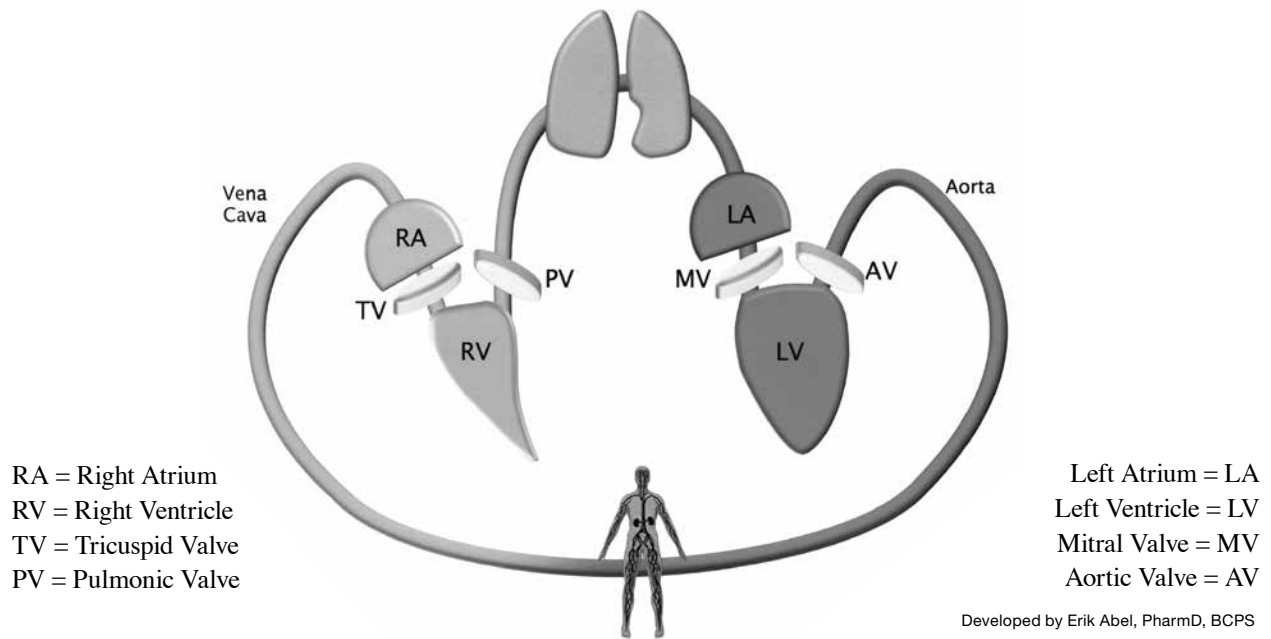


Figure 3. Cardiovascular systemic circulation.

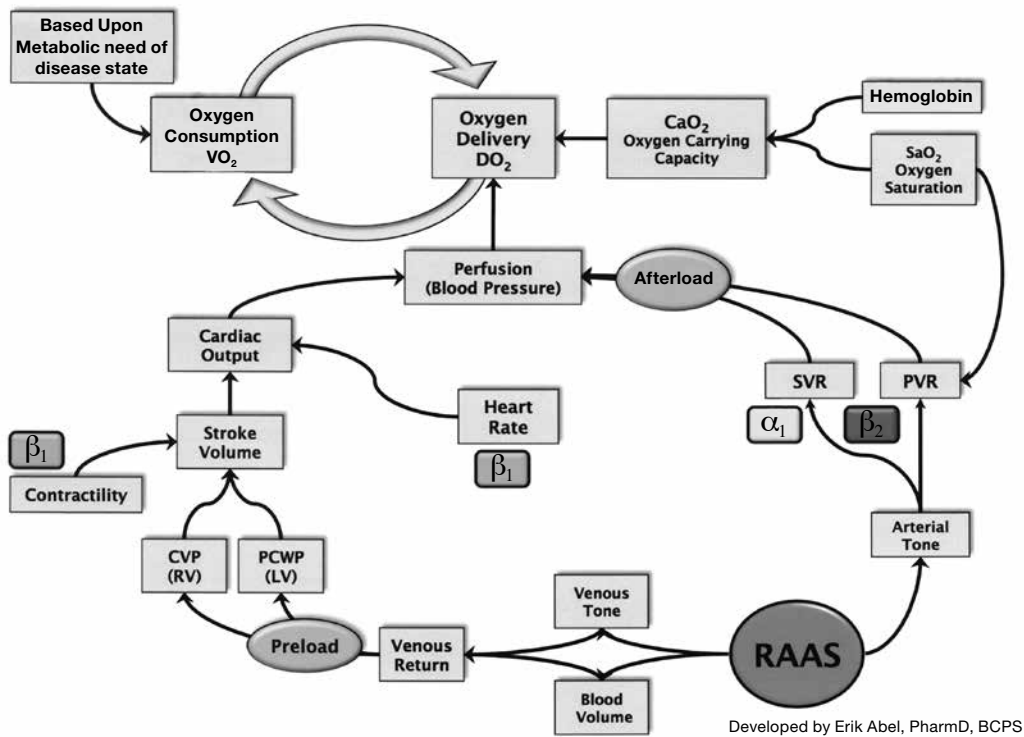


Figure 4. Integrated model of the hemodynamic variables and therapeutic targets.

III. CARDIOGENIC SHOCK

- A. Characterized by three hallmarks:
1. Sustained hypotension unresponsive to fluid administration alone (systolic blood pressure [SBP] less than 90 mm Hg for at least 60 minutes)
 2. Evidence of myocardial dysfunction with reduced cardiac index (less than 2.2 L/minute/m²)
 3. Signs and symptoms of malperfusion in the setting of elevated cardiac filling pressures (e.g., pulmonary capillary wedge pressure [PCWP] greater than 18 mm Hg)
- B. Signs and Symptoms: See Heart Failure section.
- C. Epidemiology: Without appropriate diagnosis and management, in-hospital mortality rates as high as 60% have been described (Semin Respir Crit Care Med 2011;32:598-606).

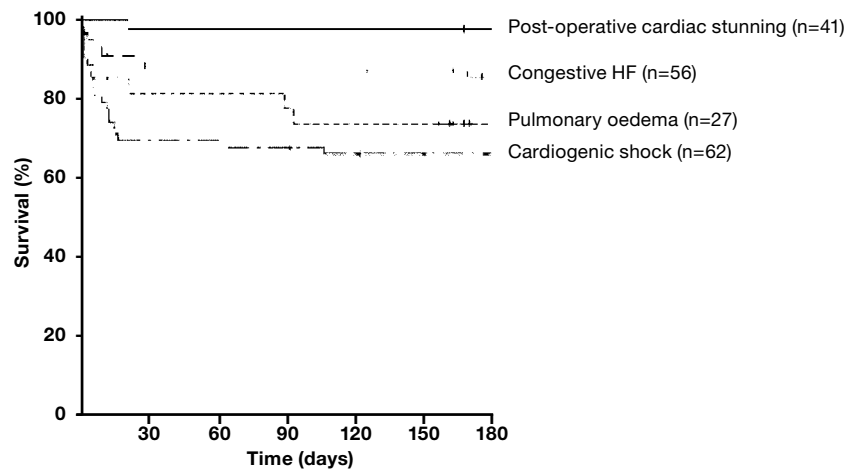


Figure 5. Survival rates of ICU patients over time presenting with different acute heart failure syndromes (Crit Care 2010;14:201).

- D. Etiology
1. Usually caused by left ventricular (LV) failure secondary to an acute MI, but a list of other potential causes can be found in Box 1
 2. May be multifactorial, including one or more of the causative etiologies; however, can also coexist with other types of shock syndromes

Box 1. Potential Causes of Cardiogenic Shock (Critical Care Medicine 2014;xix; Cardiol Clin 2013;31:567-80, viii; Cardiol Clin 2013;31:519-31, vii-viii; Semin Respir Crit Care Med 2011;32:598-606)

LV Failure

- Large MI
- Small MI with preexisting systolic heart failure
- Reinfarction
- Septic shock with severe myocardial depression

RV Failure

- RV infarction
- End-stage pulmonary hypertension

Acute Mechanical Dysfunction

- Papillary muscle rupture or chordal rupture with subsequent severe mitral regurgitation
- Free-wall rupture
- Ventricular septal rupture
- Cardiac tamponade

Cardiomyopathy

- End-stage heart failure
- Myocarditis
- Peripartum cardiomyopathy
- Left ventricular outflow tract obstruction
- Stress-induced cardiomyopathy (i.e., Takotsubo)

Valvular Disease

- Acute aortic regurgitation
- Ischemic mitral regurgitation
- Aortic or mitral stenosis with tachyarrhythmia or other condition causing decompensation
- Infectious endocarditis
- Prosthetic valve dysfunction or thrombosis

Arrhythmias

Other Conditions

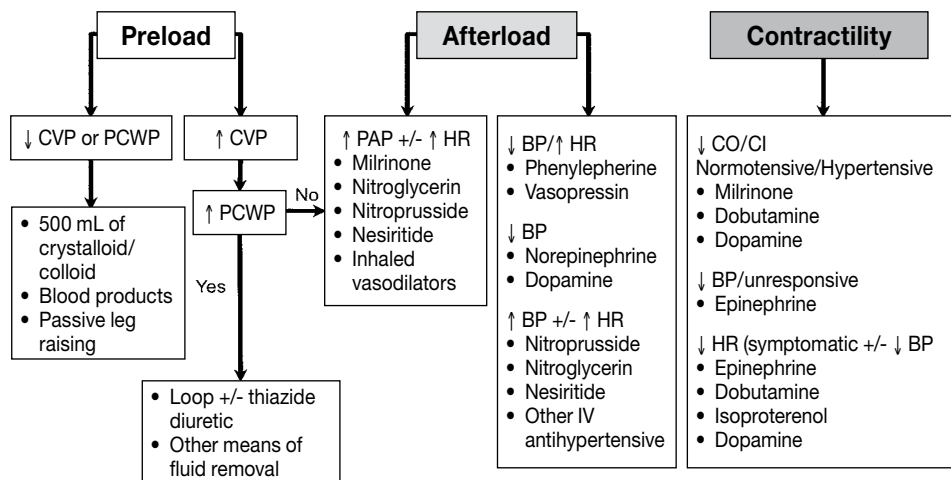
- Prolonged cardiopulmonary bypass and/or coronary air embolus
- Cardiac trauma (blunt or penetrating)
- Heart transplant rejection
- Pulmonary embolism
- Medical nonadherence

LV = left ventricular; MI = myocardial infarction; RV = right ventricular.

E. Resuscitation/Treatment

1. Treatment largely depends on managing underlying chronic or acute cardiovascular disease(s) outlined in Box 1, with consideration given to chronicity of clinical changes before onset of shock.
2. Means of management will be primarily discussed under the Major Contributing Etiologies headings in sections IV–VII.
3. Hemodynamic management and pharmacotherapeutic considerations
 - a. Because cardiogenic shock may have different underlying, contributing etiologies, hemodynamic management requires careful interpretation of clinical values. Treatment strategies could be devised according to the algorithm in Figure 6.

- b. Sepsis Occurrence in Acutely Ill Patients (SOAP) II landmark trial (N Engl J Med 2010;362:779-89)
- International multicenter trial (n=1679) that compared the 28-day mortality of norepinephrine with that of dopamine in the management of shock
 - Included if signs of malperfusion and MAP less than 70 mm Hg or SBP less than 100 mm Hg, despite adequate fluid challenge (at least 1000 mL of crystalloids or 500 mL of colloids unless the CVP was greater than 12 mm Hg or the pulmonary artery occlusion pressure was greater than 14 mm Hg)
 - Allowed titration to maximums of norepinephrine 0.19 mcg/kg/minute versus dopamine 20 mcg/kg/minute, after which open-label norepinephrine was allowed (open-label norepinephrine doses did not exceed 1.1 mcg/kg/minute during the study period)
 - Epinephrine and vasopressin were permitted as rescue agents (similar use in both groups).
 - Dobutamine use was greater in the norepinephrine group (19.4% vs. 14.8%).
 - Showed that dopamine was associated with a significantly higher mortality rate than was norepinephrine with or without dobutamine in patients with cardiogenic shock in subgroup analysis
 - Specifically, dopamine was associated with more adverse events than norepinephrine in the management of all shock subtypes, predominantly driven by the incidence of arrhythmias (24.1% vs. 12.1%, $p < 0.001$). Tachyarrhythmias with dopamine had the greatest incidence within the first 36 hours after randomization.



Adapted from: Blais, DM. PSAP- IV: Critical and urgent care. 2010

Figure 6. Shock management and treatment considerations based on hemodynamic indices.

Patient Cases

Questions 1–8 pertain to the following case.

J.M. is a 68-year-old man with a history of CAD including STEMI 6 months ago with placement of two drug-eluting stents, type 2 diabetes mellitus, hypertension, dyslipidemia, gastroesophageal reflux disease, hypertension, obstructive sleep apnea, frequent epistaxis, ischemic cardiomyopathy (LVEF 30%–35%), and moderate to severe mitral regurgitation. He is admitted to the cardiac intensive care unit for severe shortness of breath and altered mental status, and he is currently on continuous positive airway pressure (CPAP). He has gained 13 kg during the past 2 weeks (now weighs 121 kg) and has had decreased urine output, despite having had his diuretic dose increased. Home medications include the following: aspirin 81 mg once daily, ticagrelor 90 mg every 12 hours, pantoprazole 40 mg once daily, metoprolol tartrate 25 mg every 12 hours, atorvastatin 40 mg once daily, insulin glargine 10 units every night, metformin 500 every 12 hours, furosemide 40 mg twice daily, and potassium chloride 20 mEq twice daily. His wife states that he was taking clopidogrel until 1 month ago, at which time he was given ticagrelor samples from his primary care physician because of cost concerns. A physical examination reveals rales throughout his lung fields. He is afebrile, anxious, and alert.

1. Given J.M.'s comorbidities, some drugs or drug classes have proven mortality benefits. Which group of added or modified medications not on the patient's home medication profile might best help further slow the progression of his disease and confer mortality benefits?
 - A. Amlodipine, clopidogrel, and sitagliptin
 - B. Spironolactone, lisinopril, and carvedilol
 - C. Pravastatin, amlodipine, and aspirin 325 mg
 - D. Prasugrel, sildenafil, and atenolol
2. Given the patient's presentation, which group of diagnostic tests would be most helpful to guide your recommendations to the team for J.M.'s current management? (Assume that a basic metabolic panel [Chem 7], a pulse oximetry, and a capillary blood glucose have already been completed.)
 - A. Urine culture, respiratory culture, lactate, and procalcitonin
 - B. Chest radiography, arterial blood gas (ABG), liver function tests, and serial troponins
 - C. Chest radiography, echocardiogram (ECHO), lactate, and BNP
 - D. Chest radiography, arterial line, ABG, and lactate

Patient Cases (continued)

3. All tests previously mentioned have been ordered, and the following results are available. J.M.'s blood pressure is 90/56 mm Hg (MAP 67 mm Hg), and his heart rate is 56 beats/minute. A 12-lead ECG showed normal sinus rhythm without evidence of acute ST-T changes.
- Chest radiography reveals diffuse patchy opacities; however, infiltrate cannot be ruled out; lines are all in appropriate positions.
 - Serum chemistry panel results are as follows: sodium 126 mEq/L, potassium 4.8 mEq/L, chloride 102 mEq/L, carbon dioxide 21 mEq/L, BUN 32 mg/dL, SCr 1.6 mg/dL, and glucose 134 mg/dL.
 - Results of the CBC are as follows: WBC 9.8×10^3 cells/mm³, hemoglobin 11.1 g/dL, hematocrit 32.6%, and platelet count 173,000/mm³.
 - Additional laboratory values include the following: troponin 0.9 ng/mL, AST 114 IU/L, ALT 102 IU/L, and BNP 1936 pg/mL.
 - Invasive hemodynamic variables include CVP 28 mm Hg, pulmonary artery pressures 46/22 mm Hg, cardiac index 1.8 L/minute/m², and central venous oxygen saturation (ScvO₂) 53%; pulmonary artery occlusion pressure is not yet available.
 - ABG results are as follows: pH 7.36, partial pressure of oxygen (P_{O₂}) 93.7, partial pressure of carbon dioxide (P_{CO₂}) 43.2, bicarbonate 23.9, oxygen (O₂) saturation 89%, and lactate 6.9.
 - ECHO results are pending.

The patient's physical examination reveals that his extremities are cold to the touch, and his capillary refill is poor. The team has ordered furosemide 80 mg intravenously once and discontinued metoprolol; the team would like to initiate a vasopressor or inotrope for this patient. Which would be best to recommend at this time?

- A. Norepinephrine 0.08 mcg/kg/minute
- B. Epinephrine 0.08 mcg/kg/minute
- C. Milrinone 0.25 mcg/kg/minute
- D. Dobutamine 5 mcg/kg/minute

IV. ACUTE CORONARY SYNDROMES

- A. Pathophysiology
 1. Manifestation of prolonged cessation of oxygenated blood supply to a portion of the myocardium that is most commonly caused by an acute thrombus at the site of coronary atherosclerotic stenosis leading to local or regional myocardial ischemia and necrosis
 2. Other disease states leading to an elevated myocardial oxygen demand with a concurrent inability to meet such demands may result in a scenario where "demand ischemia" is considered versus a diagnosis of ACS.
- B. Presentation and Diagnosis (Circulation 2014;130:e344-426; Circulation 2013;127:e362-425) – Although other cardiac enzymes assays are available for clinical use, cardiac troponins are usually used as sensitive markers indicative of myocardial necrosis. Troponin is eliminated renally.

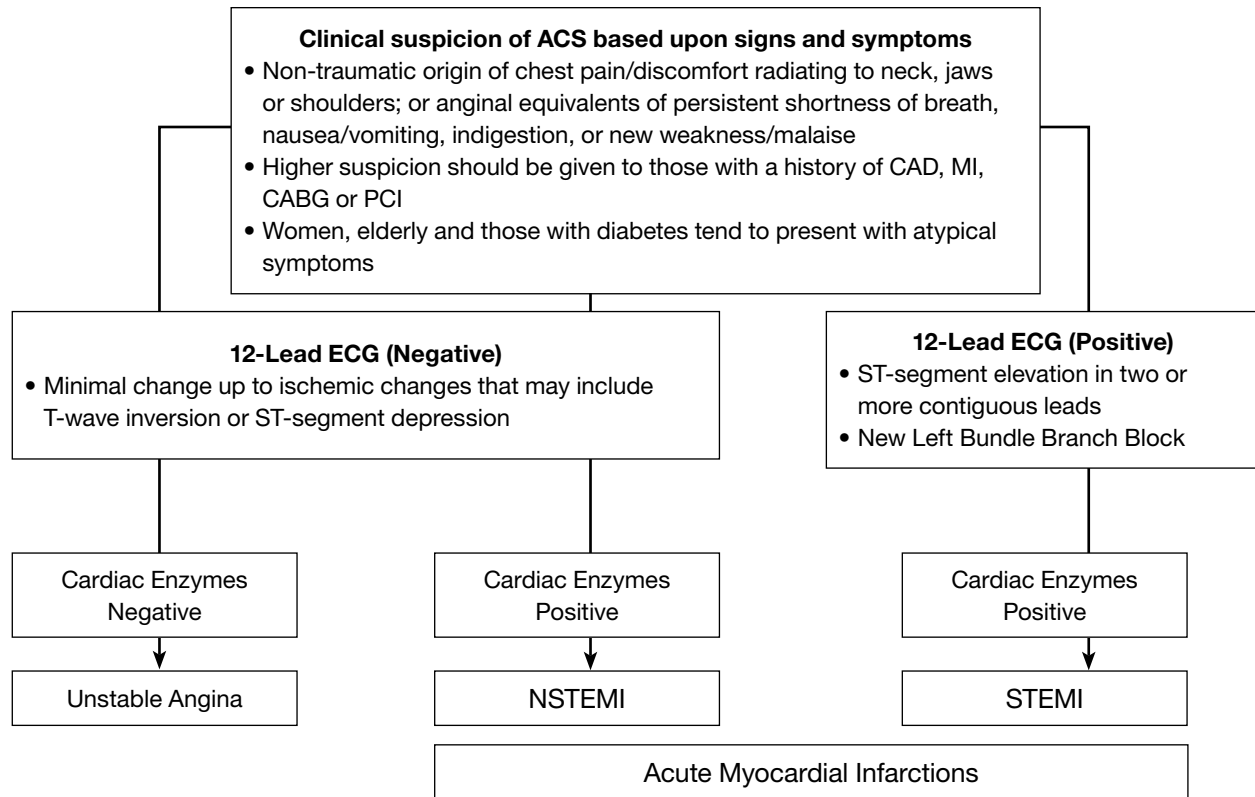


Figure 7. Presentation and diagnosis.

Box 2. Causes of Troponin Elevation (Heart 2006;92:987-93)

Acute decompensated heart failure	Early post-cardiac surgery
Acute MI	Heart transplantation
Acute pulmonary embolism	Myocarditis
Aortic stenosis	Pericarditis
Cardiac amyloidosis	Post-PCI
Cardiotoxic chemotherapy	Rhabdomyolysis
Chest compressions	Sepsis
Chest wall trauma or compressions	Severe strenuous exercise
Chronic heart failure	Tachyarrhythmia
Direct current cardioversion/defibrillation	Type A dissection

PCI = percutaneous coronary intervention.

C. Acute Management of MI

Table 2. Acute Management (Circulation 2014;130:e344-426; Circulation 2013;127:e362-425)

	STEMI	NSTEMI/ Unstable Angina
Goals of care	Reperfusion therapy as soon as possible • Primary PCI preferred if it can be performed within 90 min of medical contact • If primary PCI is unavailable within 90 min of medical contact, fibrinolytics should be administered within 30 min of presentation unless contraindications exist • Surgical revascularization may be indicated, depending on severity of CAD, complexity of anatomy, or development of other complications	Prevent total occlusion of the vessel • Decision and need for revascularization (PCI or surgery) vs. medical management should be made on the basis of risk stratification, symptom resolution, and indicators of ongoing myocardial damage/ischemia

CAD = coronary artery disease.

Table 3. Predominant Interventions on Presentation/Onset for Stabilization – Any ACS (Circulation 2014;130:e344-426; Circulation 2013;127:e362-425)

Predominant interventions on presentation/onset for stabilization – Any ACS	
Oxygen	• Can help attenuate anginal pain secondary to tissue hypoxia • Supplemental oxygen considered if $\text{Sao}_2 < 90\%$, respiratory distress, or other high-risk features for hypoxemia
Aspirin	• Inhibit platelet activation • Four aspirin 81 mg each (324 mg total) or one 325-mg tablet (non-enteric coated) should be chewed and swallowed immediately
Nitrates	• Can facilitate coronary vasodilation and may also be helpful in scenarios of severe cardiogenic pulmonary edema caused by increased venous capacitance • Nitroglycerin (NTG) 0.4 mg sublingually every minute for total of THREE doses; afterward, assess need for IV NTG • IV NTG is indicated in the first 48 hr after treatment of persistent ischemia, HF, or hypertension but should not preclude therapy such as β-blockers or ACE inhibitors when indicated Should <u>NOT</u> be administered: • If SBP < 90 mm Hg OR if SBP is ≤ 30 mm Hg below baseline • If severe bradycardia (including heart block) with HR ≤ 50 beats/min • If tachycardia (HR ≥ 100 beats/min) in the absence of symptomatic HF, or RV infarction • If patient has received an oral phosphodiesterase inhibitor within the past 24–48 hr
Morphine or other narcotic analgesic	• Provides analgesia, and decreases pain-induced sympathetic/adrenergic tone • Morphine commonly used because it may also induce vasodilation and mediate some degree of afterload reduction • Morphine now carries a class IIb-B recommendation and may be not be favored more than other narcotic analgesics, given that at least two large trials have identified an association between morphine administration and risk of death (N Engl J Med 2014;371:1016-27; Am Heart J 2005;149:1043-9)

Table 3. Predominant Interventions on Presentation/Onset for Stabilization – Any ACS (Circulation 2014;130:e344-426; Circulation 2013;127:e362-425) (*continued*)

Predominant interventions on presentation/onset for stabilization – Any ACS	
β-Blockade	- Decreases risk of ventricular arrhythmias and sudden cardiac death in early post-MI period - Decreases HR and myocardial oxygen demand and increases diastolic filling time of ventricles, thereby improving oxygen flow through the coronary arteries β-Blockade should be initiated within the first 24 hr of an ACS <u>unless</u>: - There are signs of HF - Active evidence of other shock states - If at increased risk of cardiogenic shock (SBP < 120 mm Hg), HR > 110 beats/min or < 60 beats/min <i>*Note: Intravenous β-blockers may be particularly harmful in patients with risk factors for shock.</i> Relative contraindications to β-blockade include: - PR interval > 0.24 s, second- or third-degree heart block, and active asthma/reactive airway disease
Helpful acronym	- MONA ± BB: - Morphine - Oxygen - Nitrates (unless contraindicated) - Aspirin - β-Blocker (unless contraindicated)
Other precautions	- ACE inhibitors/ARBs should be used with caution within the first 24 hr of ACS because of the risk of hypotension and potential contribution to contrast-induced nephrotoxicity - Any NSAID other than aspirin should be avoided and/or discontinued for reasons beyond GI bleeding and nephrotoxicity, which may include reinfarction, hypertension, HF exacerbation, myocardial rupture, and overall increased risk of mortality associated with their use

ACS = acute coronary syndrome(s); GI = gastrointestinal; HF = heart failure; IV = intravenous; LMNOP = lasix-morphine-nitro-oxygen-position/positive pressure ventilation; NSAID = nonsteroidal anti-inflammatory drug; Sao₂ = arterial oxygen saturation.

D. Revascularization

1. Nonsurgical – Details of interventional cardiology procedures are too broad to be discussed in great detail in this chapter; however, following are some considerations of the intervention that may play a role in post-procedural management during a left heart catheterization and percutaneous coronary intervention (PCI):
 - a. Access site
 - i. Radial artery (and, rarely, brachial artery) (Catheter Cardiovasc Interv 2011;78:840-6)
 - (a) Easily accessible
 - (b) Increased risk of vasospasm during procedure
 - (c) Easily compressible vessel when hemostasis is needed post-procedure
 - (d) Does not prevent patient mobility post-procedure
 - ii. Femoral artery
 - (a) Easily accessible
 - (b) More difficult to compress vessel when hemostasis is needed post-procedure and also associated with increased bleeding complications
 - (c) Limits patient mobility post-procedure for at least 12–24 hours (bleeding risk after sheath removal)

- b. Common interventions performed:
 - i. Thrombectomy: Thrombus aspiration generally followed by placement of a stent at site of lesion
 - ii. Percutaneous transluminal coronary angioplasty (PTCA), also referred to as “plain old balloon angioplasty” (POBA): Balloon expansion and at least temporary displacement of occlusion at site of lesion
 - iii. Stent placement
 - (a) Important to note the number of stents placed, types of stents, and locations of placement
 - (b) Bare-metal stent
 - (1) Requires aspirin for life and a P2Y₁₂ antagonist for at least 1 month (12 months preferred) to allow adequate time for endothelialization of the stent(s)
 - (2) Longer therapy durations may be considered, depending on the number of stents and/or location(s) of the stent(s).
 - (3) Higher risk of in-stent stenosis over time (a consequence of neointimal cell proliferation)
 - (4) Typically preferred for patients unable to adhere to (i.e., cost or compliance) or not appropriate for (i.e., bleed risk) longer-term dual antiplatelet therapy
 - (c) Drug-eluting stent
 - (1) Requires aspirin for life and a P2Y₁₂ antagonist for at least 12 months. Longer therapy durations may be considered, depending on the number and/or location(s) of the stent(s) as well as patient bleeding risk. Ongoing investigations are evaluating the optimal duration of dual antiplatelet therapy, but an individualized approach is also needed (J Am Coll Cardiol 2015;66:832-47; Circulation 2016;133:2094-98).
 - (2) The benefit of drug-eluting stents (i.e., everolimus, zotarolimus, biolimus) is the mitigation of in-stent restenosis, more often seen with bare-metal stenting. However, the rate of stent endothelialization is also impaired such that the risk of stent thrombosis persists for a longer period of time. Consequently, the use of drug-eluting stents mandates longer-term dual antiplatelet therapy.
 - iv. Ventriculogram: Means of assessing the ejection fraction using a larger volume of intravenous contrast dye delivered directly into the ventricle to estimate the volume of blood ejected during systole
- 2. Surgical – Details of coronary artery bypass grafting (CABG) procedures, including conduit type and use of cardiopulmonary bypass (or performing off pump), are too broad to be discussed in greater detail in this chapter. According to the Society of Thoracic Surgeons/American College of Cardiology/American Heart Association (STS/ACC/AHA) CABG guidelines, emergency CABG is recommended in patients with an acute MI in the following scenarios (J Am Coll Cardiol 2011;58:e123-210):
 - a. Primary PCI has failed or cannot be performed
 - b. Coronary anatomy is more suitable for CABG
 - c. Persistent ischemia of a significant area of myocardium at rest and/or hemodynamic instability refractory to nonsurgical therapy is present
 - d. Requirement of surgical repair of a postinfarction mechanical complication of MI (i.e., ventricular septal rupture, mitral valve insufficiency caused by papillary muscle infarction and/or rupture, or free wall rupture)
 - e. Patients with cardiogenic shock who are suitable for CABG, irrespective of the time interval from MI to onset of shock and time from MI to CABG
 - f. Patients with life-threatening ischemic ventricular arrhythmias in the presence of a left main stenosis of 50% or more and/or three-vessel CAD
 - g. CABG use is reasonable as a revascularization strategy in patients with multivessel CAD with recurrent angina or MI within the first 48 hours of STEMI presentation as an alternative to a more delayed strategy.

- h. Early revascularization with PCI or CABG is reasonable for select patients older than 75 years with ST-segment elevation or left bundle branch block who are suitable for revascularization irrespective of the time interval from MI to onset of shock.
 3. Medical management – No revascularization:
 - a. Less invasive strategies may be opted for rather than revascularization in some patients. Considerations reinforce a patient-centered approach driven by evidence of ongoing/recurrent ischemia and feasibility of revascularization, including myocardial viability, patient frailty, and comorbid disease states.
 - b. Ongoing care outlined in section E remains the focus of optimizing aggressive medical management.
- E. Antithrombotics in MI
1. The roles and combinations of antithrombotics continue to be refined in select populations (those with NSTEMI/ACS, STEMI, and PCI). For the most current guidelines and landmark trials, please see www.acc.org/guidelines.
 2. Oral antiplatelet therapy
 - a. Platelets can be activated by several different mechanisms, only some of which can be inhibited by medications.
 - b. Evaluation of antiplatelet therapy can be performed with platelet function testing and/or genotyping. However, neither are currently performed routinely in the clinical setting. Clinical outcomes with the use of platelet function testing to modify antiplatelet therapy (i.e., high-dose vs. standard-dose clopidogrel) in PCI patients with high on-treatment platelet reactivity have been negative to date (JAMA 2011;305:1097-1105). Outcomes with prospective genotype-guided antiplatelet therapy (CYP2C19) from large cohorts of PCI patients are forthcoming.
 - c. The response to antiplatelets in certain critical care patient scenarios, such as acute hepatic and kidney injury, have not been well documented. In other situations, such as when enteral administration is not an option, other parenteral antiplatelets may be considered (Table 5). However, these options, which include glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors and cangrelor, have primarily been studied in the setting of PCI only.

Table 4. Oral Antiplatelet Therapy (Circulation 2013;127:e362-425; Circulation 2014;130:e344-426; J Am Coll Cardiol 2011;58:e123-210; J Am Coll Cardiol 2011;58:e44-122; Br J Clin Pharmacol 2011;72:647-57)

Medication	Aspirin	Clopidogrel	Prasugrel	Ticagrelor
Mechanism of action	Inhibits thromboxane A ₂ -mediated platelet activation	Inhibits ADP-mediated platelet activation at P2Y ₁₂ receptor	Inhibits ADP-mediated platelet activation at P2Y ₁₂ receptor	Inhibits ADP-mediated platelet activation at P2Y ₁₂ receptor
Loading dose	162–325 mg	300-600 mg	60 mg	180 mg
Maintenance dose	81 mg	75 mg QD	5–10 mg QD ^a	90 mg BID
Route	Oral	Oral	Oral	Oral
Prodrug	No	Yes	Yes	No
Reversible platelet binding	No	No	No	Yes
Onset	30 min	2–6 hr	30 min	30 min
% Platelet inhibition	~ 10–20	30–40	60–70	60–70

Table 4. Oral Antiplatelet Therapy (Circulation 2013;127:e362-425; Circulation 2014;130:e344-426; J Am Coll Cardiol 2011;58:e123-210; J Am Coll Cardiol 2011;58:e44-122; Br J Clin Pharmacol 2011;72:647-57) (*continued*)

Medication	Aspirin	Clopidogrel	Prasugrel	Ticagrelor
Recommended holding duration before CABG ^b	Do not hold	5 days	7 days	5 days
Other notable adverse effect(s) or clinical pearls		Pharmacogenomic variability (CYP2C19) in response is well documented	Contraindication in patients with any history of stroke or TIA because of bleeding risk, and warning of use in patients > 75 yrs of age or weight < 60 kg	• Adenosine-induced dyspnea and bradyarrhythmias • Older adult patients and patients with moderate or severe hepatic impairment may be at increased risk of bleeding • Concomitant maintenance doses of aspirin > 100 mg should be avoided because of lack of efficacy

^aPatients with lean body weight (< 60 kg) should receive a 5 mg daily maintenance dose of prasugrel

^bDecisions to hold these agents before other invasive procedures must consider indications for use, risk of thrombosis (i.e., stent type, locations, and number), and risk of bleeding associated with intended procedure/surgery (JAMA 2013;310:1451-2; Catheter Cardiovasc Interv 2013;82:1113-4; JAMA 2013;310:189-98; N Engl J Med 2013;368:2113-24; J Am Coll Cardiol 2011;58:e44-122; Reg Anesth Pain Med 2010;35:64-101; J Am Coll Cardiol 2007;49:734-9).

ADP = adenosine diphosphate; BID = twice daily; QD = once daily; TIA = transient ischemic attack.

3. Parenteral antithrombotics

- Use of these agents is most concentrated in the procedural setting, although use may continue for a finite period post-procedurally.
- The selection and use among the agents in Table 5 may depend on presentation, timing/dose of pre-procedural antiplatelet medication administration, clot burden during procedure, and estimated bleeding risk of the procedure.

Table 5. Parenteral Antithrombotics (Circulation 2014;130:e344-426; Circulation 2013;127:e362-425; J Am Coll Cardiol 2011;58:e123-210; J Am Coll Cardiol 2011;58:e44-122; Br J Clin Pharmacol 2011;72:647-57)

Medication	Heparin (UFH) ^a	Bivalirudin	Abciximab	Eptifibatide	Tirofiban	Cangrelor ^b
Mechanism of action	Indirect thrombin inhibition (binds to antithrombin III)	Direct thrombin inhibitor	Binds to GP IIb/IIIa platelet receptor, inhibiting final common pathway for platelet aggregation	Binds to GP IIb/IIIa platelet receptor, inhibiting final common pathway for platelet aggregation	Binds to GP IIb/IIIa platelet receptor, inhibiting final common pathway for platelet aggregation	Inhibits ADP-mediated platelet activation at P2Y ₁₂ receptor
Bolus dose	50–100 units/kg based on target activated clotting time (ACT)	0.75 mg/kg	0.25 mg/kg	180 mcg/kg x 2, 10 min apart	25 mcg/kg	30 mcg/kg
Continuous infusion	Not typically given during PCI	1.75 mg/kg/hr	0.125 mcg/kg/min (max 10 mcg/min)	2 mcg/kg/min	0.15 mcg/kg/min	4 mcg/kg/min
Platelet inhibition	Indirectly inhibits thrombin-mediated platelet activation	Indirectly inhibits thrombin-mediated platelet activation	Irreversibly inhibits the life of the platelet (7–10 days)	Restoration of platelet function within 6–8 hr of discontinuation	Restoration of platelet function within 6–8 hr of discontinuation	Restoration of platelet function within 1 hr of discontinuation
Elimination	Hepatic and reticulo-endothelial system	80% plasma proteolysis 20% renal	Reticulo-endothelial system	Renal	Renal	Plasma dephosphorylation
Removed by dialysis	No	Partial	No	No	No	N/A
Other notable adverse effect(s) or clinical pearls	Target ACT of about 200–300 s during procedure based on presence of GP IIb/IIIa inhibitor and device used	Requires renal dose adjustment Useful in patients with suspected or confirmed HIT May be preferred in patients with higher bleeding risk (particularly compared with UFH with GP IIb/IIIa inhibitor and among patients who undergo a transfemoral PCI approach)	Murine monoclonal antibody – may produce antigenicity Acute, profound thrombocytopenia	Requires renal dose adjustment Acute, profound thrombocytopenia	Requires renal dose adjustment Acute, profound thrombocytopenia	An oral P2Y ₁₂ antagonist must be given immediately after discontinuation of cangrelor to maintain platelet inhibition

^aEnoxaparin may be used as an alternative to UFH.^bU.S. Food and Drug Administration (FDA) approved as an adjunct to PCI for reducing the risk of periprocedural myocardial infarction (MI), repeat coronary revascularization, and stent thrombosis (ST) in patients who have not been treated with a P2Y₁₂ platelet inhibitor and are not receiving a glycoprotein IIb/IIIa inhibitor.

ACT = activated clotting time; GP = glycoprotein; HIT = heparin-induced thrombocytopenia; N/A = not applicable; UFH = unfractionated heparin.

F. Post-Intervention Complications

1. Bleeding (particularly retroperitoneal bleeding)
 - a. Several antithrombotic agents are used during PCI to inhibit both the platelets and the clotting cascade, causing potential coagulopathies.
 - b. In addition to antithrombotic use, the catheterization access site has been identified as a major contributor to post-PCI bleeding complications. Note that use of the trans-radial approach has been demonstrated to be a bleeding avoidance strategy compared with the trans-femoral approach.
2. Dissection/rupture of free wall, coronary artery, or aorta: Although this may be spontaneous, it may also be caused by vessel trauma from the catheter itself.
3. Stent thrombosis
 - a. When antiplatelet therapy is discontinued early (aspirin, P2Y₁₂ inhibitor, or both), stent thrombosis may occur in up to 25% of coronary artery stents, irrespective of type of stent (drug-eluting stent or bare metal stent).
 - b. Almost 1 in 7 patients may discontinue P2Y₁₂ inhibitors within 30 days post-PCI, thus increasing mortality risk (adjusted hazard ratio [HR] 9.0; 95% confidence interval [CI], 1.3–60.6) (JAMA 2013;310:189-98).
 - c. Mortality rates associated with stent thrombosis can be as high as 45%.
 - d. Despite bleeding risks in critically ill patients, careful consideration should be given to correlating these risks with the risk of stent thrombosis.
4. Papillary muscle rupture and mitral regurgitation (mechanical complications)
5. Arrhythmias (particularly after reperfusion)
6. Contrast-induced nephropathy

G. Ongoing Care – Quality measures for NSTEMI or STEMI independent of revascularization or medical management

1. Medications that should be initiated before discharge or contraindications should be documented in the medical record:
 - a. Aspirin
 - b. Statin
 - c. P2Y₁₂ inhibitor
 - d. β -Blocker
 - e. If LVEF less than or equal to 40%, ACE inhibitor or ARB and aldosterone antagonist (if also evidence of heart failure and/or DM)
2. Interventions and/or referrals
 - a. LV function assessment (by imaging or during catheterization)
 - b. Cardiac rehabilitation
 - c. Smoking cessation counseling
 - d. Measurement of a lipid profile, including the low-density lipoprotein (LDL) cholesterol, should preferably be obtained within 24 hours of admission. Any lipid profile measured between 6 months before first medical contact and hospital discharge qualifies for this quality measure.
3. For more information on cardiology-related quality measures and registries, see www.ncdr.com/.

Patient Case

Questions 4 and 5 pertain to the case on page 2-102.

4. J.M.'s ECG results reveal no acute evidence of ST segment changes. However, the resident is still considering a diagnosis of ACS, given the patient's shortness of breath and mild troponin elevation. Which statement would be most accurate regarding the potential for other potential diagnoses?
 - A. No, this is most likely an NSTEMI.
 - B. Yes, it is likely undiagnosed chronic obstructive pulmonary disease.
 - C. Yes, it is likely early sepsis.
 - D. Yes, it is likely decompensated heart failure.

5. J.M. has been experiencing intermittent bradycardia on telemetry. The team has consulted the cardiac electrophysiology team. In the meantime, which statement most accurately reflects whether any other underlying correctable/contributing causes can be addressed?
 - A. Ticagrelor could be discontinued and switched back to clopidogrel.
 - B. Ticagrelor should be discontinued altogether.
 - C. There are no other identifiable causes, and this is likely a reflection of J.M.'s heart failure disease progression.
 - D. J.M.'s hyperkalemia should be treated.

V. ARRHYTHMIAS AND ANTIARRHYTHMICS

- A. Pathophysiology: Arrhythmias are generally caused by automaticity and/or re-entrant conduction abnormalities.
- B. Bradyarrhythmias (beyond sinus) and Types of Heart Block (Critical Care Medicine 2014:xix; Pathophysiology of Heart Disease 2011:xiv; BMJ 2002;324:662-5; BMJ 2002;324:415-8)
 1. Etiologies of heart block

Box 3. Causes of Bradycardias

- CAD
- Degenerative conduction disease
- Drug toxicity
- Electrolyte disturbances (particularly hyperkalemia)
- Endocarditis
- Myocarditis
- Surgery (particularly cardiac surgery)
- Tumors
- Vagus nerve-mediated heart block

CAD = coronary artery disease.

2. When evaluating ECGs in the presence of heart block, QRS complex evaluation can guide some differential diagnoses to the source of conduction problems (see Table 6).
 - a. Narrow QRS complexes commonly indicate AV nodal dysfunction.
 - b. Wide QRS complexes may indicate dysfunction in either the AV node or the His-Purkinje system.

Table 6. Bradyarrhythmias and Types of Heart Block (Critical Care Medicine 2014:xix; Pathophysiology of Heart Disease 2011:xiv; BMJ 2002;324:662-5; BMJ 2002;324:415-8)

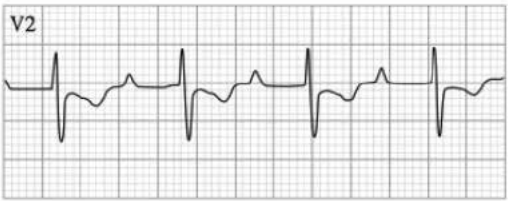
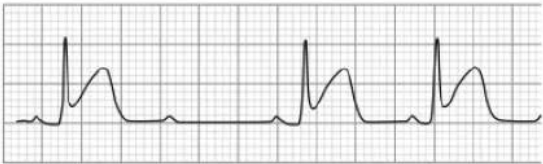
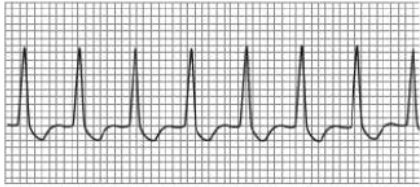
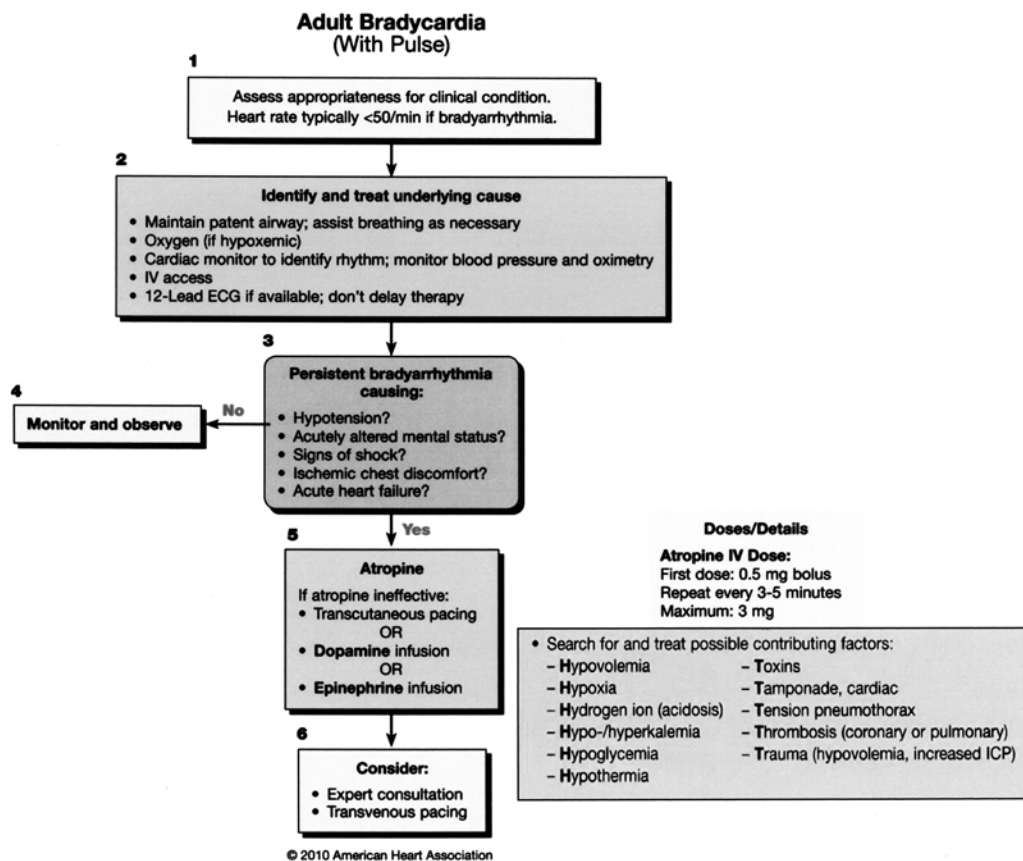
Type	ECG Example	Description
First degree	 V2	Delayed conduction from the sinoatrial (SA) node to the atrioventricular (AV) node characterized by a P-R interval > 0.2 s Relatively benign; however, underlying contributors should be evaluated and minimized (i.e., β-blockers and other agents)
Second-degree Mobitz type 1 (Wenckebach)		Consistent P-P interval with progressive prolongation of the P-R (indicating impaired SA to AV node conduction) eventually resulting in absence of a QRS complex because of the lack of AV node conduction of atrial impulse Of most concern in older adult patients in whom this may be indicative of progressive conduction disease; may be more benign in younger patients “Longer, longer, longer, drop ... must be Wenckebach”
Second degree Mobitz type 2	 (in a post-ACS setting)	Consistent P-P interval and consistent P-R interval duration with spontaneous absence of a QRS complex because of the lack of AV node conduction of atrial impulse Usually indicative of more significant conduction disease and associated with syncope, heart failure, and increased mortality rates
Third degree (Complete heart block)		Characterized by consistent P-P intervals, consistent R-R intervals, and variable/random P-R interval representing independent, uncoordinated atrial and ventricular conduction (A-V dissociation)

Table 6. Bradyarrhythmias and Types of Heart Block (Critical Care Medicine 2014:xix; Pathophysiology of Heart Disease 2011:xiv; BMJ 2002;324:662-5; BMJ 2002;324:415-8) (*continued*)

Type	ECG Example	Description
Junctional rhythm		Manifested when sinus node dysfunction allows the AV node to take over as the active cardiac pacemaker, resulting in retrograde conduction through the atria

3. Management of bradyarrhythmias includes three principal strategies (see also Figure 8). Stabilize the patient, if symptomatic.
 - a. Consider atropine for temporary correction to decrease vagal tone.
 - b. Consider pacing strategies (temporary transvenous pacer, transcutaneous pacer, pacing pulmonary artery catheter). Interrogate permanent pacemaker for malfunction/optimization.
 - c. Consider chronotropic β -agonist infusion.
 - i. Dopamine
 - ii. Epinephrine
 - iii. Isoproterenol
 - iv. Dobutamine
 - d. Identify and treat underlying causes/toxidromes.

**Figure 8.** Advanced cardiac life support bradycardia algorithm (Circulation 2010;122:S729-67).

C. Tachyarrhythmias (beyond sinus) – Etiologies and hemodynamic consequences

1. Etiologies of tachyarrhythmias
 - a. Usually related to enhanced automaticity, reentry, or triggered activity
 - b. A history that includes ischemic heart disease or congestive cardiac failure is 90% predictive of VT.
2. In evaluating ECGs for tachyarrhythmias, some fundamental considerations include:
 - a. Evaluate for the presence of P waves.
 - b. Evaluate the width of the QRS complex.

Table 7. Tachyarrhythmias (beyond sinus)^a (Circulation 2014;130:2071-104; BMJ 2002;324:594-7776-9; BMJ 2002;324:1264-7; BMJ 2002;324:1201-4; Circulation 2012;125:381-9; Heart Fail Rev 2014;19:285-93)

Supraventricular Tachyarrhythmias				
Type	Rhythm	P-wave Attributes	Atrial Rate (beats/min)	Description
Premature atrial complexes (PACs)	Irregular	N/A	N/A	Generally benign but may be more evident with increased sympathetic tone, stress, and pericarditis or with sympathomimetic use In some cases, can lead to an AV block or initiate a reentrant supraventricular tachycardia (SVT) or AF
Supraventricular tachycardia (SVT)	Regular	Hidden or can be retrograde	140–250	Usually sudden onset/offset with narrow QRS complexes Often caused by reentry within the atrium or AV node or by an accessory conduction pathway Can be subcategorized as: AV nodal reentrant tachycardia (AVNRT) AV reentrant tachycardia (AVRT) Sinus node reentry tachycardia
Atrial flutter (AFI)	Regular	Saw-tooth appearance	180–350	Generally conducts through the ventricles in a 2:1 fashion, resulting in ventricular rates of 100–150 beats/min In some scenarios, slowing the atrial rate may increase the number of conducted beats, leading to rapid ventricular rates and potential hemodynamic compromise Associated with increased risk of stroke
Atrial fibrillation (AF)	Irregular	No distinct P wave visible	Unable to determine	Most common arrhythmia, characterized by irregular ECG appearance because of multiple reentry circuits and ectopic foci (“irregularly irregular”) Often associated with structural heart disease and potentiated by increased left atrial pressures among other influencing contributors such as age, inflammation, and sympathetic tone Associated with increased risk of stroke
Multifocal atrial tachycardias (MATs)	Irregular	> 3 different types of distinct P waves	100–130	Can be misdiagnosed as AF Commonly associated with respiratory disease, heart failure, critical illness May be exacerbated by electrolyte abnormalities or toxicity with digoxin or theophylline

Table 7. Tachyarrhythmias (beyond sinus)^a (Circulation 2014;130:2071-104; BMJ 2002;324:594-7776-9; BMJ 2002;324:1264-7; BMJ 2002;324:1201-4; Circulation 2012;125:381-9; Heart Fail Rev 2014;19:285-93) (*continued*)

Ventricular Arrhythmias	
Type	Description
Premature ventricular complexes (PVCs)	Results from an ectopic ventricular focus conduction that can be identified by the lack of a preceding P wave. Commonly benign or asymptomatic but may be of concern if present in patterns or in patients with advanced heart disease Bigeminy: Every other beat is a PVC Trigeminy: Every third beat is a PVC Couplets: Patterns of two consecutive PVCs Triplets: Patterns of three consecutive PVCs
Ventricular tachycardia (VT)	Potentially lethal wide QRS complex tachycardia characterized according to morphology and duration; can degenerate into ventricular fibrillation (VF) or asystole <i>Monomorphic VT</i> : When every QRS complex appears the same and the rate is regular (100–200 beats/min); commonly caused by reentry circuit related to myocardial scar or fibrosis <i>Polymorphic</i> : When the QRS complexes continually vary in shape and rate; may be related to multiple ectopic foci, myocardial ischemia, or Torsades de pointes <i>Non-sustained VT</i> : Self-terminating episodes lasting for < 30 s <i>Sustained VT</i> : If VT persists for more than 30 s, produces severe symptoms, including syncope, or requires termination by administration of an antiarrhythmic drug or direct cardioversion/defibrillation
Ventricular fibrillation (VF)	Life-threatening arrhythmia with a chaotic ECG with no discernible QRS, representing rapid disorganized conduction with no resultant coordinated ventricular contractions

^aOther arrhythmias beyond the scope of this review include sick sinus syndrome (tachy-brady syndrome) and Wolff-Parkinson-White.

3. Management of tachyarrhythmias with a pulse includes the following strategies:
 - a. Stabilization of patient: See Figure 9 Long-term control strategies
 - i. Atrial tachyarrhythmias
 - (a) Heart rate control typically with class II agents, class IV agents, and/or digoxin (see Appendix A)
 - (b) Heart rhythm control
 - (1) Antiarrhythmic therapy typically with class Ic or class III agents (see Appendix A)
 - (2) Catheter-based ablation
 - (3) Surgical ablation
 - ii. Ventricular tachyarrhythmias
 - (a) Catheter ablation
 - (b) Antiarrhythmic therapy
 - (c) Evaluation for implantable cardioverter-defibrillator
 - b. Overall considerations for antiarrhythmics (see Appendix A) (Circulation 2014;130:2071-104; Heart Fail Rev 2014;19:285-93; Circulation 2012;125:381-9; BMJ 2002;324:594-7; BMJ 2002;324:776-9; BMJ 2002;324:1264-7; BMJ 2002;324:1201-4)
 - i. Abrupt discontinuation of chronic antiarrhythmics (i.e., chronic medication before ICU admission) should be done with caution and awareness of antiarrhythmic indication as well as risks-benefits of continuation/cessation.

- ii. Appropriate monitoring and potential adjustment may be warranted with many of these agents in the critically ill patient.
- QT/QTc prolongation increases the risk of Torsades de pointes. This risk can be influenced not only by the absolute duration of the QT/QTc but also by the rate at which the QT/QTc is changed (i.e., faster change may also increase risk).
 - The class III antiarrhythmics sotalol and dofetilide can be used for a variety of arrhythmias (most notably AF/AFL) and, because of some notable characteristics, should be watched closely when used in the critically ill patient.
 - Both are renally eliminated.
 - Both have notable interactions with several other medications (especially dofetilide on the basis of CYP3A4 and renal transport) in addition to their effect on the QT/QTc interval.
 - ECG monitoring should be performed for safety and tolerability 2–3 hours after the first five doses when initiating, reinitiating, or introducing another interacting or QT-prolonging agent.
 - Electrolyte abnormalities may place a patient at increased risk of Torsades de pointes (particularly magnesium and potassium).
 - Dofetilide is particularly useful among patients with structural heart disease (congestive heart failure [CHF]) because of a neutral effect on mortality.

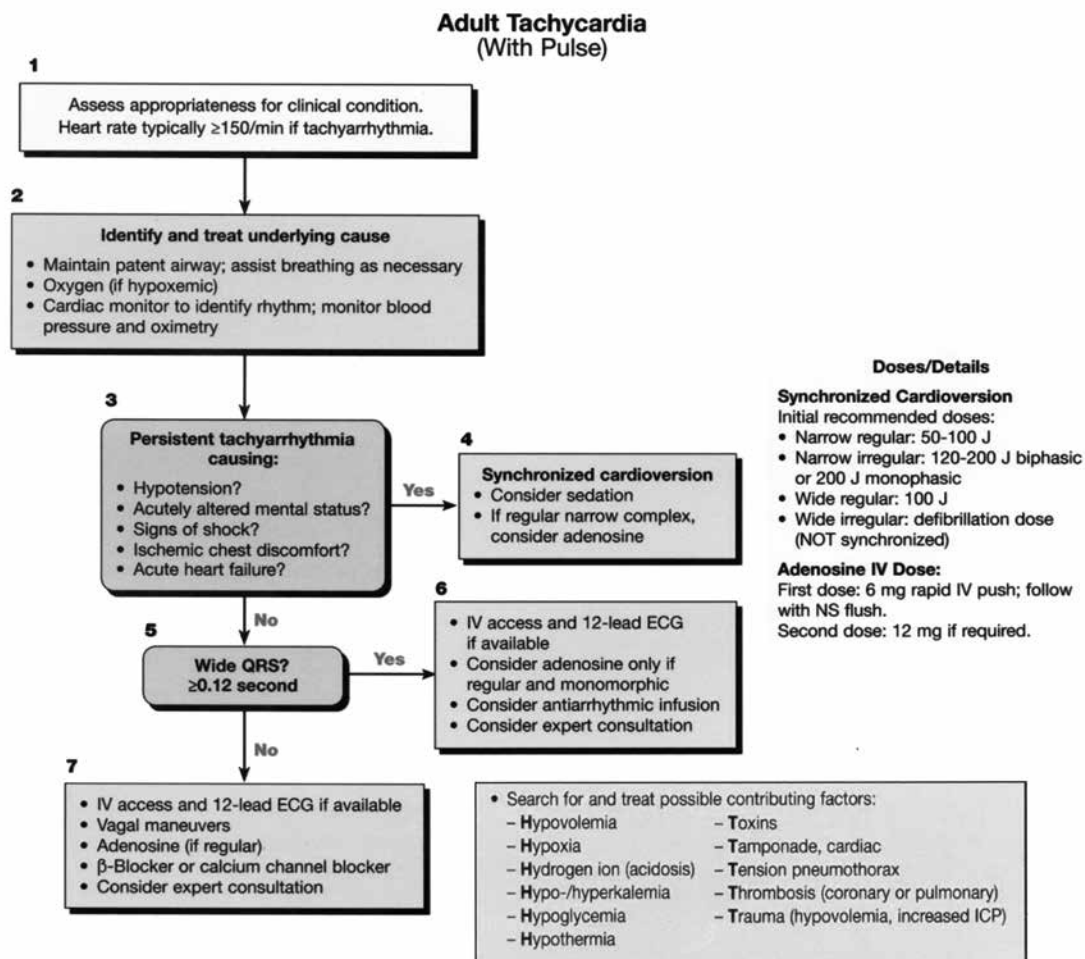


Figure 9. Advanced cardiac life support tachycardia algorithm (Circulation 2010;122:S729-67).

iii. Common agents in the ICU

(a) β -Blockade

- (1) May be of limited use in patients receiving vasopressors and/or inotropes, but can be used for both atrial and ventricular tachyarrhythmias
- (2) Esmolol has the shortest half-life (cleared by plasma esterases), and administration rates commonly coincide with high volumes of fluid.
- (3) Agents with combined α_1 -antagonism and nonselective β -antagonism will have greater effects on blood pressure than their β_1 -specific antagonist counterparts.
 - β_1 -specific antagonist examples:
 - Esmolol (intravenous), metoprolol tartrate (oral/intravenous)
 - Agents with combined α_1 - and nonselective β -antagonism effects include:
 - Carvedilol (oral) – about 25:1 ratio of β : α_1 receptor activity
 - Labetalol (intravenous) – about 7:1 ratio of β : α_1 receptor activity
 - Labetalol (oral) – about 3:1 ratio of β : α_1 receptor activity

(b) Non-dihydropyridine calcium channel blockers (diltiazem, verapamil) are not recommended in patients with heart failure with reduced ejection fraction (HFrEF) (systolic heart failure) because of potent negative inotropic effects (class III C). (J Am Coll Cardiol 2013;62:e147-239).

(c) Diltiazem – May be of limited use in patients on vasopressors and/or inotropes, but can be used for atrial tachyarrhythmias

(d) Amiodarone

- (1) Widely versatile and commonly used for both atrial and ventricular tachyarrhythmias
- (2) Demonstrated safety in patients with structural heart disease (CHF) because of neutral effect on mortality
- (3) Affects all phases of the action potential (sodium [Na], calcium [Ca], potassium [K] channel and provides some α - and β -antagonism)
- (4) Severe hypotension can occur because of the solvent polysorbate 80 (Tween 80) used in some formulations. This transient hypotension in patients with a pulse can be associated with rapid infusions, particularly of undiluted drugs, and is best avoided by dilution and slower administration. However, in pulseless patients, rapid administration of undiluted amiodarone is commonly indicated.
- (5) Among common agents used in the ICU, amiodarone has one of the largest volumes of distribution (about 60 L/kg) and prolonged half-lives (about 35–110 days).
- (6) In adults, common total intravenous or oral loading doses throughout several days are about 8–10 g before switching to a maintenance dose.

$$7.2\text{--}12\text{ g} = (1.5\text{--}2.5\text{ mg/L}) \times (60\text{ L/kg}) \times (80\text{ kg})$$

- (7) Extensive metabolism by CYP3A4 and CYP2C8 and enzyme inhibitor of CYP3A4, CYP1A2, CYP2C9, and CYP2D6, resulting in several drug-drug interactions (i.e., warfarin, statins)
- (8) If patients are to be continued on amiodarone for a prolonged duration, thyroid and liver function tests, pulmonary function tests, chest radiographs, and ophthalmic examinations should be evaluated periodically (Heart Rhythm 2007;4:1250-9).

(e) Lidocaine

- (1) Indicated only for ventricular tachyarrhythmias and is particularly useful if the tachyarrhythmia is caused by active ischemic myocardial tissue
- (2) Efficacy and toxicity are both concentration dependent.

- (3) Metabolism is largely dependent on hepatic blood flow; the primary metabolites are monoethylglycinexylidide (MEGX) and glycine xylidide (GX) and are mediated by CYP1A2. Both lidocaine and MEGX contribute to therapeutic effect and toxicity, whereas GX has predominantly toxic adverse effects. Lidocaine's metabolites are eliminated renally.
- (4) Concentration-dependent protein binding includes about 25% bound to albumin and about 50% bound to α_1 -acid glycoprotein (AAG).
- (5) As AAG increases and decreases as an acute-phase reactant within the first 12–72 hours after certain stresses (i.e., acute MI, heart failure exacerbation, trauma), an unsuspected variation can occur in free lidocaine concentrations. Because of the toxicity profile and concentration-dependent efficacy, routine concentrations should be monitored in most patients if lidocaine is to be continued beyond 24 hours (particularly in patients with advanced age, heart failure, liver disease, and renal dysfunction).

Table 8. Lidocaine Concentrations and Toxicity Symptoms

Total Serum Concentration (mg/L)	Toxicity
< 1.5–5	Typical therapeutic goal concentration with idiosyncratic reactions
> 5–8	Increasing risk of light-headedness, confusion, dizziness, tinnitus, twitching, tremor, blurred or double vision, hypotension, and bradycardia
> 8	High risk of seizures, respiratory depression, hypotension, bradycardia, AV nodal blockade, decreased cardiac output

AV = atrioventricular.

(f) Digoxin

- (1) Commonly, a last-line rate-control therapy for patients whose rhythm-control strategies have failed and who cannot tolerate or have contraindications to β -blockers and/or calcium channel blockers. Some interest has also been revived in its use for heart failure to avoid hospitalization.
- (2) Use for AF should be done with caution. Two recently published retrospective trials have shown considerable evidence for increased hospitalization rates and risk of death.
 - 71% increased risk of death (HR 1.71; 95% CI, 1.52–1.93) and 63% increased risk of hospitalization (HR 1.63, 95% CI, 1.56–1.71) (Circ Arrhythm Electrophysiol 2015;8:49-58)
 - Digoxin-treated patients had higher mortality rates (95 vs. 67 per 1000 person-years; $p < 0.001$), and use was independently associated with mortality, despite multivariate adjustment (HR 1.26; 95% CI, 1.23–1.29, $p < 0.001$) (J Am Coll Cardiol 2014;64:660-8).
 - Eliminated renally; thus, may pose risks of digoxin toxicity in patients with acute or chronic renal failure
- (3) Although the volume of distribution is relatively large (7–10 L/kg in healthy adults), only a small percentage of total body stores are present in the serum.
- (4) Digoxin has a smaller volume of distribution in patients with renal failure (around 4.5 L/kg); thus, loading doses may be lower in these patients.

- (5) Digoxin efficacy and toxicity do not correlate well with drug concentrations.
- Common therapeutic targets for heart rate control are 0.8–1.5 ng/mL, although many clinical laboratories report therapeutic concentrations within 0.5–2.0 ng/mL.
 - Toxicity, which can present at any serum concentration, should be evaluated according to clinical manifestations, including: nausea, vomiting, anorexia, mental status changes, visual disturbances, ventricular arrhythmias, bradycardia, and hyperkalemia.
 - Efficacy is largely based on clinical control of the heart rate; steady-state concentrations (more than 5–7 days after initiation) are typically used only to validate that concentrations are not supratherapeutic.
4. Anticoagulation for AF or atrial flutter
- According to the 2014 AHA/ACC/Heart Rhythm Society (HRS) AF guidelines, all patients with atrial flutter or paroxysmal, persistent, or permanent AF should be evaluated for anticoagulation, preferably using the CHA₂DS₂-VASc score to approximate stroke risk (Circulation 2014;130:2071-104).
 - Patients with a CHADS₂ score (Congestive heart failure, Hypertension, Age older than 75, Diabetes, and prior Stroke or transient ischemic attack) and a CHA₂DS₂-VASc score of 2 or greater should be evaluated for anticoagulation.
 - It is reasonable to omit anticoagulation (in lieu of aspirin) in patients with a CHADS₂ and CHA₂DS₂-VASc score of zero.
 - For patients with AF and a mechanical prosthetic heart valve or valves, bridging with unfractionated heparin or low-molecular-weight heparin should be performed in the context of bleeding versus stroke risk. Warfarin anticoagulation and international normalized ratio (INR) goals should be consistent with the type and location of the prosthetic valve.
 - In patients with AF at intermediate risk for thromboembolism (average CHADS₂ score of 2.3), the use of bridging with low-molecular-weight heparin was non-inferior to no bridging for elective procedures. However, there was a significant excess of major bleeding in the *low-molecular-weight heparin* (LMWH) group. Note that patients with a mechanical valve or stroke/transient ischemic attack/systemic embolism within the preceding 12 weeks were not eligible for inclusion in the study (N Engl J Med 2015;373:823-33).
 - Although the CHADS₂ and CHA₂DS₂-VASc scores are commonly used to estimate annual stroke risk, these scoring systems were not founded in the context of critically ill patients.

Table 9. CHADS₂ and CHA₂DS₂-VASc Stroke Risk Scores in AF (Circulation 2014;130:2071-104)

Risk Assessment	Score	Total Patient Score	Adjusted Annual Stroke Rate, %
CHADS₂		0	1.9
Heart failure	1	1	2.8
Hypertension	1	2	4.0
Age ≥ 75	1	3	5.9
Diabetes	1	4	8.5
Stroke, TIA, thromboembolism	2	5	12.5
		6	18.2

Table 9. CHADS₂ and CHA₂DS₂-VASc Stroke Risk Scores in AF (Circulation 2014;130:2071-104) (*continued*)

Risk Assessment	Score	Total Patient Score	Adjusted Annual Stroke Rate, %
CHA₂DS₂-VASc		0	0
Congestive heart failure	1	1	1.3
Hypertension	1	2	2.2
Age ≥ 75	2	3	3.2
Diabetes	1	4	4.0
Stroke, TIA, thromboembolism	2	5	6.7
	1	6	9.8
Vascular disease	1	7	9.6
65–74 yr	1	8	6.7
Sex category (female)	1	9	15.2

TIA = transient ischemic attack.

- b. Anticoagulation decisions should balance the risk of stroke versus the risks of bleeding in the context of duration of bridging and/or lack of anticoagulation. Scoring systems for bleeding risk systems have been described to help assess bleeding risk in anticoagulation decisions for patients with AF on warfarin anticoagulation. Not unlike stroke risk scoring systems, these scoring systems were not founded in the context of critically ill patients.

Table 10. HAS-BLED or HEMOR₂RHAGES Bleeding Risk Scores in AF

Risk Factor Assessment	Score	Total Patient Score	Bleeds/100 Patient-Yr of Warfarin
HAS-BLED			
Hypertension	1	0	1.13
Abnormal renal or liver function (1 point each)	1 or 2	1	1.02
Stroke	1	2	1.88
Bleeding	1	3	3.74
Labile INRs	1	4	8.70
Elderly (> 65 yr)	1	5	12.5
Drugs or alcohol (1 point each)	1 or 2	6	0
		Any score	1.56
HEMOR₂RHAGES			
Hepatic or renal disease	1	0	1.9
Ethanol abuse	1	1	2.5
Malignancy	1	2	5.3
Older age	1	3	8.4
Reduced platelet count or function	1	4	10.4
Rebleeding risk	2	≥ 5	12.3
Hypertension (uncontrolled)	1	Any score	4.9
Anemia	1		
Genetic factors	1		
Excessive fall risk	1		
Stroke	1		

AF = atrial fibrillation.

- c. In the critically ill patient, parenteral anticoagulation with unfractionated heparin or low-molecular-weight heparin may be more favorable if the benefit of anticoagulation exceeds the risk of bleeding. Unfractionated heparin infusions would be favored more than low-molecular-weight heparin in renal failure (creatinine clearance [CrCl] less than 30 mL/minute/1.73 m²).
- d. For anticoagulation of most critically ill patients, oral anticoagulation may be less favorable or even detrimental compared with parenteral anticoagulation.
 - i. Elimination of direct-acting oral anticoagulants (DOACs) (apixaban, dabigatran, edoxaban, and rivaroxaban) is significantly affected in renal compromise, and all agents (with the exception of apixaban) lack data for safety in patients with end-stage kidney disease with or without dependency on dialysis. An additional consideration in the critical care setting is the feasibility of reversal in the event of an acute bleed or need for an invasive procedure. Novel antidotes continue to be studied and approved; however, clinical experience with reversibility in these settings is evolving. Finally, the aforementioned DOACs are not devoid of relevant drug-drug interactions, particularly when given in combination with strong CYP and/or P-glycoprotein inhibitors/inducers.
 - ii. Warfarin presents potential difficulty because of its influence on malnutrition, drug interactions, and unpredictable dose response in the critically ill patient. Complications with this agent are more predictably managed than are complications with other oral anticoagulants if a patient requires an invasive procedure or develops an acute bleed, but warfarin use is still not without risk.
- e. For patients with AF/flutter for 48 hours or more (or if undetermined) without therapeutic anticoagulation, absence of thrombus on the left side of the heart should be confirmed by transesophageal ECHO before pharmacologic or direct current cardioversion.
- f. If AF/flutter for more than 48 hours or an unknown duration that requires direct current or pharmacologic cardioversion for hemodynamic instability, anticoagulation should be initiated as soon as possible and continued for at least 4 weeks after cardioversion unless contraindicated

Patient Case

Questions 6 and 7 pertain to the case on page 2-102.

The appropriate intervention has been made from question 5, and the patient has not required any need for pacing. For the next 48 hours, J.M. continues on inotrope therapy and is being diuresed (his net fluid balance has been 1250 and 900 mL negative each day for the past 2 days). The transthoracic ECHO results showed J.M.'s ejection fraction to be 15%–20%, with a dilated, hypokinetic LV, severe mitral regurgitation, and dilated atria. No evidence of intracardiac thrombus was seen, but this could not be ruled out.

6. J.M. has had increasing premature atrial complexes on telemetry, and his heart rate has consistently been 83–96 beats/minute. He is receiving dobutamine at 5 mcg/kg/minute and a furosemide infusion at 10 mg/hour. The team is notified that J.M. has gone into AF with rapid ventricular response and a heart rate of 132 beats/minute (he has been in AF for about 30 minutes). His blood pressure is now 83/52 mm Hg. Which treatment plan would be most preferred for this patient?
 - A. Synchronized cardioversion
 - B. Metoprolol 5 mg intravenous push
 - C. Adenosine 6 mg rapid intravenous push through the most proximal port on the central venous catheter
 - D. Amiodarone 150 mg intravenous push, followed by a continuous infusion at 1 mg/minute

7. J.M.'s BP and HR improved after the previous intervention; however, he remains in AF. The team is now concerned about evaluating the patient for possible anticoagulation. You are asked to provide input about the appropriateness of anticoagulation, given the patient's clinical course and past medical history. His calculated CHA₂DS₂-VASc score is 5 and HAS-BLED score is 5. The physician is considering anticoagulation with a heparin infusion while the patient is in the ICU and asks for a recommendation. Which is the most appropriate response?
 - A. According to these scores, the patient's risk of bleeding is the same as his stroke risk; therefore, it would be reasonable to initiate or withhold anticoagulation.
 - B. According to these scores, the patient's risk of stroke exceeds his risk of bleeding; therefore, it would be reasonable to initiate heparin anticoagulation.
 - C. The HAS-BLED score is less relevant because it is derived from chronic warfarin use. However, anticoagulation is still likely warranted, given the patient's CHA₂DS₂-VASc score.
 - D. The HAS-BLED and CHA₂DS₂-VASc scores are irrelevant to this patient's current care, and anticoagulation is not warranted.

VI. HEART FAILURE (HF)

- A. Clinical Syndrome – Manifested because of congenital or acquired structural or functional myocardial dysfunction that impairs filling and/or emptying of the heart
 1. Mortality rate of 50% with 5 years of diagnosis
 2. Predominantly descriptive of LV and its pump performance and the ejection fraction
 3. Prognosis and treatment of heart failure are largely dependent on the etiology and staging of HF.

Table 11. Diastolic Dysfunction Versus Systolic Dysfunction in Heart Failure

Type	Heart Failure with <i>Preserved</i> EF (HFpEF)	Heart Failure with <i>Reduced</i> EF (HFrEF)
Dysfunction	• Diastolic – blood filling the heart	• Systolic – blood emptying from the heart • May also coexist with impaired diastolic filling
Characteristics	• LVEF $\geq 50\%$ • Impaired relaxation and filling of the ventricle before contraction • Commonly described as a “stiffened” ventricle • Contractility remains “normal”	• LVEF $\leq 40\%$ • Impaired contraction and emptying of the ventricular cavity • Commonly described as a “dilated” ventricle
Clinical-management pearls	• Preload (volume optimization) is essential • As diastolic dysfunction worsens – ventricular preload and diastolic filling time must be maintained • Conditions acutely decreasing preload may lead to decompensation (e.g., tachyarrhythmias) • Keep heart rate “slow” and ventricles “full”	• Preload optimization essential – at high risk of volume overload • As systolic dysfunction worsens, cardiac output becomes increasingly afterload sensitive • Conditions acutely decreasing or increasing preload or increasing afterload may lead to decompensation • Volume overload and increasing myocardial dilation may contribute to decreased valvular coaptation and regurgitant flow
Common medications to avoid	• NSAIDs, with the exception of aspirin • Sympathomimetics	• NSAIDs, with the exception of aspirin • Sympathomimetics • Class 1a and 1c antiarrhythmics • Non-dihydropyridine calcium channel blockers

EF = ejection fraction; LVEF = left ventricular ejection fraction.

B. Heart Failure Etiologies

1. Ischemic cardiomyopathy
 - a. Accounts for about two-thirds of heart failure cases
 - b. Caused by myocardial damage/death owing to CAD
2. Non-ischemic cardiomyopathy
 - a. Accounts for about one-third of heart failure cases
 - b. May be attributed to other causes (Box 4)

Box 4. Non-ischemic Cardiomyopathies

Non-ischemic Cardiomyopathies	
• Amyloidosis • Sarcoidosis • Drug induced ◦ Alcohol ◦ Anabolic steroids ◦ Chemotherapy § Anthracyclines § Cyclophosphamide § Fluorouracil § Bevacizumab § Trastuzumab § Tyrosine kinase inhibitors • Cocaine • Methamphetamine • Tricyclic antidepressants • Anorexigens	• Familial • Hypertension • Hyper/hypothyroidism • Hypertrophic obstructive (HOCM) • Idiopathic • Myocarditis ◦ Autoimmune ◦ Eosinophilic ◦ Giant cell ◦ Viral ◦ Other infectious cause • Non-compaction • Peripartum • Obesity • Stress induced (Takotsubo)

- C. RV Dysfunction and/or Failure (Exp Clin Cardiol 2013;18:27-30; J Am Coll Cardiol 2010;56:1435-46; Circ Heart Fail 2010;3:340-6; Anesth Analg 2009;108:422-33; Anesth Analg 2009;108:407-21)
1. Less well characterized than LV heart failure
 2. No guidelines to direct management of acute RV failure
 3. RV physiology
 - a. The RV normally has only about one-sixth the myocardial mass of the LV. Primary means of compensation is heart rate increase.
 - b. Normal RV ejection fraction is 40%–45%.
 - c. Conduit to a low pressure system in the pulmonary vasculature (normally)
 - d. Physiologic deficits:
 - i. Preload dependent
 - ii. Interdependent on LV and septal contribution to contraction
 - iii. Highly sensitive to acute increases in afterload. PVR elevations may be:
 - (a) Drug induced (e.g., α_1 agents, protamine)
 - (b) Caused by ventilator settings (high positive end-expiratory pressure [PEEP], high tidal volumes)
 - (c) Caused by hypoxia
 - (d) Caused by hypercarbia
 - (e) Caused by pulmonary embolism
 - iv. Poor elastic response to acute preload increases compared with LV
 - v. Atypical geometric form contributes to:
 - (a) Difficulty in objective assessment of RV function by ECHO
 - (b) Increases susceptibility to further inefficiency/dysfunction when severely dilated

4. Etiologies of RV failure

Box 5. Etiologies of RV Failure (Exp Clin Cardiol 2013;18:27-30; J Am Coll Cardiol 2010;56:1435-46)

Arrhythmias
Cardiac tamponade
Congenital heart disease
Heart transplantation (particularly if prolonged ischemic time)
Hypovolemia
Hypoxia
LV dysfunction
Mitral valve disease
Post-cardiac surgery
Pulmonary embolism
Pulmonary hypertension
Pulmonary regurgitation
Right coronary artery infarction/ischemia
RV overload
Sepsis
Tricuspid regurgitation/stenosis

D. Diagnostic Tests for New or Worsening Heart Failure – In addition to routine chemistry and CBC tests, additional testing may include:

1. Liver function tests (may be indicative of congestive hepatopathy, if elevated)
2. 12-lead ECG
3. Troponin
4. Left heart catheterization if suspected new ischemic contribution
5. BNP or N-terminal pro-brain natriuretic peptide (NT-proBNP) (elevations may help in the diagnosis of acutely decompensated heart failure in scenarios of uncertainty)
6. Transthoracic or transesophageal ECHO
7. Invasive hemodynamic monitoring (to guide volume optimization and dosing response to inotropes or vasopressors)
8. For less common cardiomyopathies, noninvasive imaging (i.e., cardiac magnetic resonance imaging [MRI]) and/or myocardial biopsy may be required.

E. General Management Considerations

1. Assess volume status.
 - a. In selected cases of hypotension where heart failure is not known to be the exclusive culprit, small volume fluid challenges (250–500 mL intravenous fluid bolus) or passive leg raising maneuvers may help show whether a patient is volume responsive.
 - b. Physical examination will generally guide fluid status decision.
2. Once other causes of symptomatic congestion and/or low perfusion at rest have been ruled out and a diagnosis of decompensated heart failure is deemed likely, the following should be considered: If volume overloaded, provide intravenous diuretics equal to the patient's home oral dose (or alternatively up to 2–2.5 times the patient's home dose may be used).

3. Evaluate for use of vasodilator therapy.
 - a. If normotensive or hypertensive (e.g., SBP greater than 100 mm Hg) in the presence of acute pulmonary edema (despite diuretic therapy):
 - i. Continuous infusion intravenous vasodilators (e.g., nitroglycerin, nesiritide, or nitroprusside,) should be considered.
 - ii. If the presence of high afterload is confirmed (systemic vascular resistance), then nitroprusside may be warranted more than other vasodilators. However, careful attention to patient selection is important because nitroprusside elimination is dependent on both hepatic metabolism and renal clearance. Note that nitroprusside is converted to nitric oxide and cyanide, with subsequent conversion to thiocyanate. Signs of potential toxicity include metabolic acidosis and mental status changes. In addition, patients receiving nitroprusside should have an arterial line and typically a Swan-Ganz catheter in place.
 - b. If hypotensive (e.g., SBP of 100 mm Hg or less): Can consider vasodilators, but with caution
 - c. Monitor for clinical improvement of symptoms and adequate urine output.
 - i. Proactive evaluation of urine output adequacy should be used to facilitate optimization/escalation of diuretic regimen.
 - ii. An increase in loop diuretic frequency, dose, and/or the addition of sequential nephron blockade (i.e., metolazone) may be considered as needed to achieve the desired urine output and fluid balance.
 - d. If inadequate response on escalation of diuretics (and vasodilators, if appropriate), inotrope therapy should be considered, accounting for any concurrent physiologic considerations (e.g., right heart failure, pulmonary hypertension, ischemia, or valvular disease)
 - e. Dobutamine and milrinone are most often used for suspected or confirmed low cardiac output states. Milrinone may be preferred more than dobutamine in the presence of recent administration of β -blockade or in the setting of concomitant pulmonary hypertension (because of its post- β receptor effects and potent vasodilatory properties, respectively). In terms of pharmacokinetic differences, dobutamine has a faster onset and shorter half-life (2 min) compared with milrinone (half-life of 3 hrs with renal-dependent elimination). However, no differences in clinical efficacy or safety have been observed between agents. Both agents should be closely monitored for the development of proarrhythmias and worsening ischemia.

VII. VALVULAR HEART DISEASE

- A. Valvular heart disease is an important comorbid condition that must be considered in hemodynamic management of the critically ill patient. Valvular heart disease can also independently lead to the presenting critical illness.
- B. Among the four cardiac valves, several etiologies^a contribute to the manifested pathology; however, the depth and breadth of these etiologies are beyond the scope of this chapter. Nevertheless, conditions that may require repair/replacement include those listed in Table 12.

Table 12. Conditions That May Require Valvular Repair/Replacement

Stenosis	Narrowing at the opening of the valve(s) Can lead to concurrent regurgitation
Regurgitation	“Leaky” valve(s) resulting in less blood pumping forward through the heart
Prolapse	“Floppy” valve(s) with part of valve not working
Endocarditis	Infection of one or more valves
Malformation	Often occurs at birth when the valve (or valves) is defective

^aValvular disease secondary to rheumatic heart disease is a rare but possible contributor.

Table 13. Valvular Disease Characteristics and Management Considerations^{a,b}

Valvular Disease Type	Management Considerations
Aortic stenosis (AS)	• One of the most common and serious valvular diseases seen in the ICU • As stenosis and disease progresses, severe/critical AS limits the heart to a fixed stroke volume; this inability to increase stroke volume occurs despite intrinsic or extrinsic attempts to compensate (i.e., increased chronotropy or inotropy) and often only increases myocardial oxygen demand without improving delivery • Must be extremely cautious in approaching and reacting to invasive hemodynamic variables (particularly cardiac output and cardiac index) – adding agents with inotropic/chronotropic effects may expedite demand ischemia and an acute MI because of the physiologic inability to increase cardiac output with a fixed partial LV outflow tract obstruction • For reasons similar to those previously listed, treating hypertension with afterload-reducing agents must be done judiciously because as afterload (SVR) decreases, cardiac output cannot increase • Can coexist with concurrent aortic insufficiency/regurgitation because the stenotic or calcified valve leaflets may no longer move and come together (coapt) well • These patients may be at risk of developing mitral regurgitation and subsequent increases in left atrial pressures (increasing risk of AF) because of increased LV filling pressures • Must be cautious in decreasing HR in sinus tachycardia because this can be a primary means of compensation • Patients need adequate preload; however, they can become symptomatic even with slight volume overload. As an example, atrial fibrillation can be very detrimental simply because it decreases preload to the ventricle • Patients with severe aortic stenosis and systolic heart failure (described as low output – low gradient) have a poorer prognosis
Aortic regurgitation (AR)	• Also known as aortic insufficiency (AI) • Must be cautious in decreasing HR in sinus tachycardia because this can be a primary means of compensation to maintain adequate cardiac output • Patients need adequate preload, but the predominant target is to maintain decreased afterload (SVR) to facilitate forward blood flow and cardiac output

Table 13. Valvular Disease Characteristics and Management Considerations^{a,b} (*continued*)

Valvular Disease Type	Management Considerations
Mitral stenosis (MS)	• Contributes to decreased LV filling and increased left atrial pressures; can increase risk of AF and secondary pulmonary hypertension • Increasing diastolic filling time and avoiding tachycardias can facilitate stabilization until valve is corrected • Use of selective pulmonary vasodilators (i.e., inhaled nitric oxide or inhaled epoprostenol) may be detrimental because these agents can facilitate pulmonary congestion, given the preexisting pulmonary venous hypertension and elevated left atrial pressures
Mitral regurgitation (MR)	• Primary clinical target is to decrease LV afterload (SVR) to minimize augmentation of MR and to facilitate forward blood flow. If SVR is too high, blood will travel in the path of least resistance until an adequate LV pressure is generated to open the aortic valve (must exceed the systemic diastolic blood pressure) • Can coexist with concurrent mitral regurgitation because the stenotic or calcified valve leaflets may no longer move and coapt well • Use of selective pulmonary vasodilators (i.e., inhaled nitric oxide or inhaled epoprostenol) may be detrimental because these agents can facilitate pulmonary congestion, given the preexisting pulmonary venous hypertension and elevated left atrial pressures
Tricuspid regurgitation (TR)	• Likely to influence pulmonary artery catheter assessments of cardiac output by way of thermodilution technique • Can be influenced by infectious causes and presence of indwelling transvenous catheters or leads; but moderate or severe TR is more commonly a marker of RV overload and dysfunction

^aInfective endocarditis can cause progressive valve disease, leading to regurgitant flow and impaired valve leaflet coaptation; however, it can also lead to near obstruction in some cases.

^bDegree of valvular disease is graded as mild, moderate, or severe, as defined by objective ECHO or catheter-based assessments.

C. Procedural or Surgical Correction

Table 14. Procedural or Surgical Correction

Balloon valvuloplasty	• Performed by percutaneous intervention as a temporizing intervention
Valve repair	• May entail direct surgical repair of a damaged valve leaflet or implantation of a ring at the valve annulus to facilitate improved coaptation of a regurgitant valve
Tissue (bioprosthetic) valve	• Made of animal or human tissue • Usually does not require long-term anticoagulation (see Table 15) • Does not last as long as a mechanical valve (may last 10–15 yr)
Mechanical valve	• Made of synthetic materials (newer valves use ceramic or carbon) • They are durable and generally unlikely to need replacement • Require lifelong anticoagulation • Warfarin is currently the only anticoagulant approved for use by the FDA in patients with mechanical heart valves (see Table 15)

Table 14. Procedural or Surgical Correction (*continued*)

Transcatheter aortic valve replacement (TAVR)	• Made of animal tissue (bioprosthetic) and attached to a wire frame stent and placed using catheter inside the old aortic valve • This may be considered in patients who are at higher perioperative risk for surgical aortic valve replacement or when surgery is not an option • Anticoagulation and/or antiplatelet agents are required for at least a short time after TAVR
Transcatheter mitral valve repair (TMVR)	• Minimally invasive technique for treatment of symptomatic chronic moderate-severe or severe primary (degenerative) mitral regurgitation in patients at prohibitive surgical risk • A leaflet repair device (MitraClip) is currently the only FDA approved device for this indication • This device uses a cobalt chromium clip to suture the regurgitant orifices of the mitral valve leaflets together, thereby increasing coaptation • Anticoagulation and/or antiplatelet agents are required for at least a short time after TMVR

D. Anticoagulation

1. Three guidelines exist regarding valve anticoagulation, with varying agreement in the recommendations.
2. Prosthetic mitral valves have increased risk of thrombosis (blood flow across the valve is passive and occurs during diastole) versus aortic valves, where blood flow across the valve is active occurring during systole.

Table 15. Prosthetic Valve Anticoagulation: Levels of Evidence to Support Recommendations (Circulation 2013;127:e362-425; Circulation 2014;130:e344-426; J Am Coll Cardiol 2012;59:1200-54; Circulation 2014;129:e521-643; Chest 2012;141:e576S-600S; Arch Cardiovasc Dis 2012;105:465-7; The Ohio State University Wexner Medical Center. Clinician's Guide to Anticoagulation Recommendations Post-Valve Replacement. Available at <https://evidencebasedpractice.osumc.edu>. Accessed January 20, 2015.

Prosthetic Valve Anticoagulation: Levels of Evidence to Support Recommendations

Must consider relative risk of bleeding vs thrombosis given the patient's current clinical status when initiating or continuing anticoagulant therapy

Procedure	Antiplatelet Therapy		Warfarin Target INR [†]		Parenteral Anticoagulation
	NO Risk Factors	With Clotting Risk Factors [‡]	NO Clotting Risk Factors	With Clotting Risk Factors [‡]	
Mechanical AVR	ASA 81 mg	ASA 81 mg	2 – 3	2.5 – 3.5	Bridging until warfarin therapeutic for 2 days 2C for intermittent UFH subQ Q8H* or LMWH over continuous IV UFH
Level of Evidence	1B*	1B*	2C	2C	
ACC/AHA	I	I	I	I	
EACTS	IaC	IaC	IB	IB	B
Bioprosthetic AVR	ASA 81 mg	ASA 81 mg	2 – 3	2 – 3	Bridge with UFH until warfarin therapeutic for 2 days 2C
Level of Evidence	2C	2C	Ia - If less than 3 months Ib - Don't use warfarin	I	
ACC/AHA	I	I	IbC	IbC	
EACTS	IaC	IaC			IC
Transcatheter AVR	ASA 81 mg and clopidogrel 75 mg daily	ASA 81 mg and clopidogrel 75 mg daily			Bridge with UFH until warfarin therapeutic for 2 days 2C for intermittent UFH subQ Q8H* or LMWH over continuous IV UFH
Level of Evidence	2C	2C			
ACC/AHA	Discussed but not graded	Discussed but not graded			
EACTS					B
Mechanical MVR	ASA 81 mg	ASA 81 mg	2.5 – 3.5	2.5 – 3.5	Bridge with UFH until warfarin therapeutic for 2 days 2C for intermittent UFH subQ Q8H* or LMWH over continuous IV UFH
Level of Evidence	1B*	1B*	1B	1B	
ACC/AHA	I	I	I	I	
EACTS	IaC	IaC	IB	IB	IC
Bioprosthetic MVR	ASA 81 mg	ASA 81 mg	2 – 3	2 – 3	Bridge with UFH until warfarin therapeutic for 2 days 2C
Level of Evidence	2C	2C	2C	2C	
ACC/AHA	I	I	Ia - If less than 3 months	I	
EACTS	IaC	IaC	IaC	IC	IC
Other Statements			For patients who have systemic embolism despite a therapeutic INR, the addition of ASA 81 mg/day is recommended if not previously provided and/or upward titration of warfarin to achieve a higher target INR. For a previous target INR of 2.5 (range 2 to 3), it is suggested that the warfarin dose be increased to achieve a target INR of 3.0 (range 2.5 to 3.5). For a previous target INR of 3.0, it is suggested that the warfarin dose be increased to achieve a target INR of 3.5 (range 3.0 to 4.0).		
Level of Evidence	Discussed; Not graded				
ACC/AHA					

* Except in patients with a history of GI bleeding or who are more than 80 years of age.

† Risk factors for increased risk of thromboembolism include atrial fibrillation, previous thromboembolism, hypercoagulable state, left ventricular dysfunction, older generation thrombotic valve, mechanical tricuspid valve, greater than one mechanical valve.

‡ Dosing cited is UFH 15,000 units/kg subQ Q12H or 166 units/kg sub Q8H adjusted therapeutic PTT goals; Enoxaparin 1 mg/kg subQ Q12H

E. Valve Thrombosis

1. Highest risk within the first year after replacement
2. Most predominant risk is in mechanical prosthetic valves, but can also occur with bioprosthetic valves
3. Treatment involves systemic fibrinolytic treatment or surgical reoperation with varying success rates – Both carry significant risks of morbidity and mortality, including:
 - a. Thrombolysis (predominantly recommended for right-sided valve thrombosis)
 - i. Cardiac tamponade
 - ii. Stroke/transient ischemic attack
 - iii. Systemic embolization
 - iv. Major bleeding
 - v. Death
 - b. Surgery (predominantly recommended for left-sided valve thrombosis)
 - i. Cardiac tamponade
 - ii. Stroke/transient ischemic attack
 - iii. Renal failure
 - iv. Heart block
 - v. Systemic embolization
 - vi. Prolonged ventilation
 - vii. Major bleeding
 - viii. Death

F. Other Cardiac Functional Defects

1. Left ventricular outflow tract (LVOT) obstruction (Circulation 2008;117:429-39; J Am Coll Cardiol 2000;36:1344-54)
 - a. Hypertrophic obstructive cardiomyopathy (HOCM)
 - i. Genetic disease leading to hypertrophy of the LV (particularly the ventricular septum) with or without the presence of LV outflow tract obstruction
 - ii. LVOT obstruction is of greatest concern when HOCM exists with systolic anterior motion (SAM) (see text that follows); however, in HOCM, LVOT obstruction can exist in the absence of SAM because of septal hypertrophy; nonetheless, acute clinical management is predominantly the same as outlined in 1.a.i–iii and in 1.b.i.
 - iii. Treatment of HOCM without SAM relies heavily on the management of contributors to myocardial hypertrophy and diastolic heart failure.
 - (a) β -Blockers are first-line agents in the treatment of patients with HOCM and are commonly titrated to heart rate goals of 60–65 beats/minute.
 - (b) Dihydropyridine calcium channel blockers (particularly verapamil) are recommended in patients with contraindications to β -blockade or in those without advanced heart failure or bradycardia.
 - (c) For recommendations specific to HOCM (patients also with SAM), see “b” in the text that follows.
 - (d) Patients with HOCM may be at increased risk of sudden cardiac death. Evaluation should consider the patient’s candidacy for implantable cardioverter-defibrillator placement by ambulatory ECG (Holter) monitoring at least biannually.
 - iv. Treatment may be indicated by surgical septal myectomy or catheter-directed alcohol ablation.
 - b. SAM of the mitral valve
 - i. SAM and LVOT obstructions result in a systolic outflow tract obstruction and are commonly associated with HOCM but can also occur in other clinical scenarios, particularly after cardiac surgery.

- ii. Can lead to severe cardiogenic shock
 - iii. SAM is more of a dynamic obstruction in which the degree of obstruction and flow gradient is dependent on heart rate, cardiac contractility, and ventricular preload volume.
 - (a) In an underfilled LV, there is physically less distance between the mitral valve and septum, thus generating an increased risk of obstruction because the LVOT is generally narrower at the onset of systole, particularly if the mitral valve leaflet is affected.
 - (b) Increasing cardiac contractility and heart rate increases LVOT obstruction and gradient by inducing a stronger contraction, increasing the contact between the septum and mitral leaflets, and increasing the rate of systolic attempts.
 - iv. For patients with SAM who have a potential for obstructive physiology, management involves maintaining normal or increased LV preload and low heart rates.
 - (a) Acute hypotension is best managed with phenylephrine or vasopressin (pure vasoconstrictors) to selectively increase SVR without increasing contractility or heart rate.
 - (b) Inotropes and vasopressors that mediate increases in heart rate or contractility should be avoided, if possible, because they may be harmful and worsen the LVOT.
 - (c) Afterload-reducing agents (e.g., ACE inhibitors, ARBs, non-dihydropyridines) should be used with caution (if at all).
2. Septal defects (atrial or ventricular)
- a. Septal defects can be acquired (i.e., postinfarction ventricular septal defect) or can be congenital.
 - b. Diagnosed predominantly by ECHO using a bubble study. If the patient presents in a seemingly low cardiac output state, a left-to-right intracardiac shunt should be suspected if mixed venous oxygen saturation (S_{VO_2}) saturations are greater than Sc_{VO_2} saturations.
 - c. Important principles
 - i. Goals include minimizing the degree of intracardiac shunt while maintaining adequate cardiac output. It is generally favored to accept a right-to-left intracardiac shunt while recognizing that partial pressure of arterial oxygen (P_{aO_2}) saturations will be somewhat decreased and reflective of venous and arterial blood mixing in the LV before ejection.
 - ii. Decreasing right-sided cardiac filling pressures can augment left-to-right intracardiac shunting of blood. Administration of venodilators (i.e., nitrates) or aggressive diuresis could augment left-to-right intracardiac shunts and lead to clinical deterioration.
 - iii. Intravenous medications should preferably be filtered to minimize the risk of air/particulate embolus traveling through to the left side of the heart, being ejected, and causing a potential stroke.
 - d. Treatment may include surgical correction or percutaneous catheter placement of a closure device.

Patient Case

Question 8 pertains to the patient case on page 2-102.

8. J.M. is no longer in AF but remains in cardiogenic shock. The cardiac intensive care unit team has consulted the cardiothoracic surgeons for evaluation of his mitral valve disease and has considered advanced heart failure therapies. In the patient's decompensated state, he would likely need additional optimization if he were to undergo surgery. Which temporary means of mechanical circulatory support (MCS) might be most favorable to help stabilize this patient's cardiogenic shock in the setting of moderate to severe mitral regurgitation?
- A. Venoarterial extracorporeal membrane oxygenation (ECMO)
 - B. Venovenous ECMO
 - C. Intra-aortic balloon counterpulsation
 - D. None; the patient likely requires urgent surgery.

VIII. ADVANCED THERAPIES FOR HEART FAILURE AND CARDIOGENIC SHOCK

- A. The goals behind advanced therapies can be thought of as dynamic, depending on patient progression and resolution or presentation of comorbid conditions.
- B. Dynamic Progression of Heart Failure Advanced Therapies

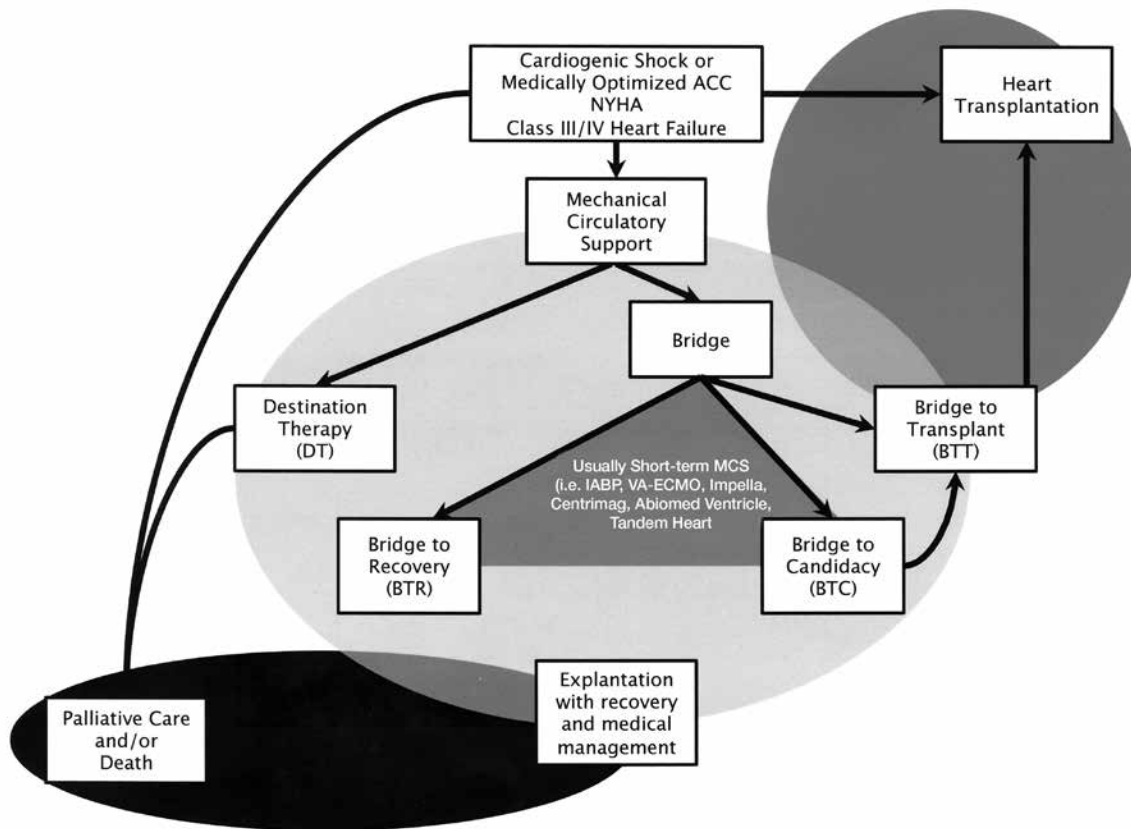


Figure 10. Dynamic progression of heart failure advanced therapies.

- C. Mechanical Circulatory Support (MCS) (J Heart Lung Transplant 2013;32:157-87)
 1. Intent, duration, and type of MCS support depend on several factors, including patient acuity, comorbidities, and prognosis.
 2. Common terms
 - a. Destination therapy – Formal designation for patients who meet the criteria for long-term mechanical support but who are not a transplant candidate because of relative or absolute contraindications
 - b. Bridge to transplantation – Formal designation for patients eligible to be listed as candidates for heart transplantation
 - c. Bridge to candidacy and bridge to recovery – Used in concept and are not formally recognized abbreviations but describe the approach to temporary MCS when short-term left ventricular assist devices (LVADs) are used to support a patient until a long-term prognosis can be determined, which may include explantation with recovery, implantation of long-term durable LVAD support, heart transplantation, or palliative care

Table 16. Mechanical Interventions for Shock

Short to Intermediate Term	
Intra-aortic balloon pump (IABP) counterpulsation	- Placed by femoral arterial catheter and advanced up the aorta - Inflation enables diastolic augmentation of systemic blood pressure to improve vital organ and coronary perfusion pressures - Deflation facilitates selective afterload during systole to ease cardiac output (does not technically increase cardiac output) - Can be set to trigger from ECG, pacer, or arterial line pressure, or can be manually set - Tachyarrhythmias and aortic regurgitation/insufficiency are not well supported with this means of MCS - Level of support coincides with timing of inflation/deflation per related heartbeat; for example: 1:1 = one inflation/deflation per every heartbeat (maximal support) 1:4 = one inflation/deflation for every fourth heartbeat (less support) - When setting duration in deflated state increases (providing less support), the thrombosis risk associated with the IABP increases, commonly requiring anticoagulation
Percutaneous VAD	- One common example is Impella: intraluminal axial support that provides varying degrees of LV output support (2.5, CP, and 5.0) and RV output support (RP) - Another example is TandemHeart: left atrium-to-femoral artery bypass using transeptal cannulation - May be considered in cardiogenic shock or as temporary support during high-risk PCI - Anticoagulation regimen is a common topic of debate and medication safety discussion - Complications may include hemolysis/bleeding, arrhythmias, and migration and/or malposition of the catheter/cannula
Extracorporeal or paracorporeal VAD	Examples include CentriMag, BVS 5000, and AB5000 ventricle
Extracorporeal life support (ECLS) or extracorporeal membrane oxygenation (ECMO)	- Similar cardiopulmonary bypass in which large-bore cannulas drain venous blood that is pumped through an oxygenator, where it is oxygenated and/or cleared of carbon dioxide and then actively pumped back into the body - Modality of support depends on the means of vascular cannulation <u>Venoarterial:</u> Removal of venous blood from the vena cava with circulation through the ECMO circuit and delivery in retrograde fashion up the aorta; potentially indicated for primary cardiogenic shock, cardiopulmonary failure, and post-cardiopulmonary circulatory shock <u>Venovenous:</u> Removal of venous blood from the vena cava with circulation through the ECMO circuit and delivery back to the right atrium; potentially indicated for hypoxic respiratory failure owing to any cause, hypercarbic respiratory failure with bronchospastic disease or other cause of carbon dioxide (CO₂) retention, or severe air leak syndromes
Long term	
Implantable LVADs	Examples include the Heartmate II, HeartWare
Total artificial heart	

LVAD = left ventricular assist device; VAD = ventricular assist device.

- d. Anticoagulation considerations
 - i. Anticoagulation strategies are specific to the proprietary device, and many institutions have standardized protocols.
 - ii. Safety and efficacy of DOACs in patients with ventricular assist devices (VADs) have not been well established.

Table 17. Example of Initial Post-Insertion Antithrombotic Regimen

LVAD	Aspirin	Heparin Infusion (once hemostasis achieved)	Initial Warfarin INR Goal
Long-term Devices			
Heartmate II	POD 0: 325 mg × 1 Ongoing: 81 mg daily	- By POD 2: —Initiate “Heparin – no dose escalation at 5 units/kg/hr” - By POD 3: —Increase to “Heparin Sliding Scale,” titrating to institutional aPTT goal	2–3
HeartWare	POD 0: 325 mg × 1 Ongoing: 325 mg daily	- Within 12 hr post-operation: —Initiate “Heparin – no dose escalation at 5 units/kg/hr” - By POD 1: —Increase to “Heparin Sliding Scale,” titrating to institutional aPTT goal	2–3
Short-term Devices			
CentriMag	POD 0: 325 mg × 1 Ongoing: 81 mg daily	- Within 12 hr post-operation: —Initiate “Heparin – no dose escalation at 5 units/kg/hr” - By POD 1: —Increase to “Heparin Sliding Scale,” titrating to institutional aPTT goal	N/A
Abiomed ventricle	POD 0: 325 mg × 1 Ongoing: 81 mg daily	- Within 12 hr post-operation: —Initiate “Heparin – no dose escalation at 5 units/kg/hr” - By POD 1: —Increase to “Heparin Sliding Scale,” titrating to institutional aPTT goal	N/A
Abiomed BVS 5000	POD 0: 325 mg × 1 Ongoing: 81 mg daily	- Within 12 hr post-operation: —Initiate “Heparin – no dose escalation at 5 units/kg/hr” - By POD 1: —Increase to “Heparin Cardiac Sliding Scale,” titrating to institutional aPTT goal	N/A

INR = international normalized ratio; POD = postoperative day; aPTT = activated partial thromboplastin time.

3. Complications of MCS (other than device failure)
 - a. Bleeding
 - i. Common sources
 - (a) Nasal/upper airway

- (b) Gastrointestinal (GI)
 - (c) Arteriovenous malformations in one of the previously stated locations
 - (d) Hemolysis
- ii. Workup and/or acute treatment options
 - (a) Laboratory workup
 - (1) Prothrombin time/INR/aPTT
 - (2) Increase frequency of hemoglobin/hematocrit evaluation.
 - (3) Multimeric von Willebrand testing for acquired von Willebrand factor deficiency (some clinicians believe that all patients with prolonged continuous flow MCS develop acquired von Willebrand disease)
 - (4) If no overt sign of bleeding – Consider hemolysis workup.
 - (b) If suspected/confirmed bleeding, hold anticoagulation and consider reversal with caution. Consider any history of bleeding/clotting-related problems and indications for antithrombotic therapy in addition to MCS.
 - (c) Obtain appropriate consults, and consider common interventions. Ear, nose, and throat:
 - Evaluate for source control and/or cauterization.
 - Mupirocin 2% (Bactroban) every 12 hours to each nostril to maintain moist nasal passages
 - Oxymetazoline 0.05% (Afrin) to each nostril every 12 hours as needed for epistaxis
 - (d) Gastroenterology
 - (1) Proton pump inhibitor continuous infusion at least until location of GI source identified
 - (2) Enteroscopy with or without colonoscopy; may consider one or more of the following:
 - Angiography and cautery
 - Balloon-assisted enteroscopy
 - Video-capsule enteroscopy
 - Surgery
- iii. Long-term management
 - (a) Consider decreasing anticoagulation/antiplatelet therapy intensity.
 - (b) Refractory bleeding despite previously stated interventions
 - (1) Consider role of oral antifibrinolytics (i.e., aminocaproic acid).
 - (2) Consider role of desmopressin or von Willebrand factor replacement if confirmed acquired von Willebrand disease and if LVAD speed cannot be further decreased.
 - (3) If GI arteriovenous malformations are present that are not amenable to intervention, octreotide 50 mcg subcutaneously every 8 hours may be considered.
- b. Hemolysis and/or thrombosis
 - i. Hemolysis may be the presenting symptom of an underlying process, including infection, pump thrombosis, or other mechanical or physiologic dysfunction.
 - ii. Common presentation includes:
 - (a) Nonhemorrhagic anemia
 - (b) Urine color changes with appearance of hematuria; in severe cases, can be brown or black
 - (c) Hyperkalemia
 - (d) LVAD pump alarms
 - iii. Workup for contributing factors:
 - (a) Evaluate LVAD and cardiac function for contributing factors, including documentation and alarm history for suction events, power spikes, speed changes, volume status, RV function, arrhythmias
 - (1) Evaluate cannula(e) position and evaluate for obstruction/thrombus by ECHO or computed tomography (CT).
 - (2) Evaluate RV function by ECHO.

- (3) Evaluate for intra-device thrombosis by ECHO ramp testing (Echocardiography 2014;31:E5-9; J Am Coll Cardiol 2013;62:2149-50; J Am Coll Cardiol 2012;60:1764-75).
 - (b) Ensure adherence to anticoagulation regimen according to patient's established goals.
 - (c) Evaluate laboratory values to establish the presence and degree of hemolysis and to identify any other potential contributors.
 - (1) Lactate dehydrogenase (LDH); normal values are 300–600 IU/L for most forms of MCS.
 - (2) Haptoglobin
 - (3) Plasma-free hemoglobin
 - (4) Blood cultures (an association has been identified with bacteremia and hemolysis in patients with LVADs – in some cases, presenting as thrombosis).
 - (5) Urine assessment – Send baseline urinalysis, urine culture, and appearance of changes daily to assess for improvement. Likely hemolysis, as evidenced by the presence of casts and color changes (darkened tea, red, or black are highly suggestive of hemolysis).
 - (d) Other laboratory values/considerations
 - (1) Hypercoagulable states (i.e., heparin-induced thrombocytopenia [HIT])
 - (2) CBC with differential
 - (3) Reticulocyte count
- iv. Treatment
 - (a) Address any evidence of mechanical dysfunction by adjusting speed/flow rates, if possible.
 - (b) Consider medical optimization of RV function.
 - (c) If hypovolemic, give volume challenge. Consider alkalization of urine and optimize fluid status (sodium bicarbonate 150 mEq/1000 mL of sterile water) at 0.5–1 mL/kg/hour; treat to a goal urine pH of greater than 7.5 to avoid additional hemolysis/hemoglobinuria-related acute kidney injury.
 - (d) Evaluate and optimize anticoagulation strategy.
 - (1) Ensure therapeutic anticoagulation with heparin or warfarin.
 - (2) Antithrombotic therapy that is more aggressive may be appropriate. Optimal acute antithrombotic strategies, although not yet defined, may include heparin infusion, glycoprotein (GP) IIb/IIIa infusions, parenteral direct thrombin inhibitors, or thrombolytics.
 - (3) Severe hemolysis can potentiate platelet activation – Can consider GP IIb/IIIa antagonist therapy (see Table 5), depending on bleeding risks and potential surgical plan.
 - (e) Reassess long-term antithrombotic strategy.
 - (1) Consider augmentation of antiplatelet therapy, or increase the INR therapeutic goal range.
 - (2) If thought to be related to a concurrent infection, can consider acutely increasing anticoagulation goals until infection control is gained
- c. Infection
 - i. LVAD infections are often complex and have been characterized by the International Society for Heart & Lung Transplantation in the following manner (J Heart Lung Transplant 2011;30:375-84):
 - (a) VAD-specific infections
 - (1) Pump and/or cannula infections
 - (2) Pocket infections
 - (3) Percutaneous driveline infections
 - Superficial infection
 - Deep infection

- (b) VAD-related infections
 - (1) Infective endocarditis
 - (2) Bloodstream infections that may be VAD related or non-VAD related
 - (3) Mediastinitis
 - Sternal wound infection: Surgical site infection-organ space
 - VAD pocket infection (continuous with mediastinum or already situated in the mediastinum, depending on the device used)
 - Other causes of mediastinitis, perforation of the esophagus
 - (4) Non-VAD infections
 - Lower respiratory tract infection
 - Cholecystitis
 - *Clostridium difficile* infection
 - Urinary tract infection
 - ii. Antibiotic treatment
 - (a) Antibiotic coverage should account for site of suspected infection, previous pathogens and susceptibilities, proximity to driveline site or VAD pocket, and any other potential exposure or bacteremia secondary to the procedure. Prophylactic antibiotic coverage for VAD-related or non-VAD-related surgical procedures should account for site of procedure, previous infections, proximity to driveline site or VAD pocket, and any other potential exposure or bacteremia secondary to the procedure. In some circumstances, this requires broader prophylactic antibiotic coverage (Interact Cardiovasc Thorac Surg 2012;14:209-14).
 - (b) Treatment duration depends largely on the type of infection. However, if the infection is VAD related or VAD specific, prolonged antimicrobial therapy (more than 4 weeks) is commonly used.
 - (c) Because LVAD exchange is not without considerable risk, long-term oral antibiotic suppression therapy may be considered for some infections.
- D. Heart Transplantation (J Heart Lung Transplant 2010;29:914-56)
- 1. Transplantation remains the gold-standard treatment for end-stage heart failure.
 - 2. Many variables limit the utility of heart transplantation, foremost of which is donor availability and donor-recipient tissue compatibility. These limitations (and potentially others) may make long-term MCS a more viable option until heart transplantation becomes an option.
 - 3. Other limitations may include recipient characteristics of:
 - a. Mental health
 - b. Social support
 - c. Adherence to medication and appointments
 - d. Severe pulmonary hypertension
 - e. Cancer
 - f. Infection
 - g. Tobacco or ethanol use
 - h. Illicit drug use history
 - 4. Additional considerations associated with thoracic transplantation in the ICU, such as immunosuppression, rejection, and other complications, are beyond the scope of this review.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: B

Given this patient's CAD, type 2 diabetes mellitus, dyslipidemia, gastroesophageal reflux disease, hypertension, obstructive sleep apnea, and ischemic cardiomyopathy, only Answer B consists of the three agents that reduce morbidity and mortality among these comorbidities: carvedilol (heart failure and potentially diabetes), spironolactone (heart failure progression post-MI), and lisinopril (heart failure and diabetes), making Answer B correct and Answers A (Amlodipine, clopidogrel, and sitagliptin.), C (Pravastatin, amlodipine, and aspirin 325 mg), and D (Prasugrel, sildenafil, and atenolol) incorrect.

2. Answer: C

Although many of these tests might be helpful in this patient's differential diagnosis, the most likely consideration would be respiratory decompensation or a heart failure decompensation, given the patient's presentation; thus, a chest radiograph, ECHO, BNP, and lactate would be most appropriate, making Answer C correct. Answer A is incorrect; although an infectious etiology cannot be ruled out, it is less likely than noninfectious cardiorespiratory differentials. Answer B is not the best answer; although serial troponins and an ABG could be argued for, liver function tests are unlikely to provide additional insight into this patient's differential. Answer D also is not the best answer; although it provides additional information for hemodynamic assessment, it is lacking in an assessment of cardiac function, which is a likely contributor to the patient's presentation.

3. Answer: D

Dobutamine would be the ideal choice, given the patient's acutely worsening cardiac index and malperfusion and its rapid onset; this would facilitate β_2 arterial vasodilation (both SVR and PVR reduction) as well as increase chronotropy and inotropy. Milrinone, although likely beneficial for both cardiac index and PVR reduction, would be less favorable, given that its time to peak effect will exceed 6 hours (the time required to achieve greater than 87.5% of steady state, even in normal renal function). Neither norepinephrine nor epinephrine would be favored (particularly at these doses) because the patient's MAP is currently elevated, and these agents would contribute to increased α_1 -mediated afterload increases, causing increased myocardial workload in a patient who already has decompensated systolic heart

failure. Answer D (dobutamine 5 mcg/kg/min) is correct, and Answers A (norepinephrine 0.08 mcg/kg/min), B (epinephrine 0.08 mcg/kg/min), and C (Milrinone 0.25 mcg/kg/min) are incorrect.

4. Answer: D

The patient's troponin elevation is most likely a result of the patient's decompensated heart failure (especially considering clinical evidence of acute HF, such as high BNP, CVP, and low cardiac output) superimposed on chronic CAD (Answer D is correct). Given the patient's chemistry and ABG results, chronic obstructive pulmonary disease (Answer B) is highly unlikely. Although this presentation could be attributed to NSTEMI (Answer A), it is less likely, given the lack of new ST-T changes on ECG and the accompanying evidence of a heart failure exacerbation. Sepsis (Answer C) is also a potential contributor to troponin elevation; by comparison, an infectious etiology is less likely in this patient's case.

5. Answer: A

Ticagrelor has been associated with adenosine-mediated dyspnea and bradycardia; therefore, this medication should be evaluated as a contributing cause. According to the current ACC/AHA guidelines, this patient should continue P2Y₁₂ inhibitor therapy because his stent was placed less than 12 months ago, and he should continue aspirin therapy indefinitely (Answer A is correct). Conversely, it would not be appropriate to stop ticagrelor without switching to an alternative P2Y₁₂ inhibitor (Answer B is incorrect). A likely cause has been identified (Answer C is incorrect), and the patient has no evidence of hyperkalemia (Answer D is incorrect).

6. Answer: A

Because of this patient's hypotension and ongoing cardiogenic shock, synchronized cardioversion would be preferred (Answer A is correct). Metoprolol (Answer B) would be unfavorable because of the patient's concurrent dobutamine use and hypotension; similarly, amiodarone 150 mg intravenous push (Answer D) could contribute to further hypotension. The primary role of adenosine (Answer C) is to slow AV nodal conduction when patients are tachycardiac with a regular rhythm (i.e., supraventricular tachycardia) to terminate the arrhythmia or to help differentiate atrial from ventricular arrhythmias.

7. Answer: C

The physician is considering heparin anticoagulation while the patient is in the ICU. Although valuable to consider for long-term anticoagulation, the HAS-BLED score is not validated for bleeding risk specific to heparin anticoagulation. Nonetheless, given the patient's CHA₂DS₂-VASc score (annual stroke risk of 6.7%), anticoagulation should be considered, making Answer C correct and Answer D ("anticoagulation is not warranted") incorrect. Answer A, "the patient's risk of bleeding is the same as his stroke risk," and Answer B, "the patient's risk of stroke exceeds his risk of bleeding," are incorrect statements because the foundation of these scores does not include risk of thromboembolism during ICU stay, nor do the scores assess risk of bleeding on heparin infusions.

8. Answer: C

Given his ongoing cardiogenic shock, this patient is unlikely to remain stable without intervention; thus, Answer D is incorrect. To help stabilize him, intra-aortic balloon counterpulsation (Answer C) would best facilitate selective afterload reduction during systole (increasing cardiac output in a patient with a low ejection fraction and severe mitral regurgitation) while providing augmented diastolic pressures. Venovenous ECMO (Answer B) is unlikely to help because this means of MCS depends on a functional LV and RV to provide forward blood flow. Venoarterial ECMO (Answer A) may stabilize the patient; however, it would increase afterload on the aortic valve, which could worsen his mitral regurgitation. Furthermore, this degree of MCS may be unwarranted at this time unless the patient develops progressive hypoxic cardiopulmonary failure.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: C

A diagnosis of cardiogenic shock is most likely, given the patient's history, presentation, ongoing vasopressor requirement, elevated BNP, and lack of infectious symptoms (Answer A is incorrect). Furthermore, this patient has positive troponins and ST segment elevation in leads II, III, and aVF (inferior leads), making STEMI the primary diagnosis and reason for cardiogenic shock (Answer C is correct; Answer D is incorrect). The presence of hypotension and bradycardia are more likely consistent with complications of an inferior MI with possible RV involvement, as opposed to an acute exacerbation of heart failure. The patient also has a preserved LVEF and not systolic heart failure (Answer B is incorrect).

2. Answer: D

ST-segment elevation in leads II, III, and aVF (inferior) are most consistent with the right coronary artery (Answer D is correct). Answers A (left main coronary artery), B (left anterior descending artery), and C (left circumflex coronary artery) are incorrect.

3. Answer: B

According to the SOAP II investigation, dopamine is associated with increased rates of adverse events in patients with cardiogenic shock compared with norepinephrine (Answer B is correct; Answer A is incorrect). Milrinone (Answer C), although helpful in some patients with heart failure, would not be favored, given the patient's current hypotension and acute renal failure. Normal saline administration (Answer D) would likely be detrimental because of the patient's signs of fluid overload, including BNP elevation, hyponatremia, and rales on examination.

4. Answer: A

Lidocaine would be most favorable in patients with ischemia-mediated ventricular arrhythmias, and although the patient is not currently in VT, he is having persistent premature ventricular contractions (bigeminy), further increasing concern for ongoing ischemia and myocardial irritability (Answer A is correct). Metoprolol (Answer C) and diltiazem (Answer D) would be contraindicated because of ongoing cardiogenic shock and vasopressor requirements. Amiodarone 300 mg intravenous push (Answer B) is no longer appropriate because the patient

has a pulse and blood pressure and is currently not in VT. Furthermore, rapid administration of amiodarone may lead to worsening hypotension.

5. Answer: A

The patient's heart catheterization was performed through the femoral artery, a vessel that is much more difficult to compress to facilitate hemostasis. Hematomas can occur at the access site; however, the most serious bleeding complication associated with this access site is a retroperitoneal bleed (Answer A is correct). Answer B (dissection/rupture), Answer C (stent thrombosis), and Answer D (papillary muscle rupture) are incorrect.

6. Answer: C

Vasopressin would be favored because, when administered at normal physiologic doses, it mediates predominant increases in SVR while minimally affecting the PVR (Answer C is correct). Phenylephrine (Answer B), however, will increase both PVR and SVR by the α_1 -receptors. Given the patient's ongoing hypotension, low cardiac index, and rising CVP, inaction (Answer A) would be inappropriate, and additional volume administration (Answer D) would be detrimental in the setting of volume overload and RV failure.

7. Answer: B

Amiodarone boluses would be safest if administered slowly for 10 minutes to avoid additional hypotension, followed by a continuous infusion (Answer B is correct; Answer A is incorrect). Metoprolol (Answer C) and diltiazem (Answer D) would be contraindicated because of ongoing cardiogenic shock and vasopressor requirements.

8. Answer: D

Because of the diagnosis of acute MI, current quality measures would require initiation of or documentation to contraindications for each item except for ACE inhibitors/ARBs (Answer D) because the patient still has an LVEF greater than 40%. Answer A (aspirin contraindication), Answer B (statin contraindication), and C (β -blocker contraindication) are incorrect.

APPENDIX A – OVERVIEW OF ANTI-ARRHYTHMICS

Class	MOA	Drug (available dosage forms)	ECG Effects			Management Considerations and Pearls	Notable Drug Interactions	Defibrillation Threshold	TdP risk (%)
IA	Sodium channel blockade (intermediate potency)	Quinidine (PO and IV)	↑↓	↑	↑	Different formulations available (no exact conversions) α-Blockade may contribute to hypotension Prolonged half-life in CHF and hepatic dysfunction May require dose adjustments in renal and/or hepatic dysfunction Enhanced AV node conduction usually requires combination with AV node-blocking agent	CYP2D6 (inhibitor) CYP3A4 (substrate and inhibitor) QT-prolonging drugs	↑	2-8
		Procainamide (IV)	↑	↑	↑	May contribute to hypotension Metabolized by hepatic acetylation Active metabolite (NAPA) renally eliminated and has increased class III properties Dialyzable	QT-prolonging drugs	↑↓	1-10
		Disopyramide (PO)	↑↓	↑	↑	May require dose adjustments in renal and/or hepatic dysfunction Potent anticholinergic adverse effects May be used to treat hypertrophic cardiomyopathy	CYP3A4 (substrate) QT-prolonging drugs	↑	1-3
IB	Sodium channel blockade (low potency)	Lidocaine (IV)	N/A	N/A	N/A or ↓	Ventricular arrhythmias only Increased risk of toxicities in hepatic dysfunction, CHF, and elderly patients Enhanced efficacy in ischemic tissue Adverse effects include CNS depression, somnolence, tremors, seizures Lidocaine concentrations may be checked (total: 1.5-5 mcg/mL; free: 0.5-2 mcg/mL)	CYP3A4 (substrate)	↑	
		Mexiletine (PO)				Ventricular arrhythmias only Prolonged half-life in CHF and hepatic dysfunction Oral derivative of lidocaine	CYP2D6 (substrate) CYP1A2	↑	
IC	Sodium channel blockade (high potency)	Flecainide (PO)	↑	↑	N/A or ↑	Useful for AF/flutter in patients without structural heart disease Increased risk of mortality post-MI (Cardiac Arrhythmia Suppression Trial [CAST]) Avoid in CHF because of its potent negative inotropic effects Combine with AV node blocker to prevent rapid atrial flutter	CYP2D6	↑	
		Propafenone (PO)				Useful for AF/flutter in patients without structural heart disease Increased risk of mortality post-MI (CAST trial) Avoid in CHF because of its potent negative inotropic effects Combine with AV node blocker to prevent rapid atrial flutter SR and IR formulations not equivalent	First-pass metabolism CYP2D6, CYP3A4, CYP1A2 substrate	↑↓	
II	β-Blockade	Ex. Carvedilol (PO) Labetalol (PO/IV) Metoprolol (PO/IV) Esmolol (IV)	N/A or ↑	N/A	N/A or ↓	Sinus bradycardia AV block Hypotension more likely with nonselective agents Continuous infusions of esmolol or labetalol may contribute to large amounts of fluid	Predominantly CYP2D6	N/A	

APPENDIX A – OVERVIEW OF ANTI-ARRHYTHMICS (continued)

III	Potassium channel blockade	Dofetilide (PO)				Requires ECG monitoring for initiation, dose titration, reinitiation, or introduction of new interacting agents Requires renal dosing adjustments	CYP3A4 Trimethoprim, verapamil, HCTZ, and many others contraindicated QT-prolonging drugs	↓	1-8
		Ibutilide (IV)							
		Sotalol (PO/IV)	N/A	N/A	↑	Only indicated for cardioversion of AF or enhancement of electrical cardioversion	QT-prolonging drugs	↓	1-8
		Amiodarone (PO/IV)	↑	or ↑	↑	Requires renal dosing adjustments Bradycardia Multi-channel-blocking properties Monitor liver, thyroid, and pulmonary function tests Average half-life 53 days; highly lipophilic; active metabolite Bradycardia and hypotension High protein binding	Inhibits CYP3A4, CYP2D6, CYP2C9 Adjust warfarin and digoxin by 50%	↑	< 1
		Dronedarone (PO)				Multi-channel-blocking properties Only approved for AF/flutter; less efficacious vs. amiodarone Less potential for organ-system toxicity vs. amiodarone Avoid in CHF, particularly NYHA class III/IV Bradycardia	Inhibits CYP3A4, CYP2D6, CYP2C9		< 1
IV	Calcium channel blockade	Verapamil (PO/IV)		N/A	N/A	Hepatic dosing Sinus bradycardia Negative inotrope – avoid in patients with systolic heart failure	CYP3A4 (substrate and inhibitor)	N/A	
		Diltiazem (PO/IV)	↑	N/A	N/A	Decreased dosing in elderly patients and patients with hepatic dysfunction Bradycardia Negative inotrope - avoid in patients with systolic heart failure	CYP3A4 (substrate and inhibitor)	N/A	
Misc.	Others	Digoxin (PO/IV)	↑	N/A	N/A	Alternative for rate control of AF/flutter; also used for systolic heart failure Decreased dosing in elderly and patients with kidney dysfunction Loading dose may be given based on ideal body weight Not dialyzable Digoxin concentrations may be checked (AF/flutter: 0.8-2 ng/mL; heart failure: 0.5-0.9 ng/mL)	Many interactions		
		Adenosine (IV)	↑			Half-life < 10 s Used for acute treatment of AV node reentrant tachycardias Can help to distinguish atrial from ventricular arrhythmias			
		Magnesium (IV)	↑			Used to treat Torsades and arrhythmias associated with hypomagnesemia			

AF = atrial fibrillation; AV = atrioventricular; CHF = congestive heart failure; CNS = central nervous system; ECG = electrocardiogram; HCTZ = hydrochlorothiazide; IR = immediate release; IV = intravenous; MI = myocardial infarction; MOA = mechanism of action; NAPA = N-acetylprocainamide; N/A = not applicable; NYHA = New York Heart Association; PO = oral; SR = sustained release; TdP = Torsades de pointes.

PRACTICE ADMINISTRATION AND DEVELOPMENT: PROTOCOL DEVELOPMENT AND QUALITY IMPROVEMENT

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Learning Objectives

1. Develop critical care pathways and formulary proposals.
2. List high-risk medications and medication-related processes that are suited for a medication use evaluation (MUE).
3. Describe how to perform an MUE.
4. Differentiate quality improvement opportunities in the critically ill patient to optimize outcomes.
5. Describe how to perform a gap analysis.
6. Describe the documentation processes for clinical pharmacy services (CPS) and the types of pharmacotherapeutic interventions.
7. Describe how to justify and document the financial value of CPS.

Abbreviations in This Chapter

ADE	Adverse drug event
ASHP	American Society of Health-System Pharmacists
CMS	Centers for Medicare & Medicaid Services
CPOE	Computerized prescriber order entry
CPS	Clinical pharmacy services
DUE	Drug use evaluation
EBM	Evidence-based medicine
ICU	Intensive care unit
LOS	Length of stay
MUE	Medication use evaluation
PAI	Practice Advancement Initiative
PI	Performance improvement
PMR	Patient medical record
P&T	Pharmacy and therapeutics (committee)
QA	Quality assurance
QI	Quality improvement
SUP	Stress ulcer prophylaxis
TJC	The Joint Commission

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

1. As the clinical coordinator/manager, you have received a request to add the critical care pharmacist's review of all intensive care unit (ICU) patients. You recognize that you lack the necessary personnel to accomplish this request. Which justification method would offer the most significant financial impact on the institution to justify the position?
 - A. Developing protocols in the critically ill patient.
 - B. Reducing prescribing errors.
 - C. Reducing medication administration errors.
 - D. Using antimicrobial stewardship.
2. You are the critical care pharmacist implementing a delirium screening in critically ill patients. After reviewing the current literature on delirium, you believe that delirium is an important aspect in screening your patients. Which best reflects what would be considered a barrier to implementing delirium screening in a practice environment?
 - A. Standards of practice.
 - B. Organizational constraints.
 - C. Medical training.
 - D. Sense of competence.
3. The pharmacy and therapeutics (P&T) committee would like to evaluate the use of pharmacotherapy in stress ulcer prophylaxis (SUP) in the ICU. Which is the best method for making this evaluation?
 - A. Perform a medication use evaluation (MUE).
 - B. Administer a performance improvement (PI) initiative.
 - C. Review adverse drug event (ADE) data from the ICU.
 - D. Review medication error data from the ICU.
4. Which medication use process is best suited for an MUE?
 - A. Pharmacist verification times for routine orders in the ICU.
 - B. Management of warfarin-induced hypoprothrombinemia.
 - C. Drug interaction warnings on the computerized prescriber order entry (CPOE) system.
 - D. Duplicate warnings on the CPOE system.

5. You have been asked to develop a quality improvement (QI) strategy for your ICU regarding when to institute hypothermia in patients after cardiac arrest. The current process has been defined. You identify key stakeholders in this patient population to collaborate with you in this process improvement. Which is the next best step in developing the QI program?
 - A. Determine the patient's involvement.
 - B. Evaluate the physician/prescriber's practice.
 - C. Determine the current process.
 - D. Evaluate the data.
6. Using the plan-do-check-act cycle, which best represents what is optimized in the "do" phase?
 - A. Details are described.
 - B. Data are collected.
 - C. Change is made.
 - D. Data are compared.
7. To quantify critical care pharmacist activities, which is the most significant metric that can be used?
 - A. Weighing each variable to quantify measured activities.
 - B. Attending an emergency cardiac arrest.
 - C. Documenting the impact on antibiotic use.
 - D. Educating health care providers.
8. As the clinical pharmacist in the ICU, you are asked to evaluate the quality initiatives specific to critically ill patients. Which best reflects the reportable quality initiatives from the Centers for Medicare & Medicaid Services (CMS)?
 - A. Sepsis and acute coronary syndrome.
 - B. Heart failure and glycemic control.
 - C. Ventilator-associated pneumonia and sepsis.
 - D. Acute coronary syndrome and ventilator bundles.

I. POLICY AND GUIDELINE DEVELOPMENT

Objective: To advance critical care pharmacy, pharmacists should participate in the development, implementation, and data collection of protocols and MUEs. The ICU pharmacist should participate in developing ICU or institutional policies, procedures, clinical pathways, and education of others.

A. Policy and Procedures

1. Policy – A course or plan of action; the existence of written policies and procedures establishes standards of practice or quality/compliance measures and protects against error. Statement that clearly and unambiguously describes the organization's guiding principles and views about a particular matter
 - a. Benefits
 - i. Keeps the institution efficient
 - ii. Provides a training tool during a new employee's orientation
 - iii. Provides reference material for consistent practice
 - iv. Minimizes practice variations
 - b. Development and implementation should involve all team members so that the process works smoothly.
 - c. Reduces the organizational risk by mandating compliance
2. Procedure – A simple course of action intended to achieve a result; describes in detail a logical sequence of a process to be followed to complete the task in a consistent manner
 - a. Aids in doing business as a team
 - b. Identifies each team member's responsibility to the respective task of the procedure
 - c. Helps team members work more effectively together because the expected outcome is identified.
 - d. Allows procedures to be described in the following forms:
 - i. Written steps of the process
 - ii. Flowcharts
 - iii. Checklists
 - e. Can be used as a QI tool or a source of measures

B. Clinical Protocol/Guidelines

1. Supports clinical decision-making by defining best practice
2. Uses evidence-based and standardized treatment options
3. Developed by examining the evidence and gaining consensus among practitioners
4. Physician champion
5. Protocol can be an extension of a clinical policy or practice standard.
6. Clinical protocols are often kept separate from institutional policies and procedures.
7. Disease and drug therapy protocols
8. Critical care pathways
9. Formulary proposals
10. Medication reconciliation – Important component of the Institute for Healthcare Improvement 100,000 Lives Campaign

C. Framework of a Policy and Procedure

Critical care pharmacists should lead the assessment of guidelines, protocols, practice changes, or PI initiatives in the ICU.

1. Purpose – What audience is the policy intended to address and why are the policy and procedure being written

2. Definitions – Any definitions needed to provide the reader with an understanding of the language
 - a. Policy – Intent of the policy
 - b. Provisions
 - c. Procedure
 - d. Resources/references
 - e. Owner
3. How to write policies
 - a. Policy (or planning/evaluation)
 - i. Identify key stakeholders in the organization.
 - ii. Appoint a facilitator, especially if there are known differences between participants.
 - iii. Keep track of the content.
 - iv. Define aims, objectives, and strategies.
 - v. Determine priorities for policy development.
 - b. Consultative process for developing a particular policy
 - i. Obtain other perspectives and viewpoints, which will include identifying organizational or external issues.
 - ii. Promote good relations between sites and service providers.
 - iii. Encourages participation and feeling of ownership in the process
 - iv. Provides new ideas and expertise
 - v. Alternative viewpoint identifies inconsistency, ambiguity, and/or duplication.
 - c. Policy review process
 - i. Formal process may or may not be required within the institution (i.e., standing Policy and Procedures Committee, which develops and reviews the policy and provides recommendations and decisions).
 - ii. Involvement and approval from the P&T and Critical Care committees or other oversight committees
 - d. General steps in drafting
 - i. Write a first draft.
 - ii. Distribute the draft, and consult across the same organization/stakeholders/experts for comments.
 - iii. Review feedback, both written and verbal, and amend/revise the draft.
 - iv. Redistribute the draft for final feedback.
 - v. Write the final draft.
 - vi. Document the date that the policy was ratified, and then review the date.
 - vii. Incorporate the new policy into the policy and procedures.
 - viii. Communicate the new policy to all relevant people.
4. Review existing policies. Continuous QI is the newest area requiring documentation and training for pharmacists and staff. Many state boards of pharmacy are requiring reportable events to be identified and documented. Policies and procedures can also be developed for analyzing the data collected to assess causes and contributing factors so that findings can be used to improve outcomes.
 - a. Every policy should regularly be reviewed for relevance and appropriateness (e.g., every 1–3 years), depending on organizational structure/standards.
 - b. Monitor and evaluate compliance with, and effect on, policies and guidelines.
 - c. Planning and evaluating
 - i. Evaluation policy and plan
 - ii. Evaluation strategies
 - iii. Ongoing monitoring
 - iv. Presentation of data

- v. Consumer feedback
- vi. Stakeholder feedback
- vii. Planning day agenda
- viii. Forms: Data collection sheets, data reporting format
- ix. Client/consumer questionnaires, community group questionnaires
- d. Evidence-based critical care literature and clinical practice guidelines in designing a patient-specific plan of care
 - i. Definition: “The conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research.”
 - ii. Pros and cons of evidence-based medicine (EBM)
 - (a) Advantages
 - (1) Critical appraisal skills of the literature improve with the review of EBM.
 - (2) Questions asked; be more skeptical of the answers
 - (3) Wasteful practices can be abandoned.
 - (4) Presupposes that we keep up-to-date; ideally, a systematic process of incorporating new EBM is included
 - (5) Makes the decision-making process transparent to colleagues and patients
 - (6) Leads to greater appreciation of the evidence for our practice as well as the inherent uncertainties
 - (b) Disadvantages
 - (1) Time-consuming
 - (2) Sometimes impossible (when there is no published literature on a question)
 - (3) Useful papers may be disregarded because of minor blemishes (“rescue bias”).
 - (4) No science to tell us how robust the evidence must be for it to be incorporated into clinical practice
 - (5) External validity is subjective, and evidence can be misapplied.
 - (6) Easy-to-prove techniques more favored in literature
 - (7) It is never “up-to-date.”
 - (8) Tends to emphasize the priority of randomized controlled trials (which have inherent flaws) to the exclusion of other study designs (which may be appropriate in certain settings)
 - (9) May underemphasize patient values and interests
 - (10) Publications with favorable results are more likely to be published than are those without favorable results (publication bias).
- e. Barriers to implementing evidence
 - i. Practice environment (organizational context)
 - (a) Financial disincentives – Lack of reimbursement
 - (b) Organizational constraints – Lack of time
 - (c) Perception of liability – Risk of formal complaint
 - (d) The patient’s expectations – Expressed wishes related to care
 - ii. Prevailing opinion (social context)
 - (a) Standards of practice – Usual routine
 - (b) Opinion leaders – Key individuals not in agreement with evidence
 - (c) Medical training – Obsolete knowledge
 - (d) Advocacy – By pharmaceutical companies

- iii. Knowledge and attitudes (professional context)
 - (a) Clinical uncertainty – Necessary test for vague symptoms
 - (b) Sense of competence – Self-confidence in skills
 - (c) Compulsion to act – Need to do something
 - (d) Information overload – Inability to appraise evidence

D. Checklist to Follow When Developing Protocols, Policies, and/or Procedures

1. Scope and purpose
 - a. Overall objectives are specifically described.
 - b. Health questions covered by the guideline are specifically described.
 - c. The patient population to which the guideline applies is specifically described.
2. Stakeholder involvement
 - a. Guideline development group includes individuals relevant to the guideline.
 - b. Target population's views and preferences have been identified.
 - c. Target users of the guideline are defined.
3. Development of guideline
 - a. Literature search is systematic.
 - b. Criteria for selecting evidence are clearly defined.
 - c. Strengths and limitations of evidence are described.
 - d. Health benefits, adverse effects, and risks are considered when developing recommendations.
 - e. Link between recommendations and supporting evidence is provided.
 - f. Guideline is externally reviewed by experts.
 - g. Defined times for guideline updates are provided.
4. Clarity of recommendations
 - a. Recommendations are clear and unambiguous.
 - b. Different options are clearly presented.
5. Applicability
 - a. Guideline describes facilitators and barriers to the application.
 - b. Guideline provides tools on how it should be applied to practice.
 - c. Guideline presents monitoring and/or auditing criteria.

Patient Case

1. As the critical care pharmacist, you have been asked to develop a clinical pathway for reversal agents used in the setting of bleeding associated with anticoagulation therapy. Which is the best example of a component that should be involved in establishing the clinical pathway?
 - A. Evaluate the closed-loop technology to support a clinical pathway, and establish a physician champion.
 - B. Use EBM supporting the clinical pathway and agreement among practitioners.
 - C. Develop a clinical protocol, and obtain agreement among practitioners.
 - D. Evaluate formulary proposals and the EBM supporting the clinical practice.

II. GAP ANALYSIS

- A. A gap analysis is an assessment of a practice model that may be within your health system or pharmacy and that is compared with a best practice model (actual vs. potential performance). A gap analysis may focus on pharmacy services, pharmacy technology, or a specific medication or medication process.
- B. Goals of a Gap Analysis – To provide the project team with an understanding of the differences between current and best practices. An assessment must be made of the barriers that exist before best practice can be implemented successfully.
 - 1. Review systems.
 - 2. Develop requirements.
 - 3. Comparisons
 - 4. Implications
 - 5. Recommendations
- C. Gap Analysis – Can also be used to analyze gaps in processes and between the existing outcome and the desired outcome. This step process can be summarized as follows.
 - 1. Identify the existing process or gap analysis questions.
 - 2. Identify the existing outcome.
 - 3. Identify the desired outcome.
 - 4. Identify the process for achieving the desired outcome.
 - 5. Assess the response to the level of compliance or implementation (e.g., fully, partly, in progress, no activity, or noncompliant).
 - 6. Develop an action plan to fill the gap.
 - 7. Develop and prioritize the requirements, and develop a timeline for completion to bridge the gap.
- D. Best Practice Evaluation
 - 1. Review of the primary literature
 - 2. Survey practitioners – Feedback from practitioners (e.g., ICU pharmacists, nurses, physicians)
 - 3. Benchmarking
 - 4. Survey strategies
 - a. Have a single well-defined objective.
 - b. Keep the survey short.
 - c. Design the survey for easily measurable results.
 - d. Ask one thing per question.
 - e. Avoid biasing the response.
 - f. Limit the number of required questions.
 - g. Question order matters – The first question or two should be easy and interesting.
 - h. Create a logical flow to the questions.
 - i. Test the survey.
 - j. Spell out the time expectations in your invitation and on the greeting page.
 - k. Survey the appropriate people.
 - l. Share the results and actions with the respondents.
- E. A gap analysis for medication safety should include strategies for prevention and mitigation, assessment and detection, therapeutic use, critical thinking and knowledge, and education. A gap analysis should also include policies, procedures, protocols, guidelines, competencies, staffing models, educational methods, and other key components to maximize efficacy and prevent medication errors and harm.

F. Examples of a Gap Analysis Include:

1. Centers for Disease Control and Prevention (CDC) Antimicrobial Management Program (Appendix 1)
2. Opioid ADE prevention
3. Anticoagulation agent ADE prevention
4. Aminoglycoside ADE prevention
5. Intravenous-to-oral conversion of antihypertensives
6. Medication labeling
7. Medication barcoding and scanning
8. Narcotic diversion prevention
9. Sterile admixture services
10. Extemporaneous compounding services
11. Pharmacist activities during a code or rapid response
12. Pharmacy staffing models – Not enough ICU pharmacists to see all ICU patients, based on workload, documentation requirements
13. American Society of Health-System Pharmacists (ASHP) Practice Advancement Initiative (PAI) adherence such that all patients have the right to a pharmacist's care
14. Delirium assessment – Practice needs
15. Wake-up assessment
16. Antibiotic streamlining
17. Criteria-based antimicrobials and non-antimicrobials for high-cost/misused drugs
18. Departmental professional development education

Patient Case

2. As a critical care pharmacist, you are involved in a QI program. Which best describes the area not known to be affected by critical care pharmacists?
 - A. Length of stay (LOS).
 - B. Identification of opportunities to increase waste within a system.
 - C. Antimicrobial use.
 - D. Mortality.

III. QUALITY ASSURANCE, QUALITY/PERFORMANCE IMPROVEMENT**A. Overview**

1. QI consists of systematic and continuous actions that lead to measurable improvement in health care services and the health status of targeted patient groups.
2. An organization's quality is based on the current system (e.g., how things are currently done).
3. Health care performance is defined by an organization's efficiency, outcome of care, and level of patient satisfaction. Using benchmarks may help with measurements/goals/outcomes.
4. To achieve a different level of performance (i.e., results) and improve quality, an organization's current system needs to change.

5. Key components of a successful QI program:
 - a. QI works as systems and processes.
 - b. Focuses on patients
 - c. Focuses on being part of the team
 - d. Focuses on use of the data
 6. Improvement strategies
 - a. Understand the delivery system and key processes.
 - b. Recognize that resources (inputs) and activities carried out (processes) are addressed together to ensure or improve the quality of care (outputs/outcomes).
 7. Quality management departments within a health care institution often share data with the risk assessment department.
 8. QI programs within an institution
 - a. Executive steering committee
 - b. Many departments
 - c. Pharmacy department
 - d. Quality department
 - e. Medical ethics committee
 - f. P&T committee
 - g. Data reporting
 9. Analyzing the quality assurance (QA)/QI program
 - a. A normal level (upper and lower control limit) should be established for a process to operate.
 - b. The process is evaluated, and the results are compared with the normal level expected. Control charts can show the variance of the output of a process over time. The process is considered *in control*, and the variance between measurements is considered the normal random variation inherent in the process. If the variance falls outside the limits or has a run of non-natural points, the process is considered *out of control*.
 - c. Example: Established process for daily wake-up assessments for mechanically ventilated patients. The preestablished expected level of daily wake-up assessments was established when the protocol was initiated. The QA data collected evaluate the frequency by which daily wake-up assessments are being performed over a time interval.
- B. Critical Care Pharmacist's Role in QI – Metrics for evaluating the quality of critical care pharmacy services
1. ICU LOS
 2. Hospital LOS
 3. Impact on mortality
 4. Impact on disease identification
 5. Evaluation of infectious diseases within the ICU
 6. Cost-effectiveness
 7. Duration of mechanical ventilation
 8. Medication management procedures need to be continuously monitored and improved because of their complexity.
 9. Medication safety
 10. Direct costs (medication costs, technological upgrades, and software)
 11. Indirect costs (salaries, power for building)
 12. Data collection, analysis
 13. Identify opportunities to reduce waste within a system – Could result in reduced patient care and medication costs

C. National Quality Initiatives

1. The Institute of Medicine – Chartered in 1970. Published reports titled “The Urgent Need to Improve Health Care Quality,” “Crossing the Quality Chasm,” “To Err Is Human”
2. The Institute for Healthcare Improvement – Founded in 1991
 - a. 100,000 Lives Campaign, 5 Million Lives Campaign
 - b. No needless list
 - i. No needless deaths
 - ii. No needless pain or suffering
 - iii. No helplessness in those served or serving
 - iv. No unwanted waiting
 - v. No waste
 - vi. No one left out
 - c. Initiatives promoted are focused in the ICU.
 - i. Acute myocardial infarction
 - ii. Catheter-associated urinary tract infections
 - iii. Central line–associated bloodstream infections
 - iv. Health care–associated infections
 - v. Severe sepsis bundles
 - vi. Medication reconciliation to prevent ADEs
 - vii. Sedation, delirium, and mobility
 - viii. Surgical site infections
 - ix. Ventilator-associated pneumonia
 - x. Rapid response teams
 - xi. High-alert medication safety
 - xii. Pressure ulcer care
3. National Quality Forum – Created in 1999
 - a. More than 300 measures, indicators, events, practices, and other products to help assess quality. Has been endorsed to become the gold standard of measuring health care quality
 - b. Associated measures notable for ICU care
 - i. ADEs
 - ii. Catheter-associated urinary tract infections
 - iii. Central line–associated bloodstream infections
 - iv. Surgical site infections
 - v. Ventilator-associated pneumonia
 - vi. Stroke
 - vii. Acute myocardial infarction
4. The Leapfrog Groups – Launched in 2000
 - a. Hospital quality and safety survey – Voluntary survey of hospitals rating themselves on quality and safety practices
 - b. Reported at www.leapfroggroup.org
 - c. ICU related
 - i. Catheter-associated urinary tract infections
 - ii. Catheter-associated bloodstream infections
5. The Joint Commission (TJC) – Founded in 1951
 - a. An independent, not-for-profit organization that sets the standards for accreditation in health care
 - b. Tracer methodology – Method of evaluation done during an on-site survey that traces the health care experiences of a patient while in the hospital
 - c. Identifies, tests, and specifies standardized performance measures

- d. 2015 National Patient Safety Goals
 - i. Preventing infection
 - ii. Uses the hand-cleaning guidelines from the CDC or the World Health Organization. Set goals for improving hand cleaning. Use the goals to improve hand cleaning.
 - iii. Uses proven guidelines to prevent infections that are difficult to treat
 - iv. Uses proven guidelines to prevent infection of the blood from central lines
 - v. Uses proven guidelines to prevent infection after surgery
 - vi. Uses proven guidelines to prevent urinary tract infections caused by catheters
 - vii. Core performance measure sets for hospitals
 - (a) Acute myocardial infarction – Electronic clinical quality measures
 - (b) Stroke
 - (c) Surgical Care Improvement Project – Electronic clinical quality measures
 - (d) VTE
 - (e) Pneumonia – Retired January 1, 2015, TJC no longer required data collection
- e. ICU measure – Not in production
 - i. Set of performance measures applicable to the ICU setting – Solicitation from key stakeholders in 2002
 - ii. Six measures contained in the Specifications Manual for National Hospital Inpatient Quality Measures – ICU underwent two phases of rigorous testing, and the results were reviewed by the technical advisory panel.
 - iii. November 2004 – Four measures were recommended for potential national implementation; two measures were to be implemented as test measures not to be publicly reported or included in TJC accreditation process until additional information on training needs and reliability could be obtained and the impact on the reliability of the predicted outcomes ascertained.
 - iv. July 1, 2005 – Measure set implementation halted – TJC suspended implementation of data collection for the ICU measure set. The suspension was implemented to allow TJC to align its ORYX performance measure requirements with respect to the ICU measures, with the decision of the Hospital Quality Alliance priority of next adding measures related to surgical care to the nationally reported measure set portrayed on the CMS Hospital Compare website.
- 6. AHRQ (Agency for Healthcare Research and Quality) – The health services research arm of the U.S. Department of Health and Human Services. Sponsors the National Quality Measures Clearinghouse – A “public repository for evidence-based quality measures and measure sets”
- 7. Hospital Quality Alliance – Created in 2002
 - a. 2004 – Hospitals could voluntarily report data on 10 “starter-set” quality performance measures and receive incentive payment.
 - b. 2005 – Quality-of-care data expanded to 21 measures
 - c. 2006 – Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS)
 - d. Reporting initiatives sharpens the focus on QI.
- 8. CMS
 - a. Mission – To “ensure effective up-to-date health care coverage and to promote quality care for beneficiaries”
 - b. Quality initiative (established in 2001) empowers consumers with quality-of-care information and encourages providers to improve the quality of care.
 - c. Hospital quality initiative (established in 2003) – Hospitals must submit data measures or accept a reduction in payment.
 - i. Pay-for-performance measures associated with quality measures
 - ii. Acute myocardial infarction – (30-day risk-standardized mortality and readmission) pertinent to pharmacy for angiotensin-converting enzyme inhibitor (ACEI), β -blocker, aspirin, statin

- iii. Heart failure – (30-day risk-standardized mortality and readmission) pertinent to pharmacy for ACEI, β -blocker
 - iv. Pneumonia – (30-day risk-standardized mortality and readmission) pertinent to pharmacy for antibiotic timing
 - v. Hip and knee replacements (30-day risk-standardized readmission)
 - vi. Sepsis – Pertinent to pharmacy for appropriate time to administer antibiotics and resuscitation fluids
9. Institute for Safe Medication Practices (ISMP)
- a. Nonprofit organization responsible for targeting medication error prevention and safe medication use; a certified patient safety organization
 - b. Established in 1975
 - c. Based on a nonpunitive approach and system-based solutions
 - d. Five key areas of focus: Knowledge, analysis, education, cooperative, and communication
 - e. Medication Errors Reporting Program – Practitioner self-reporting program
- D. The goal of the ASHP PAI, formerly known as the Pharmacy Practice Model Initiative, is to significantly advance the health of patients by supporting futuristic practice models that support the most effective use of pharmacists as direct patient care providers. The initiative aims to assist leaders and practitioners in creating a framework, determining services, identifying emerging technology, developing templates, and implementing change. The ASHP Pharmacy Practice Model Initiative started in 2010.

Select goals

1. Goal 1 – Pharmacist roles, practices, and activities will improve medication use and optimize medication-related outcomes.
 - a. 1.1. Percentage of hospitals/health systems that have pharmacist-review of all medication orders before the first dose is administered (either on-site or by telepharmacy except for procedure areas and emergencies)
 - b. 1.2. Percentage of hospitals/health systems that require that pharmacists to document their recommendations* and follow-up notes in the patient's permanent medical records. *Level and type of recommendation as determined by hospital protocol
 - c. 1.3 Percentage of hospitals/health systems where pharmacists have privileges to write medication orders (modify or initiate therapy) in the health care setting
 - d. 1.4. Percentage of hospitals/health systems where pharmacists have the authority to order serum medication concentrations and other clinically important laboratory tests
 - e. 1.5. Percentage of hospitals/health systems that have pharmacists routinely assigned to patient care units/specialty services to provide drug therapy management at least 8 hours a day, 5 days a week for most patients
 - f. 1.7. Percentage of hospitals/health systems where pharmacists provide drug therapy management to all inpatients who exceed the threshold value on the patient medication complexity index
2. Goal 4 – Pharmacy departments use available automation and technology to improve patient safety and improve efficiency.
 - a. 4.1. Percentage of hospitals/health systems using a CPOE system with clinical decision support for inpatient medication orders (e.g., rules that integrate order information, patient information, and clinical practice guidelines into computer system logic systems that provide feedback to prescribers)
 - b. 4.3. Percentage of hospitals/health systems that use automated dispensing technologies (e.g., automated dispensing cabinets, robotics)

- c. 4.4. Percentage of hospitals/health systems that have smart infusion pumps that are integrated into a closed-loop medication use process (i.e., where CPOE/pharmacy information system is integrated with pumps, and administration is documented on an eMAR [electronic medication administration record])
 - d. 4.5. Percentage of hospitals/health systems that use machine-readable coding (e.g., barcode medication administration system) to verify the patient's identity and the accuracy of medication administration at the point of care
 - 3. Goal 5 – Pharmacists will demonstrate leadership in exercising their responsibilities for medication use systems and will be accountable for medication-related patient outcomes.
 - a. 5.1. Percentage of hospitals/health systems whose pharmacists with drug therapy management responsibilities are held accountable through formal evaluation for the clinical outcomes of patients under their care
 - b. 5.3. Percentage of hospitals/health systems that regularly* conduct strategic planning to determine their optimal scope and level of pharmacy services, use of automation and technology, assignment of technicians, and readiness of staff to serve their patient population (*Strategic planning has been conducted in the past 24 months)
 - c. 5.4. Percentage of hospitals/health systems that have used the Pharmacy Practice Model Initiative Hospital Self-Assessment Tool at least annually (self-assessment survey of 106 questions)
 - d. 5.5. Percentage of hospitals/health systems that conduct proactive and ongoing assessments and mitigate the risk of medication use systems (e.g., ISMP Medication Safety Self-Assessment)
 - e. 5.6. Percentage of hospitals/health systems that routinely provide training to pharmacy students and/or residents
- E. Local Quality Initiatives (from ASHP: The ASHP Discussion Guide on the Pharmacist's Role in Quality Improvement)
 - 1. Every accredited hospital must participate in QI initiatives.
 - 2. The overall goals of the PI programs are to maintain and support the delivery of safe, quality care.
 - 3. Each program should include the following:
 - a. Adherence to standards of care
 - b. Opportunities for improvement, with action plans to implement change strategies
 - c. Strategies for the effectiveness of change strategies
 - d. Involvement of multidisciplinary teams in process improvement
 - 4. PI plans should:
 - a. Articulate the commitment to PIs
 - b. Delineate the goals of the PI process
 - c. Specify the authority and responsibilities for PI
 - d. Describe the organizational structure and process related to the PI program
 - e. Describe the method for improving organizational performance
 - f. Describe the communication and recognition of PI activities
- F. QI Tools
 - 1. Apply the LEAN health care production process (https://www.ashp.org/DocLibrary/Policy/QII/ApplyingLEAN_Flyer.pdf).
 - a. Define the problem.
 - b. Map current processes.
 - c. Identify operation barriers.
 - d. Develop future state process.
 - e. Process control strategy

2. Plan-do-check-act cycle: Means of identifying ideas for change
 - a. What are we trying to accomplish? – An aim or project goal must be developed.
 - i. Needs to describe the process to be improved
 - ii. Set a target for improvement that extends beyond current performance.
 - iii. Secure necessary resources in the process.
 - b. How will we know that a change is an improvement?
 - i. Establish baseline measurement – Select and gather data.
 - ii. Baseline data compared with the target and key causes and sources of variation
 - c. What changes can we make that will result in improvement?
 - i. Broad, general ideas and thoughts about change (“change concepts”)
 - ii. Change is tested.
 - d. Plan-do-check-act cycle
 - i. Plan
 - (a) Questions are asked and predictions are made.
 - (b) Details are described.
 - (c) Who will make the test?
 - (d) What exactly will they do?
 - (e) When will they do it?
 - (f) Where will they do it?
 - (g) How long will they do it?
 - ii. Do
 - (a) Change is made following the “plan.”
 - (b) Data collect the single change.
 - (c) Unexpected problems and observations are documented.
 - iii. Check
 - (a) Study the effect of the test change on the single measure.
 - (b) Compare data with predictions.
 - (c) Summarize what was learned.
 - iv. Act
 - (a) Select which change(s) to implement.
 - (b) Develop an implementation plan.
 - (c) Determine additional improvements.
 - (d) Determine which actions will hold the gains.
3. Example of a specific aim: Time to appropriate antibiotic therapy in patients seen in the emergency department with presumed sepsis

G. Tools Used to Summarize Data

1. Benchmarking – Compares your performance with that of another health care system
2. Describe a process.
3. Identify problem areas.
4. Suggest solutions.
5. Assess the effects of change.
6. Identify customers and their needs.
7. Show process or output variation.
8. Consensus decision-making tools (multiple voting, rank ordering, structured discussion)
9. Ground rules
10. Idea-generating tools (brainstorming, affinity diagramming, storyboards, role-playing, etc.)
11. Opportunity statements

12. Patient concerns or comments: Reports from third-party payers and regulatory agencies
13. Incident reporting
14. Root-cause analysis reports
15. Accident reports
16. Patient care conferences
17. Patient care evaluation studies
18. Patient satisfaction survey results

H. Analysis

1. Affinity diagrams
2. Cause-and-effect diagrams
3. Decision matrixes
4. Root-cause analysis
5. Error or failure models
6. Effects analysis
7. Flowcharts
8. Force-field analysis
9. Histograms, scatterplots
10. Relationship diagrams

I. Publishing QI Results

1. Important to publish QI data to promote improvement efforts in health care
2. Reduces the chances of the same mistakes being repeated
3. Shares your work by spreading important and useful information
4. Standards for Quality Improvement Reporting Excellence (SQUIRE) – Provides a framework for reporting new knowledge about how to improve health care. Available at www.squire-statement.org/

Patient Case

3. As part of the CMS QI initiatives, patients in your ICU are reviewed monthly for infection rates. You identify an increase in infection rates regarding your ICU patients for infections and find that an increased number of catheter-related bloodstream infections are occurring in your ICU. You decide to evaluate the current practice and use LEAN to determine where the practice issue is. Which is the best example of a component of LEAN?
 - A. Define the problem.
 - B. Evaluate current opinions on how to fix the process.
 - C. Identify transportation barriers.
 - D. Describe the past process.

IV. MEDICATION USE EVALUATION

- A. TJC requires drug use evaluations (DUEs) to be completed to monitor the safety of medications.
- B. *MUEs* and *DUEs* are often used synonymously. Both DUEs and MUEs are PI and QA methods that ensure optimal medication therapy management and improve patient safety and outcomes.
- C. A DUE is drug- or disease-specific, whereas an MUE provides a broader scope that focuses on a drug or class of drugs, the process or processes, and the outcome, with a specific emphasis on improving patient outcomes. MUEs focus on several elements of the medication process/use such as prescribing, pharmacist medication order validating or verifying, dispensing, preparing, administering, monitoring, patient education, and outcomes.
- D. The sample size of the MUE depends on the type of medication data being analyzed—usually, a sample of 20–30 patients is sufficient; however, more patients may need to be surveyed to analyze patient outcomes—usually, a sample of 100 or more.
- E. Data collection for specific criteria can use a yes/no format with a section for comments, or open-ended questions can be used. Using CPOE and electronic medical records, the processes of data retrieval, monitoring, and generating specialized reports have become easier.
- F. The type and number of MUEs should be determined by the risk mitigated when using a medication. Medications selected for an MUE may be based on the following:
 - 1. High risk
 - 2. High volume
 - 3. ADEs
 - 4. Preventable ADEs
 - 5. Near-miss and harmful medication errors
 - 6. Nonformulary requests
 - 7. Pharmacy intervention data
 - 8. Treatment failures
 - 9. Physician or nurse identification or request
 - 10. Patient concerns
 - 11. Off-label use
 - 12. High cost
- G. Examples of medications and medication use processes in critically ill patients that may be selected for an MUE can be found in Box 1 and Box 2.

Box 1. List of Medications Used in Critically Ill Patients and Suited for an MUE

1. Vecuronium and rocuronium	20. Midazolam
2. Warfarin	21. Hydromorphone
3. Clopidogrel	22. Naloxone
4. Argatroban	23. Fidaxomicin
5. Enoxaparin	24. Daptomycin
6. Heparin	25. Linezolid
7. Tranexamic acid	26. Polymyxin and colistin
8. Desmopressin	27. Acyclovir
9. Insulin	28. Phenytoin and fosphenytoin
10. Vasopressors	29. IV valproic acid
11. Tirofiban	30. Darbepoetin alfa
12. IV metoprolol	31. Cosyntropin
13. IV nicardipine	32. Neostigmine
14. IV verapamil	33. IV pantoprazole or esomeprazole
15. Alteplase and tenecteplase	34. Octreotide
16. Digoxin immune fab	35. IV acetaminophen
17. Propofol	36. IV ibuprofen
18. Ketamine	37. IV ketorolac
19. Dexmedetomidine	38. Conivaptan

IV = intravenous(ly); MUE = medication use evaluation.

Box 2. Examples of High-Risk Medication-Related Processes Suited for an MUE in Critically Ill Patients

Insulin infusions
 Hypoglycemic protocols
 Sedation protocols
 Management of hypoprothrombinemia
 Management of DTI overdose
 Use of pneumatic compression devices for DVT prophylaxis
 Stress ulcer prophylaxis
 Vancomycin dosing and ordering serum concentrations
 Aminoglycoside dosing and ordering serum concentrations
 Intermittent infusions of antimicrobials (e.g., carbapenems, piperacillin/tazobactam)
 Use of β -blockers in myocardial infarction
 Antihypertensive IV-to-PO switch therapy
 Antihypertensive use in acute stroke
 Antimicrobial IV-to-PO switch therapy
 Fluid resuscitation
 Management of GI bleeding
 Use of total parenteral nutrition
 Use of albumin
 Vaccine administration
 Management of *Clostridium difficile* diarrhea
 Monitoring for dysrhythmias with QTc-prolonging drugs
 Use of IV sodium bicarbonate
 IV push medication guidelines (rate of administration and medication preparation—diluted or undiluted)

Box 2. Examples of High-Risk Medication-Related Processes Suited for an MUE in Critically Ill Patients (*continued*)

Hyperkalemia management guidelines
Hypomagnesemia management guidelines
Surgical prophylaxis guidelines
Alcohol withdrawal management
Management of status epilepticus
Management of hyponatremia

DTI = direct thrombin inhibitor; DVT = deep venous thrombosis; GI = gastrointestinal; PO = oral(ly); QTc = corrected QT (interval).

- H. Use of an MUE should preferentially be proactive and should be used to determine whether there are any gaps in practice or patient safety.
 - 1. An *interventional MUE* is completed concurrently or prospectively, and if the criteria are not met, an intervention by the pharmacist can and should be made to improve the use of the medication and patient outcomes.
 - 2. A *noninterventional MUE* is completed concurrently or retrospectively by a medical record review, and data are collected, but when the criteria are not met, an intervention is not made, or an intervention cannot be made because the review is retrospective, there is no pharmacist-to-prescriber interaction during the review process.
- I. MUEs should have specific criteria set – These criteria are best determined by a multidisciplinary team of medication or disease experts.
- J. MUE criteria may be approved by the P&T committee. The P&T committee may create an MUE subcommittee. Other hospital committees such as the QI committee may also request that an MUE be performed. Other names for the MUE committees may include formulary, drug safety, therapeutic assessment, medication safety, and drug use review committees.
- K. The MUE subcommittee should be multidisciplinary and may be composed of the following:
 - 1. Clinical pharmacists
 - 2. Physicians
 - 3. Nurses
 - 4. Administrators
 - 5. PI/QA representatives
 - 6. Risk management representatives
- L. Given the pharmacist's expertise in medication management, pharmacists often chair or co-chair the MUE subcommittee and perform the MUE.
- M. The MUE subcommittee can recommend drugs and drug processes that require an MUE to the P&T committee; alternatively, the P&T committee can request MUEs from the MUE subcommittee.
- N. The MUE process includes reviewing the findings and developing plans of improvement. The results and conclusions of the MUE should be reported to the P&T committee and department chairs.
- O. After plans of correction are determined and actions taken, a follow-up MUE should be completed to document that improvement has occurred successfully.

- P. Periodic MUEs in the same area should be performed every 3–6 months for 1 year to ensure that the corrections made remain effective and that they are sustained. If any new changes have occurred in the medication use process, the MUE criteria should be reassessed and the new criteria incorporated.
- Q. To correct the findings from the MUE, policy development and educational initiatives should take place, such as:
 - 1. In-service lectures
 - 2. Newsletter publications
 - 3. Drug alerts
 - 4. Guideline development
 - 5. Protocols
 - 6. Policy and procedures
 - 7. CPOE pathways, prescribing guides, or information or pop-up warnings

Patient Case

- 4. Which medication use process is best suited for an MUE?
 - A. Review of pharmacist notes in the patient medical record (PMR).
 - B. Review of accuracy of expiration dates placed on intravenous admixture products.
 - C. Review of vancomycin dosing and ordering of vancomycin blood concentrations.
 - D. Review of frequency of drug interaction warnings on the CPOE system.

V. EDUCATION

- A. Educate health care professionals and other stakeholders concerning issues related to the care of critically ill patients.
 - 1. Provides informal instruction to pharmacists and other ICU health care professionals
 - 2. Participates in the training of pharmacy students, residents, and fellows through experiential critical care rotations
 - 3. Provides didactic lectures to health care professionals, students, residents, and fellows in critical care pharmacology and therapeutics
 - 4. Implements pharmacist and pharmacy technician training programs for ICU personnel
 - 5. Provides accredited continuing education sessions
 - 6. Educates lay group community medical personal about the role of the ICU pharmacist
 - 7. Coordinates or directs internships; experiential training; traineeships, residency, or fellowship programs
 - 8. Teaches advanced cardiac life support
- B. Communication Strategies
 - 1. 7% of the things you say are the words themselves, 38% are tone of voice and inflection, and 55% are body language.
 - 2. Evaluate the audience.
 - a. Patient/general public
 - b. Health care providers

- c. Legislators
 - d. The media
- 3. Communication:
 - a. Credibility – Is your messenger credible? Is the messenger a trusted and respected source of information with your audience?
 - b. Context – Is your message in context with reality and the environment in which your audience is located?
 - c. Content – Is your message relevant to your audience? Is the audience interested in the information?
 - d. Clarity – Is your message straightforward? How far will it travel and how long will it last? Do not use abbreviations.
 - e. Continuity and consistency – Repeat your message for audience penetration.
 - f. Channels – What channels/tools of communication are you using? What value are they bringing to your audience?
 - g. Customer benefits – What is in it for me?
 - h. Caring, compassion, and concern – Does your audience know that you care?
 - i. Capability of audience – Is your audience capable of understanding the message? Will the audience take the time to read, watch, or listen to it?
 - j. Call to action – What is your audience supposed to do now?
- 4. Sharing the message/tools to communicate
 - a. Pharmacy departmental newsletter
 - b. Hospital newsletter
 - c. Electronic screensavers providing information
 - d. Best practice advisory methods
 - e. Local/regional communication newsletter/e-mail list
 - f. Electronic message

VI. DOCUMENTATION PROCESSES USED FOR CRITICAL CARE PHARMACY SERVICES

- A. The evidence of economic benefit and improvement in patient safety for clinical pharmacy services (CPS) and critical care pharmacy services is well established. The Society of Critical Care Medicine supports an ICU pharmacist as an essential component of an ICU team.
- B. Clinical pharmacy interventions that affect patient care should be documented in the electronic medical record. Pharmacist involvement directly affects decreased drug-related costs, prevents adverse effects, improves quality and efficacy of care, reduces mortality, shortens LOS, and lowers overall patient care costs.
- C. Clinical Pharmacy Interventions of the Critical Care Pharmacist include:
 - 1. Reduced ADEs in the critically ill population
 - 2. Reduced order-prescribing errors
 - 3. Optimization of the correct drug for the correct disease process
 - 4. Promotes the safe and effective use of medication
 - 5. Decreases medication use
 - 6. Decreases LOS
 - 7. Reduces medication costs
 - 8. Reduces medication administration errors

9. Reduces the inappropriate use of antibiotics
 10. Protocol development
- D. Documenting CPS is also important to tabulate CPS and workload and to provide justification for maintaining and expanding services.
- E. A business plan should be developed when proposing an expansion in clinical services and should include:
1. Executive summary
 2. Background and description
 3. Market and competitor analysis
 4. Operational structure and processes
 5. Financial projections
 6. Milestones, schedules, and action plan
 7. References
 8. Supportive documents
 9. Financial pro forma statements
 10. Letters of support
- F. In general, there are three types of pharmacist interventions: formal consultations solicited by physicians, informal consultations solicited by physicians and health care providers, and unsolicited interventions.
- G. Collaborative Drug Therapy Management (CDTM) – When a prescriber and a pharmacist establish written guidelines or protocols authorizing the pharmacist to initiate, modify, or continue drug therapy for a specific patient. CDTM is a type of pharmacotherapeutic intervention that should be documented and reported.
- H. Documenting the pharmacotherapeutic intervention in the PMR using the electronic medical record or using handwriting on paper in the medical chart provides for transparency between all health care professionals—physicians, nurses, pharmacists, dietitians, respiratory therapists, and social workers.
- I. Pharmacists can also document interventions in the pharmacy profile; however, this method generally allows for review only by pharmacy personnel who have access to the pharmacy computer system such as pharmacists, pharmacy interns, pharmacy students, and pharmacy technicians.
- J. Both methods should be available for documenting pharmacotherapeutic interventions, and criteria should be established to determine which method is most appropriate.
- K. Pharmacists should have the authority to document pharmacotherapeutic interventions in the PMR.
- L. The Department of Pharmacy should have a policy and procedure for documenting clinical pharmacy interventions.
- M. Pharmacists should be trained and educated to document in the PMR. The ASHP Clinical Skills Program is a tool that can be used to train pharmacists to document in the PMR.
- N. Documentation methods may include using standard format documentation methods such as:
1. SOAP (subjective, objective, assessment, plan)
 2. TITRS (title, introduction, text, recommendation, signature)
 3. FARM (findings, assessment, resolution, and monitoring)

- O. Unsolicited pharmacist interventions should be documented subtly, allowing the primary provider to decline the recommendation without incurring liability. Phrases that can be used include:
 - 1. “May consider”
 - 2. “Suggest”
 - 3. “May recommend”
 - 4. Alternatively, the wording for solicited consultations may be more direct.
- P. When feasible, written notes by pharmacists should be documented in the PMR after an oral communication with the clinician; this allows for any patient data discrepancies to be corrected and for agreement and confirmation between the prescriber and the pharmacist to execute the intervention.
- Q. Pharmacists should follow up on their patient interventions daily and provide follow-up notes that include patient progress or new interventions, when needed.
 - 1. The pharmacist should provide his or her contact information.
 - 2. Co-signatures should be required for pharmacy residents (until deemed competent according to Department of Pharmacy standards), pharmacy interns, and pharmacy students.
- R. Continuous QI should include quality indicators and periodic reviews of pharmacist-written documentation and consultations.
- S. CPS should be evaluated for cost impact and cost outcomes savings. Other elements to include on CPS include the following:
 - 1. Weighted metric for each variable to quantify measured activities
 - 2. Pharmacotherapy improvement
 - 3. Cost savings
 - 4. Antibiotic stewardship
 - 5. Provider education
 - 6. Quality/safety improvement (value-based purchasing, Surgical Care Improvement Project, HCAHPS)
 - 7. Emergency cardiac arrest, stroke, sepsis
 - 8. Chart review
 - 9. Rounding with health care providers
 - 10. Formal pharmacy consults
- T. Many web-based or handheld electronic systems are available that can be used to document and report pharmacotherapeutic interventions and cost savings, such as:
 - 1. Quantifi by Sentri7, Wolters Kluwer
 - 2. Clinical Measures by Gold Standard, Elsevier
- U. These reporting systems allow for collecting, aggregating, and benchmarking data against data from other hospitals and bed size. They increase the credibility of data collection methods and results when evaluated by health care administrators. (Appendix 2)
- V. To document raw drug cost savings from switching to less expensive medications, the following method may be applied: subtract the cost of the originally prescribed drug therapy (drug daily cost multiplied by the number of days prescribed) from the cost of the less expensive drug therapy (drug daily cost multiplied by the number of days prescribed). Using this method, the cost of intravenous diluents and admixture fluids and syringes used in the preparation process may be included.

- W. Documentation of interventions for reporting to other hospital committees such as the P&T committee should include the following elements:
 - 1. Date, time
 - 2. Type of intervention
 - 3. Drug used
 - 4. Prescriber name, service, and type (attending or resident)
 - 5. Duration of time spent completing the intervention
 - 6. Whether the intervention was accepted or denied or clarification was achieved

- X. Documentation of services should show diversity, effectiveness, cost, and outcomes of activities.
 - 1. Policy development
 - 2. Education
 - 3. Research
 - 4. Resource use
 - 5. Management
 - 6. Leadership
 - 7. Education
 - a. Pharmacy students
 - b. Pharmacy residents (PGY1, PGY2)
 - c. Pharmacy personnel

- Y. Outcomes of Documentation
 - 1. Establish additional clinical services.
 - 2. Expand roles of existing services.
 - 3. Assess new processes or practices (prescriber privileges or provider reimbursement).
 - 4. Provide data for QA or research initiatives.
 - 5. Accreditation purposes
 - 6. Promotional reasons
 - 7. Financial impact can be analyzed and used to justify time spent in that area.

- Z. Reports
 - 1. Statistical interpretations of services
 - 2. Satisfaction surveys of their services
 - 3. Risk reduction
 - 4. Peer review
 - 5. Publication
 - 6. Return on investment data
 - 7. Future initiatives

- AA. Pharmacotherapeutic intervention data should be presented and emphasized at as many committee opportunities as possible—this increases the visibility and corroborates the importance of the pharmacy department and the critical care pharmacy services. Box 3 lists the types of pharmacotherapeutic interventions that can be reported. Pharmacotherapeutic intervention data should be presented to the following:
 - 1. ICU committee
 - 2. P&T committee
 - 3. QA committee
 - 4. Use review committee
 - 5. Medical executive committee

BB. Pharmacotherapeutic intervention data may be presented quarterly (Figure 1). These data should include the type of intervention (Figure 2) and both the raw drug cost savings derived from switching to less expensive drugs and the outcome cost savings such as preventing an adverse event and decreasing the LOS (Figure 3).

Box 3. Types of Pharmacotherapeutic Interventions

1. Discontinue drug 2. Switch drug 3. Switch drug for less expensive but equally safe and effective drug 4. Drug dosing 5. Drug dosage form 6. Drug route 7. Pharmacokinetic consultation 8. Pharmacotherapy consultation 9. IV-to-PO switch therapy 10. Contraindication 11. Duplicate therapy 12. Nonformulary switch to formulary 13. Nonformulary approval 14. Drug unavailable 15. IV drug incompatibility 16. Drug-drug interaction 17. Drug-food interaction 18. Drug-laboratory test interaction 19. Pharmacogenomics interaction 20. Therapeutic interchange 21. Allergy prevention	22. Medication reconciliation 23. Discharge counseling 24. Written patient education provided 25. Patient adherence to medications 26. Adverse drug reaction 27. Overdosage 28. Subtherapeutic dose 29. Medication error 30. Monitoring for efficacy 31. Monitoring for toxicity 32. Ordering laboratory tests for monitoring drug efficacy and toxicity 33. Clarification of medication order 34. Untreated indication 35. Failure to receive medication 36. Immunization recommendation 37. Immunization administered 38. Health risk assessment 39. Rapid response interventions 40. Code interventions 41. CDTM interventions

CDTM = collaborative drug therapy management.

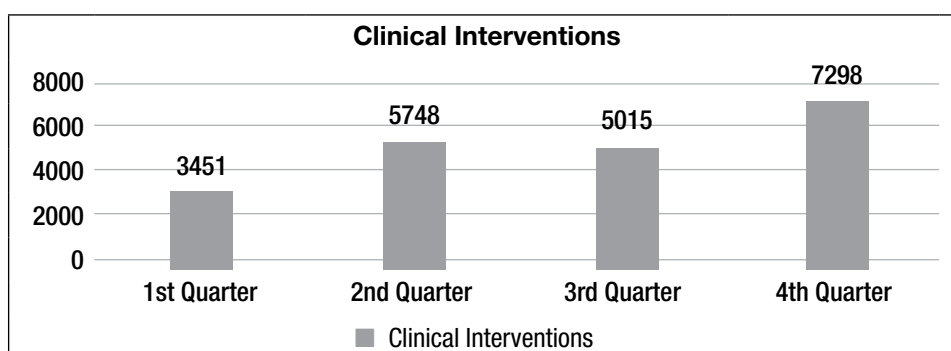


Figure 1. Clinical interventions.

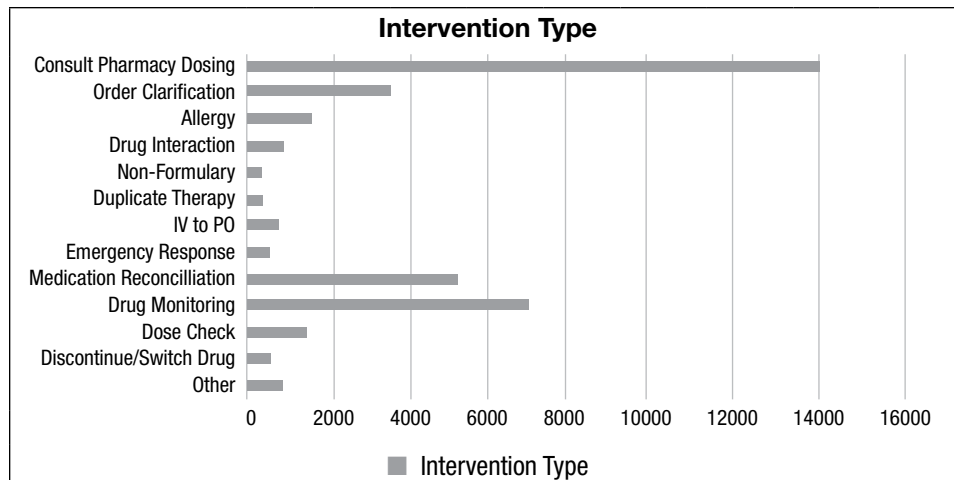


Figure 2. Pharmacotherapy intervention types.

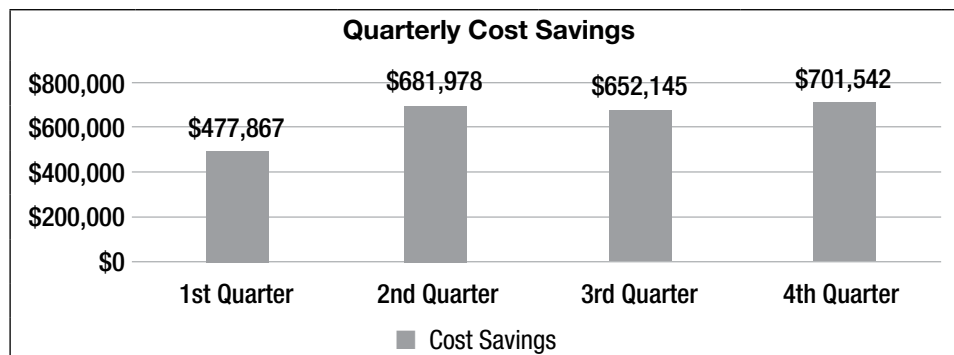


Figure 3. Raw and outcome drug cost savings, 2015.

CC. Benchmarking is important in annualizing the total number of pharmacotherapeutic interventions with previous years (Figure 4) and the cost savings with previous years (Figure 5) and in providing rational explanations for any discrepancies noted.

DD. Pharmacotherapeutic interventions that are reported may be prioritized according to their clinical impact on patient safety and cost savings. Examples of high-priority pharmacotherapeutic interventions that should be reported include the following:

1. Allergy prevented
2. Contraindication prevented
3. Drug dosing adjustments
4. Duplicate therapy avoided
5. Drug interactions avoided
6. Medication reconciliation intervention
7. Ordering laboratory tests for monitoring of drug safety and efficacy
8. Switching drug for less expensive but equally safe and effective drug

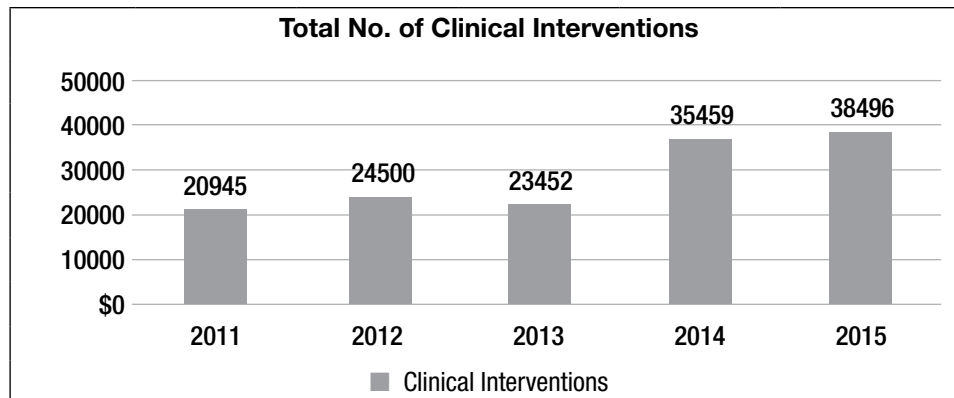


Figure 4. Annual pharmacotherapy interventions, 2011–2015.

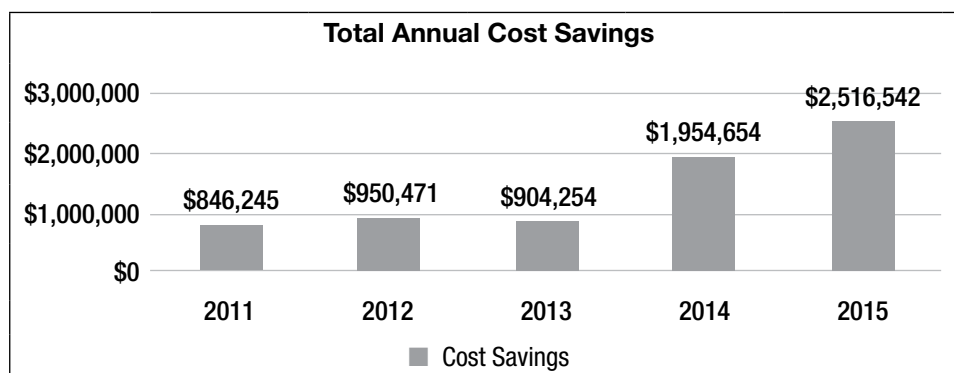


Figure 5. Annual raw drug and outcome cost savings, 2011–2015.

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Acknowledgment

I would like to sincerely thank Dr. Henry Cohen for his contribution to this chapter. His willingness to collaborate with me as we combined chapters for the 2016 ACCP SCCM Critical Care Preparatory Course is greatly appreciated. Portions of this chapter contain our combined work during this collaboration.

ANSWERS AND EXPLANATIONS TO PATIENT CASES**1. Answer: B**

Using evidence-based practice helps provide support in creating a clinical pathway with support and agreement among practitioners (Answer B is correct). Using closed-loop technology is important when implementing a clinical pathway, as is establishing a physician champion (Answer A). Developing a clinical protocol and pathway comes after the evidence is evaluated (Answer C). Formulary proposals are not a primary factor in implementing a clinical pathway (Answer D).

2. Answer: B

Current data show that the critical care pharmacist can reduce the amount of waste within a critical care system of care (Answer B). The LOS (Answer A), antimicrobial use (Answer C), and reduced mortality (Answer D), as well as many other areas, have been affected by the critical care pharmacist.

3. Answer: A

Defining the problem is the first step in LEAN (Answer A). Part of the strategy for LEAN involves initially trying to remove the team members' opinions so that their emotions do not influence the process (Answer B). Transportation barriers are not part of LEAN (Answer C). Past process is not a component in evaluating a process (Answer D).

4. Answer: C

An MUE is drug- or disease-specific and is best suited for reviewing vancomycin dosing and the ordering of vancomycin blood concentrations (Answer C is correct). Quality assurance surveys are best suited for monitoring the medication use process that may not be specific to a drug or disease, such as the review of a pharmacist's notes in the PMR, review of the accuracy of expiration dates placed on intravenous admixture products, and review of the frequency of drug interaction warnings on the CPOE system (Answers A, B, and D are incorrect).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS**1. Answer: D**

Financial justification for a critical care pharmacist has been shown by the impact of clinical pharmacists on critically ill patients. The critical care pharmacist can reduce adverse events in the critically ill population, reduce order prescribing errors, optimize the correct drug for the correct disease process, decrease the LOS, reduce medication administration errors, and reduce inappropriate antibiotic use. One of the main financial impacts on critically ill patients is antimicrobial therapy. Using an antimicrobial stewardship program will have the largest financial impact on the institution (Answer D is correct). Developing protocols is important in streamlining practice in the critically ill population and can reduce health care costs (Answer A). Making prescribing errors (Answer B) and medication administration errors (Answer C) can result in adverse events to the patient, but these would not most significantly affect finances.

2. Answer: B

Practice environment constraints include financial disincentives, organizational constraints, perception of liability, and patient expectations (Answer B is correct). Other barriers (non-practice environment) to implementing the delirium screen include standards of practice (Answer A), opinion of leaders, medical training (Answer C), and advocacy. The final barrier is knowledge and attitudes, including clinical uncertainty, sense of competence (Answer D), compulsion to act, and information overload.

3. Answer: A

Evaluating the use of pharmacotherapy in SUP in the ICU is best suited for an MUE (Answer A is correct). The goal of an MUE is to ensure optimal medication therapy management and improve patient safety and outcomes for drug-related processes—in this case, pharmacotherapy in SUP. Although one component of an MUE is PI, a review of the quality should occur before determining whether a PI project is necessary (Answer B is incorrect). An interventional MUE incorporates a review of quality in the form of making a pharmacotherapeutic intervention—PI. Although reviewing ADE data and medication error data from the ICU is helpful in detecting and determining problems associated with the use of pharmacotherapy in SUP, these are isolated

events and are reporter-dependent, and a lack of reports does not ensure that the use of pharmacotherapy in SUP is appropriate (Answers C and D are incorrect). Only an MUE is a robust and comprehensive method of evaluating the use of pharmacotherapy in SUP.

4. Answer: B

Evaluating the management of warfarin-induced hypoprothrombinemia is best suited for an MUE. The goal of an MUE is to ensure optimal medication therapy management and improve patient safety and outcomes for drug-related processes; an MUE is drug-, drug class-, or disease-specific—in this case, management of warfarin-induced hypoprothrombinemia (Answer B is correct). Quality assurance is a process for monitoring the effectiveness and safety of the medication use process that includes prescribing, dispensing, and administering medications. Evaluating pharmacist verification times for routine orders in the ICU, drug interaction warnings on the CPOE system, and duplicate warnings on the CPOE system is not necessarily drug- or disease state-specific and is best suited for a QA review (Answers A, C, and D are incorrect).

5. Answer: A

The next best step is determining the patients involved in the process (Answer A is correct). The step after that is evaluating the prescriber's practice (Answer B). Finally, data will be collected on the current process (Answer D), which will be evaluated to determine the areas for improvement in the outcome desired. The current process has already been determined, as provided in the question (Answer C).

6. Answer: C

Changes are made during the “do” part of the cycle (Answer C is correct). The planning phase involves describing the practice (Answer A is incorrect), collecting data (Answer B is incorrect), outlining the details (Answer D is incorrect), and describing who, what, when, and where the process will be done.

7. Answer: A

Using weighted metrics provides data on the quantity of the pharmacist's clinical activities (Answer A is correct). Documenting antibiotic use (Answer C), providing

education (Answer D), and attending an emergency cardiac arrest (Answer B) are important; however, these individual activities must be a weighted variable quantified over time and annualized to demonstrate the pharmacist's activities.

8. Answer: A

As of October 2015, sepsis is a reportable quality initiative for all hospitals. Acute coronary syndrome and heart failure are established quality measures (Answer A is correct). However, glycemic control alone is not a currently established quality measure (Answer B is incorrect). Ventilator-associated pneumonia and ventilator bundles to prevent pneumonia are important quality initiatives, but they are not currently reportable by CMS (Answers C and D are incorrect).

Appendix 1. CDC Antimicrobial Management Program Gap Analysis**Antimicrobial Management Program
Gap Analysis Checklist**

Executive Ownership	Y	N	Comments
Senior leadership is supportive of program and necessary requirements to meet resource needs			
Process exists to review medical staff participation in hospital quality initiatives			
Medical staff process exists to monitor compliance to quality programs • Process exists to evaluate outliers			
Process exists to evaluate critical staffing needs for quality programs • Central Order Entry (Supply Chain sponsored program has been retained as a method for pharmacist redeployment, for clinical programs as opposed to staff reduction • Microbiology services are readily available • Infection Prevention staff are readily available • Education time and resources are protected and provided to support programs – i.e. AMP development			

Information Technology	Y	N	Comments
IT resources are dedicated to the implementation of Non Programmed Reports (NPR) in MEDITECH for clinical use for all departments			
Pharmacy has an available staff member trained and dedicated to electronic formulary maintenance and decision support • Comments • Rule development (Automatic Stop Orders) • Clinical Reminders • Order set development • Triggers (Clinical Reminders) • Lab view groups			
Decision support strategy is integrated across departments			

Appendix 2. Example of Interventions and Cost Savings with Clinical Pharmacy Services**Pharmacy Department
INDICATORS 2015 Data**

Measure	Benchmark	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter
Pharmacotherapeutic interventions	None	3451	5748	5015	7298
Outcomes cost and raw drug cost savings from pharmacotherapeutic interventions	None	\$477,867	\$681,967	\$652,145	\$701,542

Findings/Conclusion: For 2011, the total number of pharmacotherapeutic interventions remained the same from the previous year with 20,940 interventions, realizing \$846,245 in outcomes and raw drug cost savings. For 2012, the total number of pharmacotherapeutic interventions remained similar to the prior year with 24,500 interventions, realizing \$950,471 in outcomes and medication use savings. For 2013, the total number of pharmacotherapeutic interventions remained similar to the prior year with 23,452 interventions, realizing \$904,254 in outcomes and raw drug cost savings. For 2014, the total number of pharmacotherapeutic interventions increased with 35,459 interventions documented, realizing \$1,954,654 in outcomes and raw drug cost savings. These findings are consistent with previous years.

Pharmacotherapeutic interventions performed by clinical pharmacists consist of making downward and upward dosing adjustments of medications, providing pharmacokinetic consultations, avoiding drug-drug and drug-food interactions, avoiding toxic medications, avoiding drug-disease contraindications, avoiding drug-allergy interactions, approving and dosing restricted antibiotics, switching patients from intravenous medications to oral medications, initiating more effective or safer drug therapies, initiating equally efficacious but less expensive medications, discontinuing unnecessary and duplicate medications, changing dosage forms according to patient tolerance, switching nonformulary to formulary medications, and making recommendations to monitor for efficacy and toxicity.

Clinical pharmacists review and respond to abnormal drug blood concentration assays and laboratory values such as serum chemistry and coagulation profiles as they pertain to medication management. Notes documenting the interventions are placed in the pharmacy profile. Depending on the quantity of pharmacotherapeutic interventions and the resulting cost savings, the Pharmacy Department's efforts to document clinical interventions, ensure medication safety, and contain medication-related costs have been very effective.

Action Indicated: No additional actions are required. The Pharmacy Department will continue to perform and document clinical interventions and evaluate the resulting cost savings.

FLUIDS, ELECTROLYTES, ACID-BASE DISORDERS, AND NUTRITION SUPPORT

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Learning Objectives

1. Describe normal fluid requirements, and identify common patient conditions that alter fluid needs and homeostasis.
2. Assess hyponatremia and hypernatremia in a critically ill patient, and develop an appropriate treatment plan.
3. Discuss the causes and treatment of common intracellular electrolyte disorders.
4. Differentiate between the causative factors for metabolic acidosis and alkalosis, and construct a therapeutic treatment algorithm.
5. Specify the appropriate route (parenteral or enteral) of nutrition administration, amount of nutrients, and micronutrients to be provided to a given critically ill patient.
6. Identify appropriate markers for assessing the tolerance, safety, and efficacy of enteral or parenteral nutrition therapy.
7. Select methods for ensuring appropriate glycemic control in critically ill patients.
8. Identify pertinent drug-nutrient interactions, and provide recommendations for the safe and effective delivery of medications to patients receiving enteral or parenteral nutrition therapy.

EDVI	End-diastolic volume index
EN	Enteral nutrition
GRV	Gastric residual volume
HCO ₃	Bicarbonate
IBW	Ideal body weight
ICF	Intracellular fluid
ICU	Intensive care unit
K	Potassium
NA	Sodium
NB	Nitrogen balance
NG	Nasogastric
NPO	Nil per os (nothing by mouth)
NRS	Nutrition risk screening score
NUTRIC	Nutrition risk in the critically ill (score)
Pco ₂	Partial pressure of carbon dioxide
PCWP	Pulmonary capillary wedge pressure
PN	Parenteral nutrition
Po ₂	Partial pressure of oxygen
REE	Resting energy expenditure
SCR	Serum creatinine
SIADH	Syndrome of inappropriate antidiuretic hormone
SOFA	Sequential organ failure assessment (score)
TBI	Traumatic brain injury
UUN	Urine urea nitrogen
WT	Body weight

Abbreviations in This Chapter

ABG	Arterial blood gas
ADH	Anti-diuretic hormone
AG	Anion gap
AKI	Acute kidney injury
APACHE	Acute physiology and chronic health evaluation (score)
BEE	Basal energy expenditure
BG	Blood glucose
BMI	Body mass index
BUN	Blood urea nitrogen
CKD	Chronic kidney disease
CL	Chloride
COPD	Chronic obstructive pulmonary disease
CRRT	Continuous renal replacement therapy
CSWS	Cerebral salt wasting syndrome
CVP	Central venous pressure
DM	Diabetes mellitus
ECF	Extracellular fluid

Self-Assessment Questions

Answers and explanations to these questions can be found at the end of this chapter.

1. Which is the most appropriate indication for parenteral nutrition (PN)?
 - A. Severe anorexia
 - B. Lack of bowel sounds
 - C. Ileus
 - D. High gastric residual volume (GRV)
2. Which is the most appropriate replacement fluid for a patient with significant nasogastric (NG) fluid drainage?
 - A. 0.9% sodium chloride and potassium chloride 20 mEq/L
 - B. 0.45% sodium chloride and potassium chloride 20 mEq/L

- C. 5% dextrose in 0.225% sodium chloride and potassium chloride 20 mEq/L
 - D. Lactated Ringer solution
3. Which trace mineral would best be increased for a PN-dependent patient with intractable diarrhea?
 - A. Zinc
 - B. Copper
 - C. Iodine
 - D. Manganese
 4. A 70-year-old man admitted to the intensive care unit (ICU) for sepsis was recently given a diagnosis of syndrome of inappropriate antidiuresis. His serum sodium acutely fell from 130 mEq/L to 115 mEq/L during the past 3 days, and he recently seized secondarily to this problem. Which would be the most appropriate treatment option?
 - A. Intravenous 0.9% sodium chloride
 - B. Intravenous desmopressin acetate (DDAVP)
 - C. Intravenous 3% sodium chloride
 - D. Intravenous conivaptan
 5. Other than the absorption/infusion rate, which best explains why enteral potassium administration is safer than parenteral potassium administration?
 - A. Bioavailability of potassium is significantly lower with enteral versus parenteral administration.
 - B. Feed-forward sensing of changes in mesenteric potassium concentration increases urinary potassium excretion.
 - C. Potassium chloride elixir is likely to cause diarrhea and reduce potassium absorption.
 - D. Wax matrix tablets sequester potassium release throughout the gastrointestinal (GI) tract.
 6. A 45-year-old woman with a history of celiac disease and alcoholism is admitted to the ICU. There is no evidence of significant acute or chronic blood loss. Her hematocrit is 30%, hemoglobin is 9 g/L, and mean corpuscular volume is 105 fL. Her serum methylmalonic acid concentration is within normal limits, and her serum homocysteine concentration is elevated. Serum ferritin is within normal limits. Which does this patient most likely have a deficiency of?
 - A. Iron
 - B. Thiamine
 - C. Folic acid
 - D. Cyanocobalamin
 7. A 40-year-old man (weight 60 kg) is admitted to the trauma ICU after a motor vehicle accident. He is noted to have a serum magnesium concentration of 1.2 mg/dL, and his family states that he has a history of alcohol abuse (6 to 12 beers/day). He is given magnesium sulfate 6 g intravenously for 6 hours by the primary service. His repeat serum magnesium concentration on the following day is 1.8 mg/dL. Which would be the most appropriate treatment for this patient?
 - A. No treatment is necessary because his serum magnesium concentration is normal.
 - B. If a repeat serum magnesium concentration is 2 mg/dL or greater, no additional magnesium therapy is indicated.
 - C. Supplemental calcium therapy should be given concurrently with the magnesium therapy.
 - D. Additional magnesium therapy should be given daily for the next 4–5 days.
 8. A 45-year-old man (weight 90 kg) admitted to the ICU after operative management of necrotizing pancreatitis is given PN consisting of 350 g of dextrose, 130 g of amino acids, and 90 g of lipid emulsion (20%) daily. A 24-hour urine collection for determining the nitrogen balance (NB) shows a urine urea concentration of 900 mg/dL for a urine output of 2700 mL. He received 100% of his PN solution, and there was no significant change in his blood urea nitrogen (BUN) during the NB study. Which most accurately depicts his NB?
 - A. -15 g/day
 - B. -7.5 g/day
 - C. -2.5 g/day
 - D. +2.5 g/day

I. FLUIDS AND ELECTROLYTES

A. General Overview

1. Body water compartments

- Total body water (TBW): About 60% of body weight for men; about 55% of body weight for women; lower percentage for those with obesity and for older adults (0.5 L/kg for men; 0.45 L/kg for women)
- About 60% of TBW is intracellular.
- About 40% of TBW is extracellular water (about 80% is interstitial fluid; about 20% plasma volume).

2. Estimating daily fluid requirements

- 30–35 mL/kg (overestimates large person, underestimates small person)
- 100 mL/kg for the first 10 kg, 50 mL/kg for the next 10 kg, and 20 mL/kg thereafter
- Increased insensible losses with fever (around 10%–15% for every degree Celsius greater than 37°C)

Table 1. Effect of Body Temperature on Insensible Fluid Losses (Surgery 1968;64:154-64)

Rectal Temperature (°C)	No. of Patients	Mean Fluid Loss (mL/m ² /day)
36.7–37.7	205	552
37.8–38.2	160	600
38.3–38.8	48	768
38.9–40	14	840

3. Estimating electrolyte requirements

- Approximate electrolyte concentrations in the extracellular and intracellular fluids (ECFs and ICFs) (Fluid, Electrolyte, and Acid-Base Disorders, Vol 1. New York: Churchill Livingstone, 1985:1-38)

Table 2. Electrolyte Concentrations in the ECF and ICF

Electrolyte	Extracellular Fluid (mEq/L)		Intracellular Fluid (mEq/L)
	(plasma)	(interstitial)	(muscle)
Sodium	140	145	12
Potassium	4.5	4.8	160
Chloride	104	117	2
Bicarbonate	24	27	10
Calcium	5.0	2.8	—
Magnesium	1.5	1.0	34
Phosphate	2	2.3	54

- “Normal” daily requirements

Table 3. “Normal” Daily Requirements

Sodium	50–150 mEq
Potassium	0.5–1.5 mEq/kg
Phosphorus	24–30 mmol
Magnesium	24–32 mEq
Calcium	10–20 mEq
Chloride ^a	80–120 mEq
Acetate ^a	80–120 mEq

^aDepending on the acid-base status of the patient.

- c. Approximate electrolyte content of GI fluids (in milliequivalents per liter) (About Surgery: A Clinical Approach. Philadelphia: Elsevier Health Sciences, 1996:5-17; Acta Chir Scand Suppl 1963:suppl 306:301-65)

Table 4. Electrolyte Content of GI Fluids

Fluid	Average Daily Volume (mL)	Sodium (mEq/L)	Potassium (mEq/L)	Chloride (mEq/L)	Bicarbonate (mEq/L)	Magnesium (mEq/L)
Stomach	1000–2000	60–90	10–15	100–130	—	0.9
Duodenum	400–600	140	5–10	90–120	80	—
Small intestine	2000–2500	140	5–10	90–120	30–40	6–12
Colon	< 300	60	20–30	50	—	6–12
Pancreas	600–800	140	5–10	75	115	0.4
Bile	300–600	140	5–10	100	30	1.1

- d. Electrolyte composition of common intravenous solutions (in milliequivalents per liter)

Table 5. Electrolyte Composition of Common Intravenous Solutions

Solutions	Na (mEq/L)	q/L	Chloride (mEq/L)	Bicarbonate (mEq/L)	Calcium (mEq/L)	Magnesium (mEq/L)	Osmolality (mOsm/kg)
5% dextrose in water	—	—	—	—	—	—	252
0.9% sodium chloride (normal saline)	154	—	154	—	—	—	308
0.45% sodium chloride (one-half normal saline)	77	—	77	—	—	—	154
5% dextrose in 0.225% sodium chloride (5% dextrose in one-fourth normal) saline)	34	—	34	—	—	—	320
3% sodium chloride (hypertonic saline)	513	—	513	—	—	—	1026
Lactated Ringer solution	130	4	109	28	2.7	—	274
PlasmaLyte/Normosol	140	5	98	27	—	3	294

4. Regulation of effective circulating volume
 - a. Kidney – Renin-angiotensin-aldosterone system
 - b. Extra-renal (carotid sinus, atrium) – Sympathetic nervous system (epinephrine and norepinephrine) and atrial natriuretic peptide

Table 6. Hemodynamic Assessment (<http://surgicalcriticalcare.net>)

Ejection Fraction	Adjusted End-Diastolic Volume Index for Normal Subjects	Adjusted End-Diastolic Volume Index for Critically Ill Patients
20	200	240
30	150	180
35	125	150
40	100	120
50	50	60

5. Regulation of plasma osmolality
 - a. Vasopressin release
 - b. Thirst
 - c. Osmoreceptor sensitivity
- B. Water and Sodium Disorders
1. Dehydration: As evidenced by decreased urine output (unless patient has glycosuria or diuretic therapy), increased serum urea nitrogen/serum creatinine ratio (SUN/SCr greater than 20), insufficient net fluid balance “from nursing records”), poor skin turgor, dry mucous membranes, orthostatic hypotension, “contraction alkalosis,” increased losses
 - a. Fever
 - b. GI fluids
 2. Volume excess: As evidenced by the presence of peripheral/sacral/pulmonary edema, anasarca, congestive heart failure, acute kidney injury (AKI)
 - a. Excessive fluid intake
 - b. Impaired ability to excrete excess water and sodium (e.g., heart failure, cirrhosis with ascites, renal failure)
 3. Hyponatremia
 - a. Classic evaluation
 - i. Exclude hyperglycemia, mannitol, and glycine for unmeasured effective osmoles (hypertonic hyponatremia).
Correct serum sodium for hyperglycemia (once the hyperglycemia is controlled, the serum sodium will rise).
For every 100-mg/dL increase in BG greater than 100 mg/dL, serum sodium will fall by about 2.4 mEq/L (or vice-versa).
Corrected serum Na = Measured serum Na + [(BG -100)/100 * 2.4]
(Am J Med 1999;106:399-403).
 - ii. Exclude factitious/pseudo-hypoglycemia (isotonic hyponatremia): Arguably still possible during lipemia (triglycerides greater than 1000 mg/dL or hyperproteinemia (e.g., multiple myeloma) if the serum is diluted under the assumption that the serum contains 7% solid-phase particles before the assay (Eur J Endocrinol 2014;170:G1-G47).

- iii. Evaluate ECF volume (increased, normal, decreased): Evaluate patient for edema, fluid balance on fluid intake/output records, hemodynamic markers, chest radiography: Pulmonary infiltrates without pneumonia, enlarged heart or evidence of diseases with decreased urinary water/sodium excretion (e.g., AKI, congestive heart failure, cirrhosis with ascites).
- iv. Consider using urine sodium and osmolality for hypotonic (serum osmolality less than 280 mOsm/kg) hyponatremia in conjunction with volume status (hypovolemic, euvolemic, hypervolemic):

Table 7. Comparative Features of Hypotonic Hyponatremia

ECF volume status	Hypervolemic		Euvolemic		Hypovolemic	
Physiologic Findings	Edema, large positive fluid balance, pulmonary infiltrates without pneumonia, enlarged heart, increased PCWP, EDVI		No evidence of edema, fluid equilibrium, no evidence of dehydration or fluid overload, normal hemodynamics		Poor skin turgor, dry mucous membranes, decreased urine output, concentrated urine, tachycardia	
Urine Osm (mOsm/kg)	> 100		> 100		> 450	
Urine Na (mEq/L)	< 20	>20	< 20	>20	< 20	>20
Potential etiologies	CHF, Cirrhosis with ascites, Nephrotic syndrome	Renal failure	Psychogenic polydipsia, Beer potomania	SIADH, Cortisol deficiency, Hypothyroidism, Drug-induced	Extra-renal losses, Third space losses	Diuretics, Adrenal insufficiency, Cerebral salt wasting, Salt wasting nephropathy

Common etiologies for SIADH (Am J Kidney Dis 2008;52:144-53; Hosp Pharm 2002;37:1336-42)

Central nervous system (CNS) disorders – Trauma, stroke, infection, brain tumors

Malignancy – Small cell carcinoma of the lung, pancreatic carcinoma, lymphoma, Hodgkin disease, sarcoma

Pulmonary infection, respiratory failure with positive pressure ventilation

Endocrine disorders – Pituitary tumor, hypothyroidism, adrenal insufficiency

Stress response (surgery, trauma, thermal injury, sepsis, pain)

Drugs

Table 8. Drug Induced SIADH (Am J Kidney Dis 1008;52:144-53)

Mechanism	Examples
Increased hypothalamic production of antidiuretic hormone (ADH)	Amitriptyline, imipramine
	Fluoxetine, sertraline, paroxetine
	Thioridazine, trifluoperazine
	Haloperidol
	Carbamazepine, valproic acid
	Vincristine, vinblastine, cisplatin, carboplatin, cyclophosphamide, ifosfamide
	Nicotine
	Bromocriptine
	Monamine oxidase inhibitors
Increased sensitivity to ADH	DDAVP, desmopressin
	Chlorpropamide
	Lamotrigine
Mixed or uncertain	Opiates
	Barbiturates
	Nonsteroidal anti-inflammatory agents
	Angiotensin-converting enzyme inhibitors

- v. If the patient has a TBI, it can be difficult to ascertain whether the patient has cerebral salt wasting syndrome (CSWS) or SIADH.

Table 9. Comparison of Features of Hyponatremia Caused by CSWS vs. SIADH (Hosp Pharm 2002;37:1336-42)

CSWS	SIADH
Decreased serum sodium	Decreased serum sodium
Decreased ECF	Normal or expanded ECF
Negative sodium balance	Variable sodium balance
CVP/PCWP/EDVI decreased	CVP/PCWP/EDVI normal or increased
Serum osmolality increased or normal	Serum osmolality decreased
Urine osmolality increased	Urine osmolality increased
Urine sodium increased	Urine sodium increased

CVP = central venous pressure; EDVI = end-diastolic volume index; PCWP = pulmonary capillary wedge pressure.

- b. 2014 European Society of Endocrinology guidelines (Eur J Endocrinol 2014;170:G1-G47)
- Exclude hyperglycemia and other causes of non-hypotonic hyponatremia.
 - Evaluate urine sodium and osmolality (the guidelines suggest that these markers should be assessed before ECF volume because the latter is difficult to determine in the critically ill patient). The European guidelines also differ because they recommend a urine sodium concentration of 30 mEq/L (instead of 20 mEq/L, as previously given) as the point of demarcation for differentiating the etiology for hyponatremia.
If urine osmolality is less than 100 mOsm/kg, the guidelines recommend accepting relative excess water intake as a cause of the hypotonic hyponatremia.
 - Assess ECF and arterial blood volume, diuretics, presence of kidney disease.

- c. Treatment of hyponatremia
 - i. Acute or severe symptoms (seizures, mental status changes) – Immediate treatment with hypertonic saline – therapy has to be adjusted to achieve a serum Na concentration change of 6–8 mEq/L in a day; no faster than 12 mEq/L in a day!
 - ii. ECF expanded – Fluid and sodium restriction
 - iii. ECF reduced and low urine sodium – Give sodium and fluids (treat etiologies if possible); reduce diuretic therapy. Sodium and fluid administration can be done using 0.9% NaCL intravenously or NaCL tablets 1 g to 2 g TID with additional water supplementation (if needed).
 - iv. ECF normal – Consider syndrome of inappropriate antidiuresis or secondary adrenal insufficiency – Fluid restriction first; consider conivaptan or tolvaptan; fluid restriction with use of 0.9% sodium chloride solution with or without diuretic therapy.
4. Hypernatremia
 - a. Excessive sodium intake (hypertonic saline, 0.9% sodium chloride solution, lactated Ringer solution) – therapy has to be adjusted to achieve a serum Na concentration change of 6–8 mEq/L in a day; no faster than 12 mEq/L in a day.
 - b. Dehydration

Estimation of free water deficit = $0.6 \times \text{Wt (kg)} \times [\text{serum sodium}/140 - 1]$ (use $0.5 \times \text{Wt (kg)}$ for women). Correct deficit for 2–3 days. This is typically accomplished with use of free water boluses (e.g., 200 mL to 300 mL every 4 to 6 hours) if patient has a nasogastric feeding or suction tube. If the enteral route is not possible or if the patient exhibits intolerance to water boluses, then intravenous D5W or D5 1/4NS can be used. Do not give water boluses if the patient has a post-pyloric tube because it causes cramping and diarrhea. There also have been some rare cases of bowel necrosis post–large water boluses when administered directly into the small bowel.

Patient Case

Questions 1–3 pertain to the following case.

A 55-year-old woman (70 kg) admitted to the ICU for pneumonia and respiratory failure develops a serum sodium of 125 mEq/L on her fifth day of hospital admission. Her other laboratory values include a serum potassium of 4.6 mEq/L, chloride (Cl) 100 mEq/L, total carbon dioxide (CO₂) content 24 mEq/L, BUN 20 mg/dL, serum creatinine (SCr) 1.1 mg/dL, and glucose 167 mg/dL. She currently receives a 1-kcal/mL, 62-g/L enteral feeding formula at 60 mL/hour and a 5% dextrose in 0.45% sodium chloride infusion at 25 mL/hour. Her fluid balance has ranged from +300 to +600 mL/day during the past 3 days. She has no evidence of any significant amount of edema. Her measured serum osmolality is 265 mOsm/kg, urine osmolality is 490 mOsm/kg, and urine sodium is 67 mEq/L.

1. Which is the most likely etiology for the patient's hyponatremia?
 - A. Factitious hyponatremia
 - B. Adrenal insufficiency
 - C. Cerebral salt wasting
 - D. SIADH
2. Which would be the most appropriate treatment for this woman?
 - A. Give sodium chloride tablets 1 g three times daily.
 - B. Limit fluids.
 - C. Change the intravenous fluid to 0.9% sodium chloride.
 - D. Provide a short-term intravenous infusion of 3% sodium chloride.

Patient Case (*continued*)

3. Which change in the enteral feeding formula would be best for this patient?

- A. Add sodium chloride 100 mEq/L to the current formula.
- B. Change the formula to a fish oil–enriched product.
- C. Change the formula to a low-carbohydrate, high-fat product.
- D. Change the formula to a 2-kcal/mL formula, and decrease the rate.

C. Disorders of Potassium Homeostasis

1. Potassium homeostasis overview

- a. 98% intracellular
- b. Total body stores: 35–50 mEq/kg in normal healthy adults; 25–30 mEq/kg if significantly undernourished
- c. Normal serum concentration: 3.5–5.2 mEq/L
- d. Serum concentration can be influenced by changes in pH (for every 0.1 increase in arterial pH, serum potassium will decrease by around 0.6 mEq/L [range 0.4–1.3 mEq/L]) (J Clin Invest 1956;35:935-9), and vice versa.
- e. Average daily requirement: About 0.5–1.2 mEq/kg
- f. Kidney is primary route of elimination.
- g. Losses can be extensive with severe diarrhea or body fluid drainages (see Table 4).
- h. Magnesium status can influence potassium homeostasis (J Am Soc Nephrol 2007;18:2649-52; Crit Care Med 1996;24:38-45; Arch Intern Med 1992;152:40-5).
 - i. Magnesium serves as a cofactor for the Na-K-ATPase pump.
 - ii. Magnesium closes potassium channels in distal nephron.

2. Hypokalemia

- a. Definition: Serum potassium less than 3.5 mEq/L, though most ICUs prefer to keep patients at 4.0 mEq/L or greater, if possible.
- b. Signs and symptoms: Weakness, cramps, cardiac arrhythmias (ST depression, QT prolongation, flat T wave, U wave). If severe hypokalemia (e.g., serum potassium less than 2 mEq/L): flaccid paralysis, ileus.
- c. Etiologies:
 - i. Inadequate intake (rare; kidneys can usually adapt)
 - ii. Increased losses
 - (a) GI fluid losses (e.g., diarrhea, fistula, drainages)
 - (b) Hypomagnesemia
 - (c) Medications (diuretics, amphotericin B, mineralocorticoid excess, extended-spectrum penicillins such as piperacillin, ticarcillin)
 - (d) Polyuria (diabetes insipidus)
 - (e) Renal potassium excretion (type I/distal and type II/proximal renal tubular acidosis)
 - (f) Diabetic ketoacidosis
 - iii. Increased requirements (building of new muscle/tissue – refeeding syndrome)
 - iv. Extracellular to intracellular shift
 - (a) Medications (β -adrenergic agonists, including albuterol, sodium bicarbonate or other alkalinizing agents; insulin)
 - (b) Acute alkalemia
 - (c) Hypothermia
 - (d) Pentobarbital

- d. Estimating total body potassium deficit
 - i. Transtubular potassium gradient to assess the contribution of the kidney to the hypokalemia is no longer recommended because of the variability in urea reabsorption in the cortical collecting duct, which alters solute removal. Use spot urine potassium if kidney-based etiology of hypokalemia is unclear.
 - ii. Stern equation (Medicine [Baltimore] 1981;60:339-54) (most commonly used method): Potassium deficit (mEq) = $100 \times (4.4 - \text{serum potassium})$
 - iii. Segal equation (Core Concepts in the Disorders of Fluid, Electrolytes, and Acid-Base Balance. New York: Springer, 2013:49-102) (makes nonlinear assumption of deficit estimate): Potassium deficit (mEq per 70 kg): $3300 \times e^{-(\text{serum potassium concentration}/1.5)} - 200$
 - iv. Stern equation (Medicine (Baltimore) 1981;60:339-54) adjusted to the extent of malnourishment: Estimate total body potassium (mEq/kg) by:
 Well nourished: 35–50 mEq/kg
 Undernourished: 20–35 mEq/kg
 Serum potassium of 3.0 mEq/L approximates a 10% total body deficit.
 Serum potassium of 2.5 mEq/L approximates a 20% total body deficit.
- e. Treatment:
 - i. Treat, alleviate, or reduce the potential etiologies for hypokalemia, if possible.
 - ii. Ensure that hypokalemia is not at least partly attributable to hypomagnesemia.
 - iii. The estimated deficit should be replaced during a period of 1–3 days (depending on the extent of deficit; the larger the deficit, the longer the repletion period) by giving boluses and increasing the potassium content in intravenous fluids and PN/enteral nutrition (EN) solutions.
 - iv. Enteral or oral potassium replacement is the preferred and safer route of delivery because of the time of absorption and feed-forward regulation of potassium homeostasis (Ann Intern Med 2009;150:619-25); administration of potassium chloride liquid directly into the small bowel (by a jejunal or duodenal feeding tube) should be avoided because of its osmolality, which can lead to abdominal cramping, distension, and diarrhea.
 - v. Short-term infusions of potassium chloride or potassium phosphate should be given only by central vein. Potassium chloride can be given at 20 mEq/hour if the patient has continuous electrocardiography (ECG) monitoring in the ICU. Ten mEq/hour is safest if the patient is asymptomatic. Potassium chloride comes prepackaged as 20- and 40-mEq units in sterile water for injection. Peripheral intravenous solutions should not contain potassium chloride at more than 40–60 mEq/L in an effort to reduce the pain associated with the infusion of a concentrated potassium chloride solution and to prevent inappropriate rapid and excessive potassium chloride dosing.
 - vi. Empiric intravenous potassium dosing. This algorithm (used by the Regional One Health Nutrition Support Service) is only a guide for critically ill patients and may need to be adjusted according to patient body size, renal function, and ongoing severity of losses.

Table 10. Empiric Intravenous Potassium Dosing

Serum Potassium (mEq/L)	Potassium Chloride Dosage (mEq) ^a	Laboratory Tests
3.5–3.9	40 to 60 mEq x 1; increase in IV/PN/EN	Obtain BMP, magnesium next AM
3–3.4	40 mEq x 2; increase in IV/PN/EN	Obtain BMP, magnesium next AM; may wish to obtain potassium 1–2 hours after second 40-mEq bolus, especially if losses are thought to be high; reassess
2–2.9	40 mEq x 3+; increase in IV/PN/EN	Obtain repeat serum potassium 1–2 hours after second 40-mEq bolus and reassess; may need one or two additional boluses; repeat; check serum magnesium next AM; reassess

^aPotassium phosphate may be considered in lieu of potassium chloride if concurrent hypokalemia and hypophosphatemia (very common in critically ill patients receiving EN/PN). Thirty millimoles of potassium phosphate is equivalent to 44 mEq of potassium.

AM = morning; BMP = basic metabolic panel; IV = intravenous.

- vii. The historical assumption of “a 0.5 to 0.6 mEq/L increase in serum potassium will occur for every 40 mEq of intravenous potassium administered” (J Clin Pharmacol 1994;34:1077-82; Arch Intern Med 1990;150:613-7) is potentially inaccurate for many critically ill subpopulations.
 - viii. Serum potassium concentrations are equilibrated within 1–2 hours after completion of the intravenous potassium chloride infusion (J Clin Pharmacol 1994;34:1077-82; Crit Care Med 1991;19:694-9) and are recommended for patients with severe and/or complicated cases of hypokalemia.
3. Hyperkalemia
- a. Definition: Serum potassium greater than 5.2 mEq/L, although usually not a significant problem until serum potassium approaches 6 mEq/L
 - i. Rule out factitious hyperkalemia (hemolysis of blood sample, white blood cell count greater than 10×10^3 cells/mm³, platelet count greater than 400,000/mm³). The potential for this error can be reduced by collecting the blood sample in a heparinized tube.
 - ii. Assess arterial blood gas (ABG) (severe acidosis).
 - iii. Immediately after a large blood transfusion
 - b. Signs and symptoms: Peaked and tented T waves on ECG, symptoms similar to those of hypokalemia (weakness, paralysis)
 - c. Etiologies:
 - i. Drugs – Potassium-sparing diuretics (spironolactone, amiloride, triamterene), angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, nonsteroidal anti-inflammatory drugs, heparin, trimethoprim, octreotide
 - ii. Excessive intake (usually in combination with compromised renal function) – Be sure to examine all intravenous fluids, EN and PN regimens, penicillin G (1.7 mEq of potassium per million units), packed red blood cells (potassium 7.5–13 mEq/L).
 - iii. Renal dysfunction (chronic kidney disease [CKD], AKI)
 - iv. Hyporeninemic hypoaldosteronism
 - v. Tissue catabolism (chemotherapy, rhabdomyolysis)
 - vi. Severe acidemia
 - vii. Older adult patients

- d. Treatment
 - i. Calcium gluconate (10%) 1- to 2-g intravenous slow push (especially if ECG changes) to stabilize the myocardium
 - ii. Regular human insulin 10 units intravenously and (optionally) 50 g of dextrose intravenously (results in only temporary redistribution)
 - iii. Sodium bicarbonate 50–100 mEq intravenously (especially if acidemic – results in only temporary redistribution)
 - iv. Sodium polystyrene sulfonate 25–50 g (intragastric administration preferred) – Increases potassium elimination
 - v. Albuterol (results in only temporary redistribution)
 - vi. Loop diuretics – Increase potassium elimination
 - vii. Hemodialysis – Increases potassium elimination
 - viii. Make sure no exogenous sources of potassium (e.g., intravenous fluids, EN, PN); to reduce intake with EN or PN; use a “renal” (no or low-electrolyte formulation, if necessary)
 - ix. Patiromer oral suspension – Zirconium citrate nonabsorbable polymer. Recently approved by the U.S. Food and Drug Administration (FDA). Delayed onset of action and designed for patients with chronic hyperkalemia (not for acute hyperkalemia) who receive angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, spironolactone, with advanced diabetes (hyporeninemic hypoaldosteronism) or kidney dysfunction. Normal starting dosage is within 4.2–16.8 g twice daily. Adverse effects include hypomagnesemia (7%), constipation (6%), and hypokalemia (6%).

D. Disorders of Magnesium Homeostasis

1. Magnesium homeostasis overview
 - a. 99% intracellular (17% of total body content is in the muscle or in the skeleton)
 - b. Total body stores: Around 2000 mEq
 - c. Normal serum concentration: 1.8–2.4 mg/dL (about 30% bound to protein)
 - d. Average daily requirement: Around 24–40 mEq/day
 - e. Kidney is primary route of elimination (around 70% reabsorbed in ascending loop of Henle) and is without any hormonal regulation of renal magnesium reabsorption.
 - f. Losses can be extensive with severe diarrhea or body fluid drainages (see Table 4).
 - g. Magnesium depletion can influence potassium and calcium homeostasis.
2. Hypomagnesemia
 - a. Definition: Although the lower limit of normal for serum magnesium concentrations is 1.8 mg/dL (1.5 mEq/L), most clinicians define significant hypomagnesemia as 1.5 mg/dL (1.3 mEq/L) or less. Many ICUs have a target serum magnesium concentration greater than 2 mg/dL (1.8 mEq/L). Serum concentrations of magnesium may be slightly falsely lowered in the presence of significant hypoalbuminemia.
 - b. Signs and symptoms: Muscle weakness, cramping, paresthesias, Chvostek and Trousseau signs, tetany, QT prolongation, hypokalemia, hypocalcemia
 - c. Etiologies:
 - i. GI losses (especially diarrhea) – Average stool loss of about 6 mEq/L; up to 10–12 mEq/L or greater for secretory diarrheal losses
 - ii. Alcohol (increased renal excretion; impaired absorption; poor nutritional status of patients who abuse alcohol)
 - iii. Sepsis/critical illness (increased urinary excretion – several factors)
 - iv. Pancreatitis (partly attributable to calcium-magnesium soap formation in peritoneum)
 - v. Thermal injury/TBI (increased urinary excretion – several factors)

- vi. Drugs – Diuretics, amphotericin B, caspofungin, cyclosporin/tacrolimus, foscarnet, pentamidine, piperacillin/tazobactam, cisplatin/carboplatin/ifosfamide/cetuximab, lactulose/orlistat, aminoglycosides, and potentially long-term use of digoxin or proton pump inhibitors
- vii. Polyuria (osmotic agents, hypercalcemia, ureagenesis)
- d. Estimating magnesium deficit: For a serum magnesium concentration of less than 1.5 mg/dL (1.3 mEq/L), a 1- to 2-mEq/kg deficit can be expected.
- e. Treatment:
 - i. Treat the etiology (if possible). Be sure to treat magnesium deficiency at the same time or before potassium therapy if the patient is also hypokalemic.
 - ii. Successful treatment of hypomagnesemia usually takes 3–5 days of intravenous therapy. Intramuscular magnesium therapy for replacement therapy is inadvisable given the limit on volume per injection site with respect to dosage requirements and tissue irritation.
 - iii. Intravenous magnesium sulfate 32–48 mEq/day (4–6 g/day) – Suggested to be sufficient to maintain serum magnesium within 2–2.5 mg/dL for most magnesium-deficient patients (Crit Care Med 1996;24:38-45; Annu Rev Med 1981;32:245-59)
 - iv. Empiric intravenous magnesium sulfate dosing. This algorithm (used by Regional One Health's Nutrition Support Service) (Nutrition 1997;13:303-8) was designed primarily for trauma and thermally injured patients but can likely be universally applied to other critically ill patient populations. The therapy may need to be adjusted according to renal function and ongoing severity of losses. Our empiric approach to dosing intracellular electrolytes for patients with significant renal impairment is to give one-half the recommended dose (see Table 7). However, electrolyte therapy for patients with renal impairment must be individualized according to individual response.

Table 11. Empiric Intravenous Magnesium Sulfate Dosing

Serum Magnesium (mg/dL)	Dose (g/kg)
1.6–1.8	0.05
1–1.5	0.1
< 1	0.15

For ease of use and preparation, intravenous magnesium sulfate should be ordered in 2-g increments (e.g., 2 g, 4 g, 6 g). The drug should be mixed in 100–250 mL of normal saline or 5% dextrose and given at a rate no faster than 1 g (8 mEq) per hour (Nutrition 1997;13:303-8). Maximum dose should be held at a ceiling of 8–10 g per administration. Magnesium concentrations are often elevated for several hours or longer after an infusion because it takes about 48 hours for the magnesium to fully redistribute to the body tissues (Nutrition 1997;13:303-8).

- v. Oral magnesium: It can be difficult to successfully replenish magnesium if given by the oral route in critically ill patients because of the adverse GI effects of oral magnesium (e.g., diarrhea) and the high elemental magnesium doses required to achieve repletion. Although it has been inferred that certain oral magnesium products are better tolerated than others (e.g., gluconate vs. oxide), this tolerability likely pertains to the elemental magnesium content of the products. The lower the elemental magnesium content, the more tolerable the oral product. However, the lower the magnesium content, the more difficult it is to achieve magnesium repletion for a patient with significant magnesium depletion.

Table 12. Common Oral Magnesium Products

Salt Form	Strength (mg)	Elemental Magnesium Content (mEq)	Usual Dosing
Oxide	400	19.8	1–2 tablets two or three times daily
	140	6.9	
Gluconate	500	2.2	1–2 tablets two or three times daily
Chloride	100	2.6	1–2 tablets two or three times daily

Table 13. Oral Magnesium Content

Salt Form	% Elemental Magnesium Content
Oxide	60
Carbonate	45
Hydroxide	42
Citrate	16
Lactate	12
Chloride	12
Sulfate	10
Gluconate	5

3. Hypermagnesemia

- a. Definition: Serum magnesium concentration greater than 2.4 mg/dL; patients usually do not experience symptoms until the serum magnesium concentration exceeds about 4 mg/dL.
- b. Signs and symptoms: Hypotension, decreased deep tendon reflexes, cardiovascular manifestations (e.g., bradycardia, somnolence, muscle paralysis, arrhythmias) generally do not occur until serum concentrations are greater than 4 mg/dL.
- c. Etiologies: Renal failure or impairment early post-infusion elevation of serum magnesium concentration, excessive dosing of magnesium/antacids, post-cathartic use (e.g., magnesium citrate) – To develop hypermagnesemia, these events usually occur together with renal impairment.
- d. Treatment:
 - i. Remove source of magnesium intake.
 - ii. Intermittent slow bolus doses of calcium gluconate (2 g) for 5–10 minutes until severe symptoms abate (the effect of calcium is transient, and repeat therapy may be needed as often as every hour)
 - iii. Ventilate the patient, if necessary.
 - iv. 0.9% NaCl infusion with loop diuretic therapy
 - v. Hemodialysis

Patient Case

Questions 4 and 5 pertain to the following case.

A 65-year-old man (weight 87 kg) is admitted to the hospital because of a bout of acute pancreatitis. A computed tomography (CT) scan of the abdomen reveals a pancreatic pseudocyst. He is to remain NPO (nothing by mouth) because of marked abdominal pain on eating a low-fat diet and is given PN. He is a 2 pack/day tobacco smoker and has a history of frequent alcohol consumption. His serum laboratory values are as follows: sodium (Na) 139 mEq/L, potassium (K) 3.3 mEq/L, Cl 102 mEq/L, total CO₂ content 25 mEq/L, BUN 14 mg/dL, SCr 0.8 mg/dL, calcium 7.6 mg/dL, phosphorus 2.2 mg/dL, magnesium 1.5 mg/dL, and albumin 2.5 g/dL.

4. Which potassium-phosphorus dosing regimen would be most appropriate for this patient?
 - A. Potassium chloride liquid 40 mEq through NG tube for two doses, 2 Neutra-Phos capsules in water through NG tube
 - B. Potassium phosphate 30 mmol intravenously x 1 dose, followed by two 40-mEq potassium chloride doses through NG tube
 - C. Potassium phosphate 60 mmol intravenously x 1 dose
 - D. Potassium chloride 40 mEq intravenously x 1 dose and potassium phosphate 30 mmol intravenously x 1 dose
5. In addition to potassium and phosphorus supplementation, the patient is given magnesium sulfate 6 g intravenously for 6 hours. His repeat serum magnesium the next day is 2.0 mg/dL. Which therapeutic option would be best for this patient?
 - A. Give magnesium oxide 500 mg twice daily for the next few days.
 - B. Give magnesium sulfate 2–4 g intravenously daily for the next few days.
 - C. Give an additional dose of 8 g of magnesium sulfate intravenously.
 - D. No additional treatment is necessary.

E. Disorders of Calcium Homeostasis

1. Calcium homeostasis overview

- a. Most prevalent intracellular cation in body; 99% of body's calcium is in bone; highly protein bound in plasma
- b. Total body stores: About 1–1.2 kg of calcium
- c. Normal serum concentration: 8.5–10.5 mg/dL; normal serum ionized concentration 1.12–1.32 mmol/L
- d. Serum concentration can be influenced by:
 - i. Changes in plasma albumin concentration – For every 1 g/dL in serum albumin below 4 g/dL, serum calcium will decrease by around 0.8 mg/dL (Clin Chim Acta 1971;35:483-9); do not use in critically ill patients (inaccurate) (JPEN J Parenter Enteral Nutr 2004;28:133-41). Use ionized calcium concentration for critically ill patients. However, most critically ill patients (85%) with a total serum calcium concentration less than 7 mg/dL are hypocalcemic (ionized serum calcium of 1.12 mmol/L or less) (Nutr Clin Pract 2007;22:323-8).
 - ii. Changes in pH (for every 0.1-unit increase in arterial pH, serum ionized calcium will decrease by about 0.05 mmol/L) (Arch Pathol Lab Med 2002;126:947-50) because of increased protein binding
- e. Average daily requirement: 15 mEq/day intravenously with PN (Ann Surg 1983;197:1-6); 1–3 g/day orally
- f. Kidney is primary route of elimination.

- g. Magnesium status can influence calcium homeostasis.
 - i. Hypomagnesemia results in end-organ resistance to parathyroid hormone.
 - ii. Hypomagnesemia may impair parathyroid hormone secretion.
 - iii. Hypocalcemia will correct within 2 days after hypomagnesemia is corrected.
- 2. Hypocalcemia
 - a. Definition: Corrected serum total calcium less than 8.5 mg/dL (non-ICU patients); ionized serum calcium concentration less than 1.12 mmol/L
 - b. Signs and symptoms: Tingling, paresthesias, hyperactive deep tendon reflexes, Chvostek and Trousseau signs, prolonged QT interval
 - c. Etiologies
 - i. Critical illness
 - ii. Continuous renal replacement therapy (CRRT) (citrate anticoagulation)
 - iii. Massive blood transfusion
 - iv. Hypomagnesemia
 - v. Hyperphosphatemia
 - vi. Pancreatitis
 - vii. Drugs (amphotericin B, cisplatin, cyclosporine, foscarnet, bisphosphonates, loop diuretics)
 - viii. Malabsorption
 - ix. Hypoparathyroidism
 - x. Chronic kidney injury/AKI
 - xi. Vitamin D deficiency
 - xii. Severe alkalemia
 - d. Treatment: Regional One Health Nutrition Support Service intravenous calcium gluconate dosing guidelines (JPEN J Parenter Enteral Nutr 2007;31:228-33; JPEN J Parenter Enteral Nutr 2005;29:436-4; Nutrition 2007;23:9-15)

Table 14. Regional One Health Nutrition Support Service Intravenous Calcium Gluconate Dosing Guidelines

Ionized Calcium (mmol/L)	Intravenous Calcium Gluconate Dosage (mEq)
1–1.12	2 g (9.3 mEq) of calcium gluconate in 100 mL of 0.9% NaCl or D ₅ W for 2 hours
≤ 0.99	4 g (18.6 mEq) of calcium gluconate in 100 or 250 mL of 0.9% NaCl or D ₅ W for 4 hours

For ease of use and preparation, calcium gluconate should be ordered in gram increments. Calcium chloride should be used (preferably) only in code situations, not for routine replacement therapy, because the chloride salt contains about 2.5 times the amount of elemental calcium and can cause tissue necrosis when given peripherally in contrast to calcium gluconate. However, during extreme circumstances, such as a national drug shortage of intravenous calcium gluconate, calcium chloride can be given in 0.67- and 1.3-g doses in lieu of 2- and 4-g calcium gluconate doses. In addition, calcium chloride should never be added to the PN solution unless there is no phosphate in the PN solution and the commercial amino acids used in the PN solution do not contain phosphorus (some amino acid products do contain phosphate). A serum ionized calcium concentration determination should be repeated several hours after completing the calcium gluconate infusion to allow equilibration (Nutrition 2007;23:9-15). More aggressive therapy may need to be considered for patients with tetany or life-threatening cardiac arrhythmias caused by hypocalcemia.

Intravenous calcium administration should be used with extreme caution in patients with severe hypokalemia or in those receiving digoxin or other digitalis alkaloids.

Always check the serum phosphorus concentration because hyperphosphatemia can induce hypocalcemia, given the metastatic precipitation of calcium phosphate in the soft tissues and lungs (usually associated with renal disease).

D5W = 5% dextrose in water; NaCl = sodium chloride.

Patient Case

Questions 6 and 7 pertain to the following case.

A 24-year-old man (weight 90 kg) is admitted to the trauma ICU postoperatively from repair of his duodenal, jejunal, ileal, and colon injuries; hepatorrhaphy; and splenectomy after several gunshot wounds to the abdomen. He also received 10 units of packed red blood cells. He has a serum ionized calcium concentration of 0.86 mmol/L, K 4.6 mEq/L, and magnesium 1.8 mg/dL. His SCr concentration is 0.8 mg/dL, and his urine output is 0.5 mL/kg/hour.

6. Which is the most likely etiology of his hypocalcemia?
 - A. Hypomagnesemia
 - B. Excessive urinary diuresis
 - C. Blood transfusion
 - D. Critical illness
7. Which therapeutic regimen would be best for this patient?
 - A. Calcium gluconate 2 g intravenously for 2 hours
 - B. Calcium gluconate 4 g intravenously for 4 hours
 - C. Calcium chloride 1 g intravenous push for 5–10 minutes
 - D. No calcium therapy necessary.

3. Hypercalcemia

- a. Definition: Corrected serum calcium greater than 10.5 mg/dL or ionized calcium greater than 1.32 mmol/L; signs and symptoms are more evident when total serum calcium of 12 mg/dL or greater or ionized calcium of 1.5 mmol/L or greater.
- b. Signs and symptoms: Mental status changes, polyuria, shortened QT interval, bradycardia, atrioventricular block
- c. Etiologies:
 - i. Immobilization
 - ii. Chronic critical illness—associated metabolic bone disease
 - iii. Excessive calcium intake
 - iv. Hyperparathyroidism
 - v. Granulomatous diseases (tuberculosis, sarcoidosis)
 - vi. Malignancy
 - vii. Drugs (thiazide diuretics, vitamin D)
 - viii. Dehydration
- d. Treatment:
 - i. Mobilize the patient (if possible); discontinue calcium from the PN solution.
 - ii. Intravenous fluids with 0.9% sodium chloride (if dehydrated) at 200–300 mL/hour x 48 hours or until rehydrated with or without furosemide 40–80 mg intravenously every 12 hours
 - iii. Calcitonin 4 units/kg intramuscularly or subcutaneously every 12 hours; can be increased to 8 units/kg every 12 hours as needed
 - iv. Pamidronate 90 mg intravenously once for acute hypercalcemia unrelated to etiologies i and ii
 - v. Pamidronate 30 mg intravenously daily for 3 days if hypercalcemia caused by etiology i or ii
 - vi. This author's practice: Salmon calcitonin 200 units intramuscularly or subcutaneously every 12 hours for 48 hours (rapid tachyphylaxis often limits therapy duration). Two hundred units is selected as the dosage because it comes from the manufacturer in a 200-IU/mL vial

and is usually near the initial appropriate dosage range for many patients. If the patient is thought to have chronic critical illness–associated metabolic bone disease or hypercalcemia from immobilization, it is suggested to simultaneously add pamidronate 30 mg intravenously daily for 3 consecutive days because of the delay in bisphosphonate’s onset of action (Chest 2000;118:761-6). Monitor for hypocalcemia. Zoledronic acid may also be an option; however, evidence regarding its efficacy for chronic critical illness associated metabolic bone disease is lacking. Do not use bisphosphonates in patients with renal impairment.

- vii. Parathyroidectomy for patients with primary hyperparathyroidism
- viii. Prednisone 40 mg/day and greater for 10 days for patients with granulomatous diseases (e.g., sarcoidosis, tuberculosis)

F. Disorders of Phosphorus Homeostasis

1. Phosphorus homeostasis overview

- a. 99% intracellular, of which 85% is bound to bone
- b. Extracellular pool of phosphorus: Around 600 mg (about 20 mmol), 10% protein bound
- c. Normal serum concentration: 2.5–4.5 mg/dL
- d. Serum concentration can be influenced by parathyroid hormone (increased parathyroid hormone leads to increased urinary excretion of phosphorus), and alkalemia can decrease serum phosphorus concentration.
- e. Average daily requirement: Around 20 mg/kg/day
- f. Kidney is primary route of elimination.

2. Hypophosphatemia

- a. Definition: Serum phosphorus less than 2.5–3 mg/dL; severe hypophosphatemia less than 1–1.5 mg/dL
- b. Signs and symptoms: Weakness, paresthesias; severe depletion can lead to congestive cardiomyopathy, cardiac arrest, seizures, coma, respiratory arrest, rhabdomyolysis
- c. Etiologies:
 - i. Alcoholism
 - ii. Malnutrition/refeeding syndrome
 - iii. Critical illness (especially trauma, TBI, thermal injury)
 - iv. Diabetic ketoacidosis
 - v. Hepatic resection
 - vi. Drugs – Insulin, catecholamines, antacids, sucralfate, calcium
 - vii. Alkalemia
 - viii. Malabsorption – Chronic diarrhea
 - ix. Hyperparathyroidism
 - x. Cancer (phosphatonins [e.g., fibroblast growth factor-23])
- d. Treatment
 - i. Target serum phosphorus concentration when patient is in the ICU and ventilator dependent: 4 mg/dL (Intensive Care Med 1995;21:826-31; N Engl J Med 1985;313:420-4).
 - ii. Intravenous dosing guidelines

Table 15. Intravenous Phosphorus Dosing Guidelines

Serum Phosphorus (mg/dL)	General Medical-Surgical Population Dosage (mmol/kg) (Crit Care Med 1995;23:1504-11)	High Requirements^a Population Dosage (mmol/kg) (JPEN J Parenter Enteral Nutr 2006;30:209-14)
2.3–3	0.16	0.32
1.6–2.2	0.32	0.64
< 1.6	0.64	1

^aPatients with thermal injury (JPEN J Parenter Enteral Nutr 2001;25:152-9), those with trauma (especially those with a TBI) (Nutrition 2010;26:784-90; JPEN J Parenter Enteral Nutr 2006;30:209-14), those malnourished with evidence of significant complications from refeeding syndrome, or those with hepatic resections.

The drug should be mixed in 100–250 mL of normal saline or 5% dextrose in water and given at a rate no faster than 7.5 mmol/hour. Phosphorus should always be ordered in millimoles for ease of use and preparation. For ease of use and preparation in the pharmacy, phosphorus should be ordered in units divisible by 3 mmol (e.g., 15, 30, 45, 60) whenever possible.

Potassium phosphate salt can be used for patients with a serum potassium less than 4 mEq/L (3 mmol of phosphorus = 4.4 mEq of potassium). Sodium phosphate salt should be used for patients with a serum potassium of 4 mEq/L or greater (3 mmol of phosphorus = 4 mEq of sodium).

iii. Oral or enteral phosphorus dosing:

- Difficult to accomplish in patients not receiving EN because of single-entity products and doses needed for repletion and adverse GI effects (e.g., diarrhea)
- Neutra-Phos and Neutra-Phos K (only 8 mmol of phosphorus per tablet/packet)
- Can add potassium phosphate/sodium phosphate injection to enteral feeding solution (e.g., 30 mmol/L) or oral sodium phosphate solution 5–10 mL per liter of EN (5 mL = 20 mmol of phosphorus)

3. Hyperphosphatemia

- Definition: Serum phosphorus concentration greater than 5 mg/dL, usually not clinically relevant until serum phosphorus is greater than 6 mg/dL
- Signs and symptoms: Hypocalcemia and metastatic calcification (e.g., neuromuscular irritability, prolonged QT interval, tetany) – Usually does not occur until the serum calcium-phosphorus product approaches 55 mg/dL or greater (Adv Exp Med Biol 1978;103:195-201).
- Etiologies:
 - Renal failure
 - Immobility
 - Chronic critical illness–associated metabolic bone disease
 - Excessive phosphorus intake
 - Vitamin D toxicity
 - Tumor lysis syndrome
 - Hypoparathyroidism
- Treatment:
 - Reduce phosphorus intake (omit from PN solution, plus or minus reduce lipid content of PN solution if a high-fat formulation [controversial as phosphorus in organic form: phospholipids and not inorganic such as sodium phosphate]; change to “low- or no-electrolyte” renal enteral formula).
 - Phosphate binders (Am J Health Syst Pharm 2005;62:2355-61)

Table 16. Phosphate Binders

Drug	Available Strength	Phosphorus-Binding Capacity	Recommended Empiric Initial Dose
Calcium carbonate ^a	500, 750, 1000 mg per tablet	Calcium 43 mg/g	1 g QID
Calcium acetate ^a	667 mg per tablet	Calcium 106 mg/g	1334–2001 mg TID
Sevelamer ^b	800 mg per capsule or packet	Sevelamer 80 mg/g	800–1600 mg TID
Lanthanum	250, 500, 750, 1000 mg per tablet	Data not available	500 mg TID

^aDo not use if the patient is hypercalcemic.

^bCarbonate comes in a powder; easier for administering to tube-fed patients; less likely to worsen metabolic acidosis than gel capsule in patients with renal failure because gel capsule is in hydrochloric acid salt form.

QID = four times daily; TID = three times daily.

II. ACID-BASE DISORDERS

A. Normal Homeostasis

1. Normal values

Table 17. Normal Blood Gas Values

Variables	Arterial Blood	Mixed Venous Blood
pH	7.35–7.45	7.31–7.41
P _{CO} ₂	35–45	41–51
P _O ₂	80–100	35–40
HCO ₃	22–26	22–26
Base excess	-2 to +2	-2 to +2
O ₂ saturation	> 95%	70%–75%

HCO₃ = bicarbonate.

2. Interpreting ABGs

- Acidemia (pH less than 7.35) versus alkalemia (pH greater than 7.45)
- Acidemia and alkalemia refer to an abnormal pH being either low or high, respectively. Acidosis and alkalosis refer to the metabolic or respiratory processes that led to the abnormal pH. Although the terms *emia* and *osis* are similar, they are different.

Table 18. Adverse Effects of Severe Acidemia (pH 7.25 or less)

Impaired cardiac output	Increased metabolic demands
Peripheral ischemia (centralization of blood)	Insulin resistance
Increased pulmonary vascular resistance	Decreased ATP synthesis
Hypotension	Increased protein breakdown
Increased risk of arrhythmias	Hyperkalemia
Decreased catecholamine responsiveness	Diaphragmatic fatigue/dyspnea
Obtundation/coma	Hyperventilation

Table 19. Adverse Effects of Severe Alkalemia (pH of 7.55 or greater)

Arteriolar constriction	Hypokalemia
Hypotension	Hypophosphatemia
Increased risk of arrhythmias	Hypocalcemia/tetany
Decreased coronary blood flow/decreased angina threshold	Organic acid production
Seizures	Hypoventilation/hypercapnia/hypoxemia
Lethargy, delirium, stupor	

For simple acid-base disorders, identify pH, P_{CO_2} , and HCO_3^- in that order. Whichever side of 7.40 the pH is on, the respiratory or metabolic processes that coincide with that pH abnormality are the primary etiology. If the pH is less than 7.40, an elevated P_{CO_2} (respiratory acidosis) or a decreased HCO_3^- (metabolic acidosis) is the primary etiology. If the pH is greater than 7.40, a decreased P_{CO_2} (respiratory alkalosis) or an increased HCO_3^- (metabolic alkalosis) is the primary etiology. An easy introductory overview to acid-base disorders by Haber is provided in the references (West J Med 1991;155:146-51).

However, sometimes more than one primary abnormality is present, or the anticipated compensatory process (metabolic or respiratory) is inadequate and may be contributing to the acid-base disorder. As a result, various formulas have been developed to predict what may be considered adequate compensation. However, many of these mathematical equations have limitations in their clinical utility and accuracy (J Trauma Acute Care Surg 2012;73:27-32; Clin J Am Soc Nephrol 2007;2:162-74; Crit Care Med 2007;35:1264-70; Am J Respir Crit Care Med 2000;162:2246-51; Arch Intern Med 1992;152:1625-9) and can be difficult to memorize (West J Med 1991;155:146-51).

In addition, the issue of mixed acid-base disorders is confounded by several factors that can lead to errors in interpreting acid-base disorders. These include non-steady-state conditions as well as the inability for the patient to adequately compensate through the respiratory pathway because of mechanical ventilator restrictions. Some of the more common equations for assessing acid-base disorders are discussed later in this chapter.

3. Use of base excess
 - a. Reflects the amount of base needed in vitro to return the plasma pH to 7.40 at standard conditions (P_{CO_2} 40 mm Hg, 37°C)
 - b. Base excess reflects the metabolic component to interpreting the ABG. Some have described its use as a means for almost freeing the clinician from memorizing the “acid-base” correction formulas (described as follows). Despite its simplicity, it has limitations (J Trauma Acute Care Surg 2012;73:27-32). Crystalloid resuscitation (leading to hyperchloremic acidosis), exogenous bicarbonate (HCO_3^-) administration, ethanol ingestion, and acetate/ HCO_3^- buffer in hemodialysis or CRRT solutions can lead to erroneous base excess calculations and errors in interpretation (J Trauma Acute Care Surg 2012;73:27-32).
4. Compensatory response to acid-base disorders

Table 20. Anticipated Compensation to Acid-Base Disorders (Crit Care 2000;4:6-14)

Primary Disorder	Serum Bicarbonate (mEq/L)	Anticipated P_{CO_2} (mm Hg)
Metabolic acidosis	≤ 22	$(1.5 \times HCO_3^-) + 8 (\pm 2)$
Metabolic alkalosis	≥ 28	$(0.7 \times HCO_3^-) + 21$
Primary disorder	P_{CO_2} (mm Hg)	Anticipated serum bicarbonate (mEq/L)
Respiratory acidosis (acute) ^a	> 45	$[(P_{CO_2} - 40)/10] + 24$
Respiratory acidosis (chronic) ^a	> 45	$[(P_{CO_2} - 40)/3] + 24$ Or HCO_3^- should increase by ~4 mEq/L per 10-mm Hg increase in $P_{CO_2} > 40$
Respiratory alkalosis (acute) ^a	< 35	$24 - [(40 - P_{CO_2})/5]$
Respiratory alkalosis (chronic) ^a	< 35	$24 - [(40 - P_{CO_2})/2]$ Or For each 10-mm Hg decrease in P_{CO_2} , HCO_3^- should decrease by ~5 mEq/L

^aCompensation is different for acute versus chronic respiratory disorders because it takes about 2 days for the kidneys to adapt to a persistent change in respiratory status.

B. Respiratory Acidosis

1. Make sure it is not caused by excessive sedation/analgesia or overfeeding with EN/PN.
2. Metabolic compensation – See Table 19.

C. Respiratory Alkalosis

1. Make sure the patient is getting adequate sedation/analgesia, fever/pneumonia is being treated; nicotine and drug withdrawal regimen is/are appropriate.
2. Metabolic compensation – See Table 19.

D. Metabolic Acidosis

1. Use of the serum anion gap (AG)

- a. Used to determine the etiology for the metabolic acidosis. AG is the difference between major cations and anions in blood (trying to detect whether there is an abundance of unmeasured anions).

$$AG = Na - (Cl + HCO_3)$$

- b. Normal range is about 3–14 mEq/L. Some clinicians will include serum potassium when calculating cations (and the normal AG will need to be adjusted), but this is uncommon.
- c. Adjust AG for serum albumin (Crit Care Med 1998;26:1807-10). The difference in serum albumin concentration (grams per deciliter) from normal should be multiplied by 2–2.5 and added to the anions (chloride and bicarbonate).

$$\text{Albumin adjusted AG} = Na - Cl - HCO_3 - (2.5 \times [4 - \text{serum albumin}])$$

Some clinicians also adjust for serum phosphorus (Crit Care Med 2007;35:2630-6). Serum phosphorus (milligrams per deciliter) can be multiplied by 0.5 and added to anions, and lactate can also be included but is not common in routine clinical practice. Using this method (and including serum potassium), the adjusted AG (or sometimes called the strong ion gap when referring to the physico-chemical methodology for interpreting acid-base disorders) should be close to 0 (± 2) if the patient does not have an AG acidosis.

- d. Causes of an AG acidosis: One easy mnemonic to remember (there are others) is A MUD PIE:

A = Aspirin (or other salicylates)

M = Methanol

U = Uremia (including rhabdomyolysis)

D = Diabetes (diabetic ketoacidosis)

P = Paraldehyde

I = Infection or ischemia (lactic acidosis)

E = Ethylene glycol or ethanol toxicity

- e. Types of lactic acidosis (lactate greater than 18/dL and pH less than 7.35)

- i. Type A: Hypoperfusion (cardiogenic or septic shock, regional ischemia, severe anemia)

- ii. Type B: Metabolic – No tissue hypoxia

(a) B1 = sepsis without shock, liver disease, leukemia, lymphoma, AIDS

(b) B2 = drugs/toxins (metformin, didanosine/stavudine/zidovudine, ethanol, linezolid, propofol, propylene glycol toxicity caused by intravenous lorazepam or pentobarbital), nitroprusside (cyanide) toxicity

(c) B3 = inborn errors of metabolism (pyruvate dehydrogenase deficiency)

- f. Causes of a normal AG acidosis

2. Another easy mnemonic to remember (there are others) is ACCRUED.

A = Ammonium chloride/acetazolamide (urine bicarbonate loss)

C = Chloride intake (PN, intravenous solutions)

- C = Cholestyramine (GI bicarbonate loss)
 R = Renal tubular acidosis: Types I, II, and IV
 U = Urine diverted into the intestine (e.g., ileal conduit, vesicoenteric fistula)
 E = Endocrine disorders (e.g., aldosterone deficiency)
 D = Diarrhea or small/large bowel fluid losses (e.g., enterocutaneous fistulas)
3. Use of the delta ratio for determining mixed acid-base disorders
- Delta ratio =

$$\Delta AG/\Delta HCO_3 = (\text{measured AG} - \text{normal AG})/(\text{normal HCO}_3 - \text{measured HCO}_3) =$$

$$(AG-14)/(24 - \text{measured HCO}_3)$$

Table 21. Interpreting Delta Ratio^a

Delta Ratio	Assessment
< 0.4	Hyperchloremic normal AG acidosis
< 1	High AG acidosis and normal AG acidosis
1–2	AG acidosis
> 2	High AG acidosis and concurrent metabolic alkalosis OR a preexisting compensated respiratory alkalosis

^aThe ratio should be used cautiously in interpreting mixed acid-base disorders, given that it is associated with poor sensitivity because of several influencing factors (J Am Soc Nephrol 2007;18:2429-31). This author prefers to look at current clinical state/diagnoses and recent therapeutic interventions for the patient to ascertain whether a mixed acid-base disorder is potentially present.

4. An alternative method (and perhaps a simpler approach) to the delta ratio is to calculate the “excess gap” compared with the AG (West J Med 1991;155:146-51).
 Excess gap = AG – 14.
5. The excess gap is then added to the measured serum bicarbonate concentration. If the sum is less than a normal serum bicarbonate concentration (e.g., 28–30 mEq/L), a mixed AG and non-AG acidosis is present. If the sum is greater than a normal HCO₃ concentration, the patient likely has an AG acidosis and concurrent metabolic alkalosis.
6. Evaluation of respiratory compensation: See Table 19.
7. Treatment
- Aggressive interventional therapy unnecessary until pH less than 7.20–7.25
 - Treat primary etiology! This should be the focus of treating the acid-base disorder.
 - Intravenous sources of alkali – Done conservatively in conjunction with treating primary disorder whenever possible. The intent is not to normalize the pH but to improve the pH (definitely avoid overcorrection).
 - Sodium bicarbonate – Most commonly used
 - Sodium acetate – Available in PN solutions
 - Sodium citrate – Used orally for patients with chronic kidney injury
 - Total bicarbonate dose (mEq) = 0.5 x Wt (kg) x (24 - HCO₃)
 - Give one-third to one-half of the calculated total dose (or 1–2 mEq/kg) for several hours to achieve a pH of around 7.25 (avoid boluses if possible).
 - Once the pH is around 7.25 or greater, slower correction without increasing bicarbonate more than 4–6 mEq/L to avoid exceeding the target pH
 - Serial ABGs (e.g., every 6 hours); watch rate of decrease in serum potassium
 - Use of sodium bicarbonate injection is controversial in patients with lactic acidosis (Curr Opin Crit Care 2008;14:379-83).
 - Adverse effects of excess sodium bicarbonate:
 - Hypernatremia, hyperosmolality, volume overload

- ii. Hypokalemia, hypocalcemia, hypophosphatemia
- iii. Paradoxical worsening of the acidosis (if the fractional increase in PCO_2 production exceeds the fractional bicarbonate change)
- iv. Over-alkalinization

Patient Case

Questions 8 and 9 pertain to the following case.

A 60-year-old woman (weight 80 kg) was admitted to the hospital after 1 week of severe diarrhea. She presents with clinical evidence of dehydration (hypotension, tachycardia, decreased urine output) and is weak. Her serum laboratory values are as follows: Na 145 mEq/L, K 3.0 mEq/L, Cl 118 mEq/L, total CO_2 18 mEq/L, BUN 29 mg/dL, SCr 0.9 mg/dL, glucose 122 mg/dL, calcium 9.1 mg/dL, phosphorus 3.7 mg/dL, magnesium 1.4 mg/L, albumin 3.9 g/dL, and lactate 1.6 mmol/L. Her ABG is pH 7.29, Po_2 93 mm Hg, PCO_2 34 mm Hg, HCO_3 17 mEq/L, and base excess -5 mEq/L. She has a 30 pack/year smoking history.

8. Which best describes the patient's type of acid-base disorder?
 - A. Hyperchloremic, normal AG acidosis
 - B. AG acidosis
 - C. AG acidosis with hyperchloremia
 - D. Respiratory alkalosis with concurrent metabolic alkalosis
9. Which is the most appropriate initial fluid therapy for this patient?
 - A. 0.45% sodium chloride with potassium chloride 20 mEq/L
 - B. 0.9% sodium chloride with potassium chloride 20 mEq/L
 - C. Lactated Ringer solution
 - D. 5% dextrose

E. Metabolic Alkalosis: pH greater than 7.45; symptoms are not usually severe until pH is greater than 7.55–7.60.

1. Assessment (to help guide treatment) based on urinary chloride
 - a. Saline responsive (urinary chloride less than 10 mEq/L)
 - i. Excessive gastric fluid losses
 - ii. Diuretic therapy (especially loop diuretics)
 - iii. Dehydration (contraction alkalosis)
 - iv. Hypokalemia
 - v. (Over-) Correction of chronic hypercapnia
 - b. Saline resistant (urinary chloride greater than 20 mEq/L)
 - i. Excessive mineralocorticoid activity (e.g., hydrocortisone)
 - ii. Excessive alkali intake
 - iii. Profound potassium depletion (serum potassium less than 3 mEq/L)
 - iv. Excess licorice (mineralocorticoid) intake
 - v. Massive blood transfusion
 - c. Respiratory compensation (highly variable and may not be possible for ventilator-dependent patients)
 - d. Intravascular volume status (important for saline-responsive alkalemia)
2. Treatment – Saline-responsive alkalemia
 - a. Treat underlying cause (if possible).
 - b. Decreased intracellular volume? Give intravenous 0.9% sodium chloride infusion (with potassium chloride, if necessary).

- c. Increased intracellular volume? Acetazolamide 250–500 mg orally or intravenously once to four times daily plus potassium chloride if necessary (Intensive Care Med 2010;36:859-63; Crit Care Med 1999;27:1257-61; Acta Anaesthesiol Scand 1983;27:252-4).
 - i. Hydrochloric acid therapy if alkalosis persistent or initial pH greater than 7.6
 - (a) N or 0.2 N of hydrochloric acid (use 0.2 N for patients requiring fluid restriction). Hydrochloric acid should be given by central venous administration, and the solution must be in a glass bottle.
 - ii. Dosage of hydrochloric acid:
 - (a) Chloride deficit (Arch Surg 1975;110:819-21):
Dose (mEq) = 0.2 L/kg x Wt (kg) x (10^3 – serum chloride)
 - (b) Bicarbonate excess (J Am Soc Nephrol 2000;11:369-75):
Dose (mEq) = 0.5 L/kg x Wt (kg) x (serum bicarbonate – 24)
 - (c) Dickerson empiric approach: Give one-half of calculated dose over 12 hours, repeat ABG at 6 and 12 hours after initiating hydrochloric acid infusion, and readjust infusion rate if necessary; continue therapy and monitoring until pH less than 7.5; then stop and reassess
 3. Treatment – Saline-unresponsive alkalosis: Treat underlying cause (if possible).
 - a. Exogenous corticosteroids – Decrease dose or use drug with less mineralocorticoid effect.
 - b. Excessive alkali intake – Alter regimen.
 - c. Profound hypokalemia (serum potassium less than 3 mEq/L) – Aggressive potassium supplementation
 - d. Rare causes: Endogenous mineralocorticoid excess (Bartter or Gitelman syndrome) – Spironolactone, amiloride, or triamterene; consider surgery
 - e. Liddle syndrome: Amiloride or triamterene
- F. The Stewart or Physicochemical Approach to Acid-Base Disorders – This emerging approach to acid-base disorders is based on charge differences between ions. Essentially, acid-base disorders can be defined by differences between the activity of abundant cations (sodium, potassium, ionized calcium, ionized magnesium) and the activity of all abundant anions (chloride, lactate). The influence of albumin and serum phosphate is also considered. Although this technique has advantages over the traditional method discussed herein, the Stewart approach has been criticized by others because it offers no diagnostic or prognostic advantages over the traditional/bicarbonate analysis (Crit Care Med 2007;35:1264-70). The reader is referred elsewhere for additional information on this methodology (J Trauma 2009;66:1045-51; Crit Care Med 2004;32:1120-4; J Crit Care 1995;10:51-5).

III. NUTRITION SUPPORT

- A. Nutritional Assessment
 1. Classes of malnutrition
 - a. American Society for Parenteral and Enteral Nutrition (ASPEN) international consensus nomenclature (JPEN J Parenter Enteral Nutr 2010;34:156-9)
 - i. Starvation-related malnutrition (e.g., anorexia nervosa)
 - ii. Chronic disease–related malnutrition (e.g., Crohn’s disease, organ failure)
 - iii. Acute disease or injury-related malnutrition (e.g., major infection, burns, trauma)
 - b. “Determination of Nutrition Risk – recommended by 2016 SCCM/ASPEN guidelines (JPEN J Parenter Enteral Nutr 2016;40:159-211)
 - i. Nutritional Risk Screening (NRS 2002; Clin Nutr 2003;22:321-36)

Table 22. Determination of Nutrition Risk by NRS 2002 score

Nutritional Status		Severity of Disease	
	Score		Score
Normal Nutritional Status	0	Normal nutritional requirements	0
Wt loss > 5% in 3 months or food intake < 50% to 70% of normal in preceding week	1	Hip fracture, chronic patients with acute complications (e.g., cirrhosis, COPD, DM, oncology)	1
Wt loss > 5% in 2 months or body mass index (BMI) 18.5 to 20.5 + impaired general condition or food intake < 25% to 50% of normal in preceding week	2	Major abdominal surgery, stroke, pneumonia, hematologic malignancy	2
Wt loss > 5% in 1 month (~15% in 3 months) or BMI < 18.5 + impaired general condition or food intake 0 to 25% of normal in preceding week	3	Head injury, bone marrow transplantation, ICU patient	3
Add the two scores (nutritional status + severity of disease). If age 70 years or greater, add 1 to total score. If age-corrected score 3 or greater, start nutritional support.			

ii. Nutrition Risk in the Critically Ill (NUTRIC) score (Crit Care 2011;15:R268)

Table 23. Determination of Nutrition Risk by NUTRIC score

Variable	Range	Points
Age, yrs	< 50	0
	50 - 74	1
	> 74	2
APACHE II	< 15	0
	15 -19	1
	20 - 28	2
	> 28	3
SOFA	< 6	0
	6 – 9	1
	> 9	2
Number of comorbidities	0 - 1	0
	> 9	1
Days from hospital to ICU admission	0 - < 1	0
	> 1	1
High Score = 6 to 10 points: Associated with worse clinical outcomes and are most likely to benefit from aggressive nutrition therapy		
Low Score = 0 to 5 points: These patients have a low nutrition risk		

- c. “Classic” definition – not in favor with conventional assessment techniques and tools
 - i. Marasmus (e.g., decreased fat/muscle protein stores but normal serum proteins)
 - ii. Kwashiorkor (e.g., normal fat, decreased muscle protein, decreased serum proteins)
 - iii. Kwashiorkor-Marasmus mix (decreased fat, muscle protein, and serum proteins)
- d. Based on weight loss – A 10% unintentional weight loss within a 6-month period is considered significant.

- e. Based on current weight
 - i. Mild malnutrition: 80%–89% ideal body weight (IBW)*
 - ii. Moderate malnutrition: 70%–79% IBW*
 - iii. Severe malnutrition: Less than 70% IBW*
 - iv. Obese: Greater than 130% IBW*

*IBW: Female = 45.5 kg/5 ft plus 2.3 kg per inch above 5 ft
 Male = 50 kg/5 ft plus 2.3 kg per inch above 5 ft
- f. Based on body mass index (BMI) = weight (kg)/height² (m²)
 - i. Less than 18.5 kg/m²: Underweight
 - ii. 18.5–24.9 kg/m²: Normal
 - iii. 25–29.9 kg/m²: Overweight
 - iv. 30–34.9 kg/m²: Class I obesity
 - v. 35–39.9 kg/m²: Class II obesity
 - vi. Greater than 40 kg/m²: Class III obesity
- g. Empiric weight adjustment for amputations

Table 24. Body Compartments' Contribution to Body Weight (J Am Diet Assoc 1995;95:215-8)

Body Part Amputation	Approximate Contribution to Body Weight (%)
Foot	1.5
Calf, foot	5.9
Leg (from hip)	16
Hand	0.7
Hand and forearm	2.3
Arm	5

2. Serum proteins used in nutritional assessment
 - a. Albumin: Half-life 20 days
 - i. Depletion: Mild 2.8–3.5 g/dL, moderate 2.1–2.7 g/dL, severe less than 2.1 g/dL
 - ii. Limitations: Long half-life, large body pool; is a negative acute-phase reactant protein that decreases in response to infection, inflammation, surgery, injury, or other acute event
 - b. Transferrin: Half-life 7 days
 - i. Depletion: Mild 150–250 mg/dL, moderate 100–150 mg/dL, severe less than 100 mg/dL
 - ii. Limitations: Increased with iron deficiency; is a negative acute-phase reactant protein that decreases in response to infection inflammation, surgery, injury or other acute event
 - c. Prealbumin: Half-life 2 days
 - i. Depletion: Mild 10–15 mg/dL, moderate 7–10 mg/dL, severe less than 7 mg/dL
 - ii. Limitations: Increased with CKD; is a negative acute-phase protein that decreases in response to infection, inflammation, surgery, injury, or other acute event. Some institutions will determine C-reactive protein concentration as a measure of inflammation to assess prealbumin concentration.
 - d. Physical examination: Loss of subcutaneous body fat, muscle atrophy (including temporal wasting), presence of lower extremity edema and/or ascites
 - e. Subjective Global Assessment (JPEN J Parenter Enteral Nutr 1987;11:8-13): Incorporates overall evaluation by incorporating five elements of the patient's history (presence of weight loss during the past 6 months; dietary intake change; presence of significant adverse GI symptoms such as diarrhea, vomiting, nausea, or anorexia that were persistent for more than 2 weeks; physical functional

capacity including difficulty with ambulation/normal activities or bed/chair-ridden, and metabolic demands of the patient's disease state); and physical examination (presence of subcutaneous fat, muscle wasting, edema, ascites). The final Subjective Global Assessment rating is classified as A = well nourished, B = moderately malnourished, or C = severely malnourished.

B. Energy Requirements

Assessing caloric requirements: Indirect calorimetry – Measured energy expenditure by oxygen consumption and CO₂ production – The “gold standard”

1. Respiratory quotient (VCO₂/VO₂); 1 for carbohydrate oxidation; 0.7 for fat oxidation; 0.8 for protein oxidation; greater than 1 usually implies overfeeding (net fat synthesis), less than 0.7 suggests ketosis or an error in measurement (too much fraction of inspired oxygen [FIO₂] variability at higher FIO₂ concentrations)
2. Organization guideline recommendations

Table 25. Guideline Recommendations for Caloric Intake

Organization	Recommendation
American College of Chest Physicians (Chest 1997;111:769-78)	25 kcal/kg/day; increase by 10%–20% with SIRS
SCCM/ASPEN (JPEN J Parenter Enteral Nutr 2016;40:159-211)	25–30 kcal/kg/day or use of indirect calorimetry (lesser amounts may be given to medical ICU patients with ARDS for the first week)
ESPEN PN (Clin Nutr 2009;28:387-400)	25 kcal/kg/day (in the absence of measured REE)
ESPEN EN (Clin Nutr 2006;25:210-23)	20–25 kcal/kg/day (during acute phase) 25–30 kcal/kg/day (during recovery)
ASPEN Obesity Guidelines (JPEN J Parenter Enteral Nutr 2013;37:714-44)	< 14 kcal/kg actual weight/day or 50%–70% of estimated requirements when given with a high-protein intake
Eastern Association for Surgery of Trauma (J Trauma 2004;57:660-9)	25–30 kcal/kg/day or 1.2–1.4 x BEE (Harris-Benedict equations) or 1.2–1.4 x BEE (Harris-Benedict equations), 30 kcal/kg/day (1.4 x BEE) for patients with TBI, 22–25 kcal/kg/day for patients with paraplegia, 20–22 kcal/kg for patients with quadriplegia

BEE = basal energy expenditure; ESPEN = European Society for Clinical Nutrition and Metabolism; REE = resting energy expenditure; SCCM = Society of Critical Care Medicine; SIRS = systemic inflammatory response syndrome.

3. Predictive methods

- a. Mifflin-St. Jeor equations (preferred for non-ventilator-dependent patients with obesity with AKI or CKD or hepatic encephalopathy when a hypocaloric, high-protein regimen is not possible)
 - i. Women = $(10 \times \text{Wt}) + (6.25 \times \text{Ht}) - (5 \times \text{A}) - 161^*$
 - ii. Men = $(10 \times \text{Wt}) + (6.25 \times \text{Ht}) - (5 \times \text{A}) + 5^*$

*Age (years); Ht (centimeters); Wt = actual body weight (kilograms).
- b. Penn State equation (preferred for ventilator-dependent patients with obesity with AKI or CKD or hepatic encephalopathy when a hypocaloric, high-protein regimen is not possible):
 $\text{REE} = (\text{Mifflin} \times 0.96) + (\text{Tmax} \times 167) + (\text{Ve} \times 31) - 6212^*$

*REE = resting energy expenditure; Tmax = maximum temperature in degrees Celsius; Ve = minute ventilation, liters per minute.
- c. Modified Penn State equation (preferred for ventilator-dependent patients with obesity 60 years or older with AKI or CKD or hepatic encephalopathy when a hypocaloric, high-protein regimen is not possible)
 $\text{REE} = (\text{Mifflin} \times 0.71) + (\text{Tmax} \times 85) + (\text{Ve} \times 64) - 3085^*$

- d. Basal energy expenditure (BEE) – Harris-Benedict equations (preferred for small adults and older adult patients)
 - i. Women = $655 + (9.6 \times \text{Wt}) + (1.7 \times \text{Ht}) - (4.7 \times \text{A})^*$
 - ii. Men = $66 + (13.7 \times \text{Wt}) + (5 \times \text{Ht}) - (6.8 \times \text{A})^*$

*Wt (kilograms), Ht (centimeters), Age (years).
4. Adverse effects of overfeeding – Do not exceed 5 mg/kg/minute of glucose/carbohydrate (Ann Surg 1979;190:274-85); limit total caloric intake (do not exceed 1.3–1.5 x measured resting energy expenditure); do not exceed intravenous fat intake of 2.5 g/kg/day (most clinicians limit intravenous fat to around 1.5 g/kg/day or less).
 - a. Hypercapnia: It was traditionally thought that excessive glucose intake alone was responsible for hypercapnia observed during overfeeding. However, studies of acutely ill patients showed that aggressive feeding resulted in marked increases in CO₂ production (Ann Surg 1980;191:40-6; JAMA 1980;243:1444-7). Substitution of glucose kilocalories with lipid decreases CO₂ production (Anesthesiology 1981;54:373-7) when overfeeding but does not alter CO₂ production if not overfeeding (e.g., 1.3 x BEE) (Chest 1992;102:551-5). Because most institutions lack the ability to measure energy expenditure, estimates are used. If the patient experiences hypercapnia without a known cause, the nutrition therapy should be suspected and the caloric intake empirically decreased (especially if the patient is having difficulty weaning from the ventilator).
 - b. Hyperglycemia: In a retrospective study of 102 PN-fed patients not predisposed to hyperglycemia, dextrose intakes in excess of 5 mg/kg/minute resulted in substantial hyperglycemia (blood glucose [BG] greater than 200 mg/dL) in 18 of 37 patients (Nutr Clin Pract 1996;11:151-6). Patients with stress-induced hyperglycemia or diabetes are even more susceptible to hyperglycemia with EN or PN.
 - c. Fatty infiltration of the liver: May be because of overfeeding with fat or carbohydrate. Usually presents as a cholestatic liver disease (increased gamma-glutamyl transferase (GGT), alkaline phosphatase, and ultimately bilirubin) after at least 1 week to 10 days of overfeeding (Arch Surg 1978;113:504-8). May be transient or reversible or can progress to end-stage liver disease. Throughout a few weeks, patients can appear jaundiced. Patients with critical illness and/or infections tend to be more susceptible to hepatic steatosis compared with non-critically ill patients (possibly because of an exaggerated inflammatory process). Although treatment with fish oil appears promising in infants and children (Nutr Clin Pract 2013;28:30-9; Ann Surg 2009;250:395-402), data for adults are lacking. Usual treatment for adult patients with suspected PN-associated liver disease is first to ensure that the patient is not being overfed and given a mixed-fuel PN solution, followed by cyclic PN (PN is infused for part of the day). Reinstating EN as soon as possible (if possible) is of utmost importance.
5. Recommendations for caloric requirements*
 - a. Maintenance OR elective surgery: 25 kcal/kg/day
 - b. Malnourished, nutritionally depleted: 1.4–1.5 x BEE
 - c. Medical ICU patients: 25–30 kcal/kg/day (most clinicians lean toward the lower intake)
 - d. Minor infection or surgery: 25–30 kcal/kg/day
 - e. Major surgery/trauma/sepsis: 30–32 kcal/kg/day (do not exceed 35 kcal/kg/d)
 - f. Obese (hypocaloric) nutrition: 22–25 kcal/kg IBW/day or less
 - g. Older (older than 65 years): 1.3–1.5 x BEE
 - h. Smaller patients (weight 50 kg or less): 1.3–1.5 x BEE

*These are general recommendations, based on the lack of measured energy expenditure, from this author's practice, which are subject to exception depending on prevailing disease states, organ failures, extent of malnourishment, provision of paralytic drugs/pentobarbital/propofol, and types of injuries.

C. Protein Requirements

1. Guideline recommendations

Table 26. Guideline Recommendations for Protein Intake

Organization	Recommendation
American College of Chest Physicians (Chest 1997;111:769-78)	1.2–1.5 g/kg/day; 1.5–2 g/kg/day not to exceed 2 g/kg/day with SIRS; routine NB determinations recommended
SCCM/ASPEN (JPEN J Parenter Enteral Nutr 2016;40:159-211)	1.2–2 g/kg/day; higher amounts are likely needed for multiple trauma or burns
ESPEN PN (Clin Nutr 2009;28:387-400)	1.3–1.5 g/kg IBW/day
ESPEN EN (Clin Nutr 2006;25:210-23)	Not given
ASPEN Obesity Guidelines (JPEN J Parenter Enteral Nutr 2013;37:714-44)	1.2 g/kg actual weight/day or 2–2.5 g/kg IBW/day when given with a hypocaloric regimen
Eastern Association for Surgery of Trauma (J Trauma 2004;57:660-9)	1.25–2 g/kg/day; 2 g/kg/day for burns

2. Recommendations for protein requirements*

- a. Maintenance or elective surgery: 0.8–1 g/kg/day
- b. Minor infection or surgery: 1.2–1.5 g/kg/day
- c. Malnourished, nutritionally depleted: 1.5 g/kg/day
- d. Medical ICU patients: 1.5–2 g/kg/day
- e. Major surgery/trauma/sepsis: 2–2.5 g/kg/day
- f. Renal failure
 - i. AKI: 0.6–1 g/kg/day
 - ii. CKD: 0.6–1 g/kg/day
 - iii. Hemodialysis: 1–1.5 g/kg/day
 - iv. CRRT: 2–2.5 g/kg/day
- g. Obese, hypocaloric
 - i. BMI less than 40 kg/m²: 2 g/kg IBW/day
 - ii. BMI of 40 kg/m² or greater: 2.5 g/kg IBW/day

*Ideally, this intake should be adjusted according to the results of an NB determination, when possible.

Patient Case

10. A 40-kg woman admitted to the trauma ICU receives a PN solution containing 350 g of dextrose, 160 g of amino acids, and 80 g of lipid daily. She has normal renal and hepatic function. Her most recent ABG from the morning shows a pH of 7.30, Pco₂ 55 mm Hg, Po₂ 96 mm Hg, and HCO₃ 31 mEq/L. Her fingerstick BG values from the past 24 hours are 180–200 mg/dL. Which would be best to recommend regarding her PN?

- A. Decrease dextrose to 175 g/day, and increase lipid to 120 g/day.
- B. Add 20 units of regular human insulin per day to the PN solution.
- C. Decrease all the macronutrients by about one-half.
- D. Increase the acetate content of the PN solution.

3. Assessing protein requirements: NB
 - a. $NB = \text{nitrogen in } (N_{in}) - \text{nitrogen out } (N_{out})$
 - b. To calculate N_{in} :
 - i. Add all daily protein intake sources together, including the protein in EN, liquid protein supplements, oral dietary supplements, and/or PN solution.
 - ii. Convert protein intake (grams per day) to nitrogen intake (grams per day):
 $N_{in} \text{ (g/day)} = \text{protein (g/day)} / 6.25$ (assumes good-quality protein as 16% nitrogen content).
 - iii. To calculate N_{out} : $N_{out} \text{ (g/day)} = (UUN + 4 \text{ g})^* + \text{BUN change correction (if necessary)}$, where UUN is 24-hour urine urea nitrogen excretion (grams per day).
 - iv. *For patients with high UUN excretion (e.g., greater than 15 g/day), $UUN/0.85 + 2$ may be a more reliable estimate of total urinary nitrogen excretion loss and stool/integumentary losses (Nutrition 2005;21:332-8).
- BUN Change Estimation**
- BUN adjustment (g/day) = [change in BUN (mg/dL) x 0.01] x [body water (L/kg) x Wt (kg)]
 Use only if BUN change is 5 mg/dL or greater.
 Body water = 0.6 L/kg for men; 0.55 L/kg for women
- v. Calculate the NB: $NB \text{ (g/day)} = N_{in} \text{ g/day} - N_{out} \text{ g/day}$.
 - vi. Measured versus predicted creatinine clearance (for gross assessment of adequacy in the 24-hour urine collection)
 - vii. Serum prealbumin changes are unreliable because of the influence of stress/inflammation; some clinicians will obtain a serum C-reactive protein concentration together with a serum prealbumin concentration for assessment.
 4. Does more protein really make a difference?
 - a. Weijs et al. (2012) (JPEN J Parenter Enteral Nutr 2012;36:60-8): 28-day mortality improved in those who received an average of 1.3 g/kg/day versus 1.1 or 0.8 g/kg/day (886 mixed ICU patients).
 - b. Allingstrup et al. (2012) (Clin Nutr 2012;31:462-8): 28-day mortality improved in those who received an average of 1.5 g/kg/day versus 1.1 or 0.8 g/kg/day (113 mixed ICU patients).

Patient Case

Questions 11–13 pertain to the following case.

A 60-year-old man (weight 65 kg; about 90% IBW) is admitted for acute pancreatitis. After 4 days, he still has significant abdominal pain and distension without resolution. He has a fever, and blood/urine cultures are obtained. A CT scan of the abdomen reveals an ileus and an intra-abdominal abscess. He is given a goal PN regimen containing 300 g of dextrose, 100 g of amino acids, and 40 g of 20% lipids daily.

11. Which best depicts the kilocalories and protein this regimen will provide?
 - A. 26 kcal/kg/day and 1 g/kg/day
 - B. 26 kcal/kg/day and 1.5 g/kg/day
 - C. 28 kcal/kg/day and 1.5 g/kg/day
 - D. 30 kcal/kg/day and 1.5 g/kg/day

Patient Case (*continued*)

A 24-hour urine collection was done to determine the NB. The UUN concentration was 600 mg/dL, and the urine volume output was 2000 mL. The patient's BUN was unchanged during the NB determination.

12. Which most accurately depicts the patient's NB?
 - A. -4 g/day
 - B. 0 g/day
 - C. +2 g/day
 - D. +4 g/day
13. Which changes would be best to make to the patient's PN regimen?
 - A. Increase the protein and nonprotein energy content.
 - B. Increase the protein content, and decrease the nonprotein energy content.
 - C. Increase the nonprotein content.
 - D. No change is necessary.

D. Principles of EN and PN

1. Indications for EN: If the patient is unable to eat adequate amounts to achieve goal nutritional intakes. EN is preferred to PN because EN has fewer infectious complications (JPEN J Parenter Enteral Nutr 2009;33:277-316; Ann Surg 1992;215:503-13). This position has been challenged recently because of newer literature indicating a reduction in infectious complications with PN as compared with the past literature (likely because of improvements in catheter care and PN) with the difference in infectious complications between EN and PN narrowing.
 - a. Lack of bowel sounds, flatus, or bowel movement is not a contraindication for EN because these are nonspecific indicators of GI function (JPEN J Parenter Enteral Nutr 2009;33:277-316; SCCM/ ASPEN 2009).
 - b. Evidence of ileus (e.g., dilated loops of bowel on abdominal radiography) is, however, a contraindication for EN.
 - c. High NG output (greater than around 800 mL NG output) in a 24-hour period may indicate delayed gastric emptying, and the patient may not be ready for EN when fed into the stomach and post-pyloric feeding is not possible. If the patient's GI function appears to be improving, clamp NG tube for 4 hours and check GRV (if GRV is less than about 300 mL and the abdomen is not distended, the patient is probably ready for gastric feeding). Note: This is our Nutrition Support Service's empiric practice and cannot be found in any guideline recommendations.
 - d. Refusal to eat/anorexia is not an absolute contraindication for EN. Ensure appropriate dietary preferences, and add high-calorie/protein liquid supplements to meals and bedtime snack first.
2. EN formulas

Table 27. EN Formulas

Product Category	Indication	Macronutrients	Additional Comments	Examples
Standard tube feeding	Minimal stress	1–1.2 kcal/mL Protein 40–50 g/L	Polymeric, 300–500 mOsm/kg, fiber	Jevity, Nutren 1.0, Fibersource HN
Volume restricted	Congestive heart failure, fluid-restricted patients	2 kcal/mL Protein 60–80 g/L	Polymeric, 700–800 mOsm/kg, fiber	Nutren 2.0, Resource 2.0, TwoCal HN
Renal	AKI (predialysis), renal dysfunction with increased serum potassium, phosphorus, magnesium	2 kcal/mL Protein 30–40 g/L	High calorie, low protein, no or low electrolytes, 600 mOsm/kg, volume restricted, fiber	Renalcal, Suplena
Renal	Renal failure with hemodialysis	2 kcal/mL Protein 80–90 g/L	High calorie, modest electrolytes, volume restricted, 1000 mOsm/kg, fiber	Novasource Renal, Nepro
Increased protein needs	Critically ill patients (especially trauma, surgical, burns)	1 kcal/mL Protein 62 g/L	High-protein content, fiber, isotonic	Replete, Promote
Glucose intolerance	Hyperglycemia, diabetes mellitus	1.2 kcal/mL Protein 60 g/L	Low-carbohydrate content, fiber	Diabetisource AC, Glucerna 1.2
Immune enhancing	Critically ill surgical and trauma patients, perioperative GI cancer	1.5 kcal/mL Protein 90–94 g/L	Additional arginine, glutamine; fish oil	Impact Peptide 1.5, Pivot
Bariatric	Patients with obesity with good renal function	1 kcal/mL Protein 93 g/L	High protein, low calories	Peptamen Bariatric
Elemental diet	Malabsorption, fat intolerance	1–1.5 kcal/mL Protein 50–68 g/L	Low fat/MCT, di/tri-peptides/free AA, no fiber, low residue	Vivonex RTF, Vital
Pulmonary (Not recommended per 2016 SCCM/ ASPEN guidelines)	ARDS, ALI	1.2–1.5 kcal/mL Protein 63–76 g/L	Volume restricted, fish oil, low omega-6 fats	Oxepa, Peptamen AF
Hepatic (not recommended per 2016 SCCM/ASPEN guidelines)	Cirrhosis with hepatic encephalopathy	1.2–1.5 kcal/mL Protein 40–44 g/L	High branched chain, low aromatic AA	NutriHep, Hepatic-Aid II
Protein supplement	High protein needs		Protein	Liquid or powder

AA = amino acids; ALI = acute lung injury; ARDS = acute respiratory distress syndrome; MCT = medium-chain triglyceride.

3. Tube feeding (TF) – Medication interactions: Hold TF 1 hour before and after drug administration (Pharmacotherapy: A Pathophysiologic Approach, 8th ed. New York: McGraw-Hill, 2011:2493-503).
 - *Increase TF rate to account for time off TF.
 - a. Warfarin (Pharmacotherapy 2008;28:308-13)

- b. Phenytoin (Nutr Clin Pract 1996;11:28-31)
 - c. Levothyroxine (J Endocrinol Invest 2014;37:583-7; Nutr Clin Pract 2010;25:646-52)
 - d. Itraconazole (Antimicrob Agents Chemother 1997;41:2714-8)
 - e. Fluoroquinolones (J Antimicrob Chemother 1996;38:871-6)

*Some clinicians have empirically increased the dosage of these drugs while giving continuous enteral feeding rather than holding the EN for 1 hour before and after drug administration. This author discourages this practice, especially for warfarin and phenytoin, because the doses necessary to overcome the effects of drug binding to the continuous EN are potentially toxic when the EN is held or discontinued without a dose adjustment. Others have increased the ciprofloxacin dose to 750 mg twice daily during continuous EN to achieve therapeutic plasma concentrations well above the MIC (minimum inhibitory concentration) for a gram-negative urinary tract infection (J Antimicrob Chemother 1996;38:871-6).
4. Indications for PN
- a. European Society for Clinical Nutrition and Metabolism (ESPEN) PN guidelines (2009) (Clin Nutr 2009;28:387-400): Patients who are not expected to receive EN within 3 days should receive PN within 24–48 hours if EN is contraindicated or if they cannot tolerate EN.
 - b. SCCM/ASPEN (2016) (JPEN J Parenter Enteral Nutr 2016;40:159-211) It is recommended to initiate PN as soon as possible after intensive care unit (ICU) admission if patients have contraindications to EN and are severely malnourished or at “high nutrition risk” as indicated by the NRS 2002 or NUTRIC score. It is also recommended that supplemental PN be initiated in “at risk” patients after 7 to 10 days if patients are not able to meet at least 60% of energy and protein requirements.
 - c. Dickerson interpretation: The approach depends on several factors (e.g., if the patient is malnourished or well nourished before ICU admission, patient acuity). Early nutrition (defined as within 24–72 hours according to published studies) appears to be beneficial for those with prolonged ICU stays and a high level of catabolism, including trauma, TBI, and thermal injury and for some surgical subpopulations. Impact of early nutrition appears more variable with respect to clinical outcome for medical ICU patients and is likely related to a shorter duration in ICU stay and a lower level of catabolism for many patients. Recent literature supports the safe use of PN as a substitute for EN (when EN is contraindicated or when EN delivery is inadequate) with no difference in the incidence of infections.
5. PN formulations
- a. Peripheral versus central venous administration
 - i. Osmolality of peripheral administration is limited to about 800 mOsm/kg.
 - ii. Because of the osmolality issue, peripheral PN solutions are “diluted,” requiring large volumes (contraindicated for fluid-restricted patients and difficult for older patients).
 - iii. Estimating the osmolality of PN solutions:
 Approximate osmolality = [glucose g/L x 5] + [AA% x 100] + [lipid % x 15] + 200*
 *Accounts for electrolytes/vitamins and can be variable, depending on amounts provided.
 AA = amino acids.
 - iv. Phlebitis common with peripheral PN and difficult to use beyond 2–3 days
 - b. Safe practice guidelines for prescribing PN solutions – Should be prescribed in total amount per day (e.g., glucose 200 g/day, amino acids 150 g/day, lipid 30 g/day, fluid volume 2500 mL/day, sodium chloride 60 mEq/day, potassium acetate 80 mEq/day), NOT by concentrations (e.g., 20% dextrose in water, 8% amino acids) or by compounding techniques (e.g., 500 mL of 50% dextrose in water plus 500 mL of 10% amino acids)
 - c. Glucose requirements
 - i. Obligatory requirements for CNS, renal medulla, bone marrow, leukocytes, etc.: Around 130 g/day

- ii. Surgical wound about 80–150 g/day (based on atrioventricular differences and blood flow from a burned limb)
- iii. Caloric contribution of glucose: 3.4 kcal/g (as opposed to carbohydrate 4 kcal/g)
- iv. Mean glucose oxidation rate in critically ill patients is around 5 mg/kg/day (or about 25 kcal/kg/day as glucose). In general, most clinicians avoid exceeding this glucose intake.
- d. Lipid requirements
 - i. Main source is soybean oil – May be given separately from the PN admixture or as part of the PN solution. When given separately from the dextrose/amino acid formulation, the maximum allowable hang time according to the FDA is 12 hours. With recent lipid shortages, olive oil–based intravenous lipid (which provides a more favorable cardiovascular lipid profile in patients on long-term PN) is now available from Canada. Intravenous fish oil requires permission from the FDA.
 - ii. Caloric contribution of intravenous fat emulsion: 10% = 1.1 kcal/mL; 20% = 2 kcal/mL; 30% = 3 kcal/mL or around 11 kcal/g for 10% emulsion, 10 kcal/g for 20% and 30% emulsion
 - iii. Dosage: About 100–150 g weekly (or 1–1.5 g/kg weekly) is enough to prevent essential fatty acid deficiency (EFAD). The FDA states a maximum upper limit of 2.5 g/kg/day in adults, though most clinicians try to keep the daily dose to 1.5 g/kg/day or less.
 - iv. Biochemical evidence for EFAD (the “classic definition” is an increased triene/tetraene [eicosatrienoic acid/arachidonic acid] ratio greater than 0.4) occurs in 30%, 66%, 83%, and 100% of patients after 1, 2, 3, and 4 weeks of fat-free “full-calorie, continuous” PN (Surgery 1978;84:271-7). Clinical signs and symptoms of EFAD usually do not occur until about 2 weeks after biochemical evidence in adults. Because the investigators initiated intravenous lipid emulsion soon after the biochemical appearance of EFAD, only 2 of 32 patients developed clinical evidence suggestive of EFAD. EFAD can occur much sooner for infants and children. Patients with obesity receiving hypocaloric high-protein therapy can maintain normal plasma fatty acid profiles for up to 5 weeks (J Nutr Biochem 1994;5:243-7). Cyclic PN has been suggested to mobilize lipid from endogenous depots, but conclusive data are lacking.
 - v. Clinical symptoms (dry, scaly skin; hair loss; poor wound healing) occur about 2 weeks after biochemical evidence of deficiency in adults. Therefore, in most adults, the earliest appearance of EFAD is after about 3 weeks of fat-free full-calorie continuous PN.
 - vi. Serum triglyceride concentration should be monitored at least weekly and more often for those with proven or suspected impaired triglyceride clearance.
 - vii. Predisposing conditions that may result in impaired clearance of triglycerides:
 - (a) Excessive lipid intake (often caused by propofol therapy)
 - (b) Acute pancreatitis
 - (c) Uncontrolled diabetes
 - (d) Liver failure
 - (e) Kidney failure (decreased lipoprotein lipase activity, carnitine deficiency with long-term hemodialysis patients)
 - (f) End-stage sepsis (multisystem organ failure)
 - (g) History of hyperlipidemia
 - (h) Obesity
 - (i) HIV (occurred even before current antiretroviral therapy) (Am J Med 1989;86:27-31)
 - (j) Pregnancy
 - (k) Small-for-gestational-age neonates (carnitine synthesis is maturational-dependent)
 - viii. Propofol – A hidden source of lipids (10% soybean emulsion containing 1.1 kcal/mL)
- e. Electrolyte requirements (see the Fluids and Electrolytes section)

- f. Vitamins (multivitamin infusion or multivitamin complex 10 mL/day; extra vitamins if patient has any vitamin deficiencies)
- g. Trace minerals (MTE-5 cocktail for normal requirements)
 - i. Zinc 3 mg/day normal requirements; 5 mg/day during critical illness; increased requirements for patients with diarrhea, intestinal fistulae. An additional 10 mg/day for a total of 13 mg/day is usually sufficient to meet increased intestinal losses (Gastroenterology 1979;76:458-67). Deficiency is characterized by loss of hair; erythematous rash, especially in periorbital regions of face; poor wound healing. Classic zinc deficiency is termed *acrodermatitis enteropathica*.
 - ii. Copper 0.3–0.5 mg/day is usually sufficient (Gastroenterology 1981;81:290-7). Copper deficiency is rare but is becoming more apparent in patients with obesity after gastric bypass procedures. Classic presentation of copper deficiency includes a “microcytic anemia unresponsive to iron therapy” or pancytopenia.
 - iii. Chromium 10–12 mcg/day normal requirements, up to 20 mcg/day for diarrhea. Deficiency rare. Classic presentation is hyperglycemia.
 - iv. Manganese 150–300 mcg/day is probably enough. Some studies state that the amount of manganese contamination in the compounding of PN may be adequate as opposed to supplementation. Deficiency is very rare. Deficiency has been reported to present as a “diaper rash.” Several case reports of manganese toxicity associated with liver disease and high manganese intake (800 mcg – 1 mg/day) (Nutrition 2001;17:689-93). Signs and symptoms of toxicity emulate those of Parkinson disease.
 - v. Selenium 60 mcg/day up to 120 mcg/day for patients with diarrhea or short bowel syndrome. Deficiency results in extreme muscle weakness and congestive cardiomyopathy. Classic presentation with cardiomyopathy has been termed *Keshan disease* (named after a province in China where the first cases of selenium deficiency with cardiomyopathy were discovered).
 - vi. It is common clinical practice to withhold copper and manganese in the PN formulation for patients with hepatobiliary/cholestatic liver disease or a direct (conjugated) bilirubin concentration greater than 2 mg/dL.
 - vii. Some clinicians withhold selenium for patients with significant renal disease who do not receive hemodialysis or CRRT, though data in support of this practice are lacking.
- 6. Should supplemental PN be given to patients intolerant of EN?
 - a. ESPEN PN (2009) (Clin Nutr 2009;28:387-400): All patients receiving less than their target EN after 2 days should be considered for supplemental PN.
 - b. ESPEN EN (2006) (Clin Nutr 2006;25:210-23): For patients intolerant of EN, supplemental PN should be considered. Overfeeding should be avoided.
 - c. SCCM/ASPEN (2016) (JPEN J Parenter Enteral Nutr 2016;40:159-211): It is recommended that supplemental PN be initiated in “at risk” patients after 7 to 10 days if patients are not able to meet at least 60% of energy and protein requirements. This is a marked departure from the 2009 guidelines that indicate PN should not be given to [all] patients that are unable to receive EN within the first 7 days and to reserve supplemental PN for patients unable to meet 100% of caloric goal after 7 to 10 days.
 - d. Canadian Practice Guidelines Update (2014) (Nutr Clin Pract 2014;29:29-43): It is strongly recommended that early supplemental PN or large volumes of hypertonic dextrose solutions not be used in unselected critically ill patients (i.e., low-risk patients with short stay in ICU). In the patient who is not tolerating adequate EN, data are insufficient to recommend when PN should be initiated.

- e. Casaer/EPaNIC study (N Engl J Med 2011;365:1-17) – 4640 mostly surgical patients, randomized controlled trial: EN only x 7 days; then PN initiated (hypertonic dextrose solutions x 2 days; then PN) versus supplemental PN in addition to whatever EN patients can tolerate during the first 7 days
 - i. Worsened survival (72% vs. 75%), more infections (26% vs. 23%), ICU length of stay greater than 3 days (51% vs. 48%) with early supplemental PN
 - ii. The patient population was limited because malnourished (BMI less than 17 kg/m²) patients were excluded. In addition, about 60% of the population were cardiac surgery patients, for whom the indication for PN is questionable, 50% of patients were extubated by ICU day 2, and 70% of patients had an ICU length of stay of only 3–4 days (which would imply a questionable severity of critical illness). Finally, only 58% of patients in the early PN group were even given PN (for 1–2 days), and only 25% patients in the late PN group ever received PN.
 - f. Heidegger (2013) (Lancet 2013;381:385-93): 307 patients, two medical centers, randomized controlled trial: Patients who received less than 60% target from EN by day 3 with an anticipated ICU stay greater than 5 days received supplemental PN or EN alone. Supplemental PN was discontinued by day 8.
 - i. Supplemental PN group had decreased infections (27% vs. 38%).
 - ii. Smaller study than the Casaer study. Not all patients had resting energy expenditure measured (some were predicted resting energy expenditure). Protein target was only 1.2 g/kg/day. No difference in ICU/hospital length of stay, mortality.
 - g. Dickerson interpretation: Many of the patients in the Casaer study should not have been given PN in the first place as it was not indicated. The majority of those patients were discontinued from ventilator support within 2 or 3 days, able to eat, and discharged from the ICU within 4 to 5 days. This study is a reminder that PN should not be given indiscriminately to patients as proved by the VA Cooperative Trial (1991) because PN resulted in increased infectious complications in perioperative GI cancer patients who were not malnourished as opposed to improved morbidity when given to those who were malnourished. The Heidegger data showed a benefit from supplemental PN in a sicker patient population than Casaer et al.'s population. Short-term supplemental PN may be indicated for patients who are anticipated to have prolonged duration of inability to use GI tract, anticipated prolonged duration of ICU stay, and who are either malnourished or who have a high level of catabolism. A more objective, evidence-based approach would be the use of the NRS 2002 or NUTRIC score to evaluate the patient. Effective use of prokinetic pharmacotherapy may also reduce the need for supplemental PN.
- E. Timing of Initiation of Nutrition Support: Early or not for ICU patients?
1. ESPEN EN (2006) (Clin Nutr 2006;25:210-23): Questionable benefit of early versus delayed EN; however, it was recommended that critically ill patients who are hemodynamically stable and have a functioning GI tract be fed early (less than 24 hours), if possible.
 2. ESPEN PN (2009) (Clin Nutr 2009;28:387-400): All patients not expected to receive EN within 3 days should receive PN within 24–48 hours if EN is contraindicated or not tolerated.
 3. SCCM/ASPEN (2016) (JPEN J Parenter Enteral Nutr 2016;40:159-211): Early EN should be initiated within 24 to 48 hours in the critically ill patient who is unable to maintain volitional intake once the patient is hemodynamically stable. It is suggested that very early EN (within 4 to 6 hours if possible) be initiated in a patient with burn injury.
 4. Surviving Sepsis Campaign guidelines (2013) (Crit Care Med 2013;41:580-637): Administer oral nutrition or EN within the first 48 hours after severe sepsis is diagnosed.

5. Dickerson interpretation: The data are confusing because several studies have used different times for the definition of early nutrition therapy: 24, 36, 48, and 72 hours. Most evidence-based clinicians would suggest that nutrition therapy be initiated for most patients within 48 hours of ICU admission and definitely no later than 72 hours. Surgical ICU patients, including those with trauma and thermal injury, have been more consistently shown to benefit from early EN as opposed to medical ICU patients, for whom results are more variable.

F. Glycemic Control

1. Definition of the appropriate BG target range
 - a. Society of Critical Care Medicine (SCCM) guidelines (2012) (Crit Care Med 2012;40:3251-76): A BG of 150 mg/dL or greater should trigger initiation of insulin therapy to keep BG less than 150 mg/dL for most patients and maintain BG absolutely less than 180 mg/dL.
 - b. ASPEN guidelines (2013) (JPEN J Parenter Enteral Nutr 2013;37:23-36): A target BG range of 140–180 mg/dL is recommended.
 - c. Surviving Sepsis Campaign guidelines (2013) (Crit Care Med 2013;41:580-637): An insulin dosing protocol to keep BG less than 180 mg/dL, rather than an upper target of 110 mg/dL, is recommended when the patient has two consecutive BG measurements greater than 180 mg/dL.
 - d. American Diabetes Association (2016) (Diabetes Care 2016;39(suppl 1):S99-104): An insulin infusion should be used to control hyperglycemia, starting with a threshold of greater than or equal to 180 mg/dL. BG should be maintained between 140 and 180 mg/dL. More stringent goals, such as 110 to 140 mg/dL may be more appropriate for selected critically ill patients, as long as this can be accomplished without significant hypoglycemia.
 - e. Dickerson interpretation: Many evidence-based clinicians use a target BG range of 140–180 mg/dL when caring for patients in a mixed medical-surgical ICU. A growing amount of evidence from smaller studies shows that certain subpopulations such as trauma, traumatic brain injury, cardiothoracic surgery, and thermal injury may benefit from tighter BG (e.g., less than 140–150 mg/dL) control if it can be done safely without hypoglycemia.
2. BG monitoring frequency
 - a. SCCM guidelines (2012) (Crit Care Med 2012;40:3251-76): BG should be monitored every 1–2 hours for most patients receiving an insulin infusion; monitoring every 4 hours is not recommended because of the risk of unrecognized hypoglycemia.
 - b. Surviving Sepsis Campaign guidelines (2013) (Crit Care Med 2013;41:580-637): BG should be monitored every 1–2 hours during the insulin infusion and then extended to every 4 hours thereafter once stability in BG control is achieved.
 - c. American Diabetes Association (2016) (Diabetes Care 2016;39(suppl 1):S99-104): BG should be monitored every ½–2 hours during the insulin infusion.
 - d. Dickerson interpretation: With insulin infusions, we monitor BG every hour and then extend it to every 2 hours once there is stability in BG control and the intravenous insulin infusion rate is demonstrated. Although some of the major trials show that BG monitoring could be extended to every 4 hours once two consecutive BG concentrations in the target range are achieved, we believe our patients are too labile to safely extend monitoring to every 4 hours. If they are stable enough to warrant BG monitoring every 4 hours, the EN-fed patient is transitioned to intermediate- or long-acting subcutaneous insulin therapy (JPEN J Parenter Enteral Nutr 2013;37:506-16).
3. Point-of-care BG monitoring
 - a. SCCM guidelines (2012) (Crit Care Med 2012;40:3251-76): Point-of-care glucose meters are acceptable but not optimal for routine BG testing during an insulin infusion because of their inaccuracy at low BG concentrations. Arterial or venous blood sampling, instead of fingerstick capillary BG testing, is suggested for patients in shock, on vasopressor therapy, or with severe peripheral edema.

- b. At BG concentrations greater than 80 mg/dL, there was strong agreement (73% and 85%) in glycemic interventions when using either capillary or arterial BG measurements in critically ill patients (Intensive Care Med 2004;30:804-10).
 - c. High doses of drugs such as acetaminophen, ascorbic acid, dopamine, or mannitol may interfere with the accuracy of BG measurements, and false elevation of results by point-of-care glucose meters that use the glucose-oxidase method may occur (Crit Care Med 2012;40:3251-76). Glucose dehydrogenase-based assays are sensitive to interference and false elevation of results if the patient receives medications containing maltose (immunoglobulins) or icodextrin (used in some dialysis solutions).
 - d. Dickerson interpretation: Point-of-care meters with capillary BG testing may be reasonable for most critically ill patients and still in use by many institutions as long as the patient's BG concentrations are greater than 80 mg/dL the vast majority of the time. For low BG concentrations, point-of-care meters may erroneously report BG concentrations higher than measured (Crit Care Med 2009;37:2691-6). Patients with significant peripheral edema may also have erroneous BG concentrations.
4. Hypoglycemia
 - a. Most guidelines define hypoglycemia as a BG less than 70 mg/dL because increased glucagon, catecholamine, and growth hormone production occurs when the BG falls below this concentration. Mild to moderate hypoglycemia is usually defined as a BG concentration of 40–60 mg/dL (because autonomic symptoms often appear) and severe (life-threatening) hypoglycemia as less than 40 mg/dL.
 - b. Most common risk factors for hypoglycemia during insulin therapy (Crit Care Med 2007;35:2262-7; Crit Care Med 2006;34:96-101)
 - i. Excessive insulin dose
 - ii. Abrupt discontinuation of EN or PN without an adjustment in the insulin therapy (purported to cause 62% of severe hypoglycemic events in the 2006 Van den Berghe trial of medical ICU patients) (Crit Care Med 2012;40:3251-76)
 - iii. Renal failure (half-life of insulin is prolonged, impaired renal gluconeogenesis in response to hypoglycemia)
 - iv. Advanced age
 - v. Inotropes, vasopressor agents, octreotide with insulin therapy
 - vi. Sepsis
5. Transitioning from a continuous intravenous insulin infusion
 - a. Lack of a transition plan has been shown to result in loss of glycemic control. Different methods have been described in the literature, and the best approach depends on whether the patient is transitioning to an oral diet, bolus EN, or continuous EN (Diabetes Care 2014;37(suppl 1):S14-80; JPEN J Parenter Enteral Nutr 2013;37:506-16; Crit Care Med 2012;40:3251-76; The ASPEN Adult Nutrition Support Core Curriculum, 2nd ed. Silver Spring, MD: American Society for Parenteral and Enteral Nutrition, 2012:580-602):
 - b. Example for transitioning from a continuous intravenous regular human insulin infusion to a subcutaneous intermediate-acting insulin (neutral protamine Hagedorn [NPH]) for patients who receive continuous enteral feeding (JPEN J Parenter Enteral Nutr 2013;37:506-16)*
 - i. Give 30%–50% of the daily required intravenous regular human insulin, divided into two separate doses and given every 12 hours. Continue the graduated intravenous insulin infusion according to the algorithm.
 - ii. BG measurements are continued every 1–2 hours and are mapped to the timing of the subcutaneous NPH therapy to ascertain its pharmacokinetic peak and duration.
 - iii. The NPH dosage and interval are adjusted accordingly daily until the intravenous regular human insulin infusion is “auto-weaned” to 1–2 units/hour.

- iv. The regular human insulin infusion is then discontinued with BG determinations, with sliding-scale regular human insulin coverage every 3–4 hours. The NPH is further titrated daily according to the required amount of corrective regular human insulin required to maintain BG within the target BG range.
- v. Frequency of BG measurements is decreased because the patient has stability in glycemic control.

*This method was evaluated in 32 patients who transitioned from a continuous intravenous regular human insulin to subcutaneous NPH and intermittent sliding-scale regular human insulin coverage (JPEN J Parenter Enteral Nutr 2013;37:506-16). BG concentrations were maintained in the target range for 18 ± 3 hours/day. Eighteen patients (56%) had at least one episode of moderate hypoglycemia (40–59 mg/dL), and three patients (9%) had an episode of severe hypoglycemia (BG less than 40 mg/dL). The overall rates of moderate and severe hypoglycemia were 1.3% and 0.1% of all BG determinations. Patients older than 60 years were at a higher risk of hypoglycemia than were younger patients.

Patient Case

14. A 55-year-old woman (weight 75 kg) without diabetes is given PN after a major GI resection. She has been weaned from mechanical ventilation and is being transferred from the ICU to the floor. Her current PN formulation is 200 g of dextrose (1.8 mg/kg/minute), 110 g of amino acids, and 80 g of lipids (1.1 g/kg/day), which meets her goal requirements of protein at 26 kcal/kg/day and 1.5 g/kg/day. It contains regular human insulin at 20 units/day. During the past 24 hours, her fingerstick BG measurements have been 170–210 mg/dL, and her serum glucose concentration is 182 mg/dL. She has received 14 units of sliding-scale regular human insulin coverage. Which would be best to suggest for optimal glycemic control?
- A. Increase regular insulin to 30 units/day.
 - B. Decrease dextrose to 100 g/day.
 - C. Increase regular insulin to 50 units/day.
 - D. Do not change the current regimen.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: D

Hyperglycemia and other causes of non-hypotonic hyponatremia have been excluded. Urine osmolality is greater than 100 mOsm/kg, which rules out psychogenic polydipsia, and a large amount of hypotonic fluids were not being given. Urine sodium was greater than 30 mEq/L, and the patient did not receive diuretic therapy or have kidney disease. The patient appeared to be normovolemic without evidence of significant edema (expansion of the ECF compartment). Because the patient also has pneumonia (a common cause of SIADH), all of these factors indicate that the patient has hyponatremia caused by SIADH (Answer D is correct). Answer A is incorrect because the serum glucose concentration is not high enough to cause hyponatremia; nor has the patient received mannitol, glycine; nor is the patient hypertriglyceridemic. Answer B is unlikely because there was no evidence of adrenal insufficiency given in the case. Answer C is impossible because the patient did not have a traumatic brain injury.

2. Answer: B

Fluid restriction in which excess water is retained relative to sodium is the most appropriate treatment of SIADH (Answer B is correct). The “vaptans” may also be considered; however, this was not a choice. Answer A is incorrect because giving salt tabs may result in worsened fluid overload and edema. Answer C is incorrect for the same reason as Answer A. Answer D is incorrect because the severity of hyponatremia and lack of symptoms does not warrant the emergency use of hypertonic saline.

3. Answer: D

The best way to fluid-restrict an enterally fed patient is to use the most concentrated formulas, which are the 2-kcal/mL formulations that are specifically designed for patients with congestive heart failure. Unfortunately, protein intake may be inadequate with the use of these formulations in certain populations, and supplemental protein may have to be provided. Answers A, B, and C are incorrect because they do not result in the appropriate therapeutic decision to reduce fluid intake.

4. Answer: D

These dosages should be selected as the correct answer because they follow the dosing guidelines given in this chapter (unlike the doses given in answers A, B, C). Given that the patient is NPO, oral options (Answers A and B) are not practical. If the patient had a history of significant recent weight loss or if he did not respond adequately to these doses, the dose could be increased. Answer C is not correct as the dosage phosphorus is excessive. Supplemental potassium and phosphorus would be added to the PN solution, in addition to daily intravenous doses of potassium and phosphorus.

5. Answer: B

Because it takes about 48 hours for serum magnesium to redistribute, the next day's serum magnesium concentration is falsely elevated. In general, it will take 4–5 days to replete this patient's magnesium deficiency (presumably caused by chronic alcohol ingestion). Thus, answer B would be the best option for this patient. Given that the patient is NPO, oral dosing options (answer A) are less desirable. Answer C is incorrect because it is too aggressive a dosage given the current serum magnesium concentration of 2.0 mg/dL (despite it being falsely elevated). Supplemental magnesium would be added to the PN solution in addition to daily doses of intravenous magnesium sulfate if he remained low or in the low-normal range or if he was also hypocalcemic (because hypomagnesemia can elicit hypocalcemia secondary to end-organ resistance to parathyroid hormone). Answer D is incorrect as the serum magnesium concentration is falsely elevated to within the normal range but has not fully redistributed yet. It would be anticipated that the concentration will decrease the following day since it takes multiple days to replenish magnesium stores.

6. Answer: C

Although critical illness (Answer D) and fluid resuscitation therapy may have been a factor in the development of his hypocalcemia, massive blood transfusion is the most profound cause. Citrate, added to the blood as an anticoagulant, readily binds calcium and can cause hypocalcemia. Previous studies have shown that hypocalcemia is common when patients are given more than 5 units of blood at a time (Answer C is correct). Answer A is incorrect because a low-normal serum magnesium

concentration of 1.8 mg/dL is unlikely to contribute to the pathogenesis of hypocalcemia. A serum magnesium concentration of less than or equal to 1.5 mg/dL is more likely to contribute to the pathogenesis of hypocalcemia. Answer B is incorrect because a urine output of 0.5 mL/kg/hr is not excessive.

7. Answer: B

A short-term intravenous infusion of 4 g of calcium gluconate (1 g = 4.6 mEq) for 4 hours has been shown to be a safe and effective therapeutic regimen for moderate to severe hypocalcemia (ionized calcium less than 1 mmol/L) (Answer B is correct). Answer A is incorrect because it is an insufficient dosage of elemental calcium. A bolus/push dose of calcium chloride (1 g = 13.6 mEq), as given in answer C, would be an effective means for treating symptomatic severe hyperkalemia, but it would be unnecessarily aggressive for treating hypocalcemia in this patient scenario. Answer D is incorrect because the moderate to severe hypocalcemia should be corrected in this post-operative trauma patient who is anemic and at high risk for bleeding complications.

8. Answer: A

Examination of the pH indicates that the patient has an acidemia because it is lower than normal. Looking at PCO_2 and serum bicarbonate would indicate that the primary etiology is metabolic because both are low. Calculation of the AG ($145 - 118 - 18 = 9$) shows that no AG is present (Answers B and C are incorrect). A correction for serum albumin concentration is not needed because it is normal. The serum lactate is near the high end of the normal range but still within the normal range. This would indicate that the patient's dehydration has not become so extreme that a significant decrease in tissue perfusion was not evident (yet). Respiratory compensation appears to be intact ($[1.5 \times 17] + 8 = 33$ vs. 34 mm Hg) on the blood gas, and it appears that the patient's history of smoking did not compromise her ability to mount a reasonable respiratory response to the alkalosis. The serum chloride of 118 mEq/L indicates hyperchloremia. A non-AG hyperchloremic metabolic acidosis is common for patients with severe diarrhea. The low serum potassium and magnesium would also strongly suggest that the patient has significant diarrhea (Answer A is correct). Answer D is incorrect because the decreased PCO_2 is in response to the metabolic acidosis and the patient does not have a metabolic alkalosis but rather an acidosis.

9. Answer: C

Initial therapy with lactated Ringer solution would be the ideal choice (Answer C is correct). Treatment with 0.9% sodium chloride (Answer B) is incorrect because it would worsen the hyperchloremic acidosis. A 5% dextrose solution (Answer D) would be a poor choice because sodium/isotonic fluids are necessary to restore intravascular volume. Because the severity of the patient's acidemia is mild (pH 7.29), aggressive therapy with sodium bicarbonate or THAM is not indicated. After the first day of lactated Ringer solution to restore intravascular volume and improve pH, it would be reasonable to change to 0.45% sodium chloride to continue to restore volume depletion, depending on the patient's response to the lactated Ringer solution (e.g., restoration of normal pH, adequate urine output, resolution of tachycardia). Thus, answer A would be incorrect as the question asked for the most appropriate *initial* treatment. Of course, aggressive potassium and magnesium repletion is indicated as well. This could be done with infusions as previously discussed, and it would be reasonable to add 20 mEq of potassium chloride per liter to the 0.45% sodium chloride upon discontinuation of the lactated Ringer solution.

10. Answer: C

The current PN regimen provides 61 kcal/kg/day total (glucose 6.1 mg/kg/minute and lipid emulsion 1.5 g/kg/day) and protein 4 g/kg/day. The PN regimen represents gross overfeeding of this small woman and can explain her hyperglycemia and hypercapnia. Cutting all macronutrients by about one-half would result in a more reasonable regimen for this patient: 30 kcal/kg/day (glucose 3 mg/kg/minute and lipid emulsion 0.8 g/kg/day) and protein 2 g/kg/day. Because she is so small (weight 40 kg), it would be important to double-check the weight-based calculation to see whether this new regimen is appropriate to meet her caloric needs without overfeeding by calculating the BEE using the Harris-Benedict equation for women (caloric intake should not exceed $1.3\text{--}1.5 \times \text{BEE}$ for a critically ill patient with traumatic injuries) (Answer C is correct). Although answer A reduces the respiratory quotient of the nutrient admixture, this will not solve the primary problem of overfeeding the patient because excessive calories are being provided. Answers B and D may help with the consequences of overfeeding (e.g., hyperglycemia and respiratory acidosis) but do not address the primary problem (overfeeding) and are inappropriate management techniques.

11. Answer: C

Total kilocalories per day = (300 g x 3.4 kcal/g of dextrose) + (100 g x 4 kcal/g of protein) + (40 x 10 kcal/g of lipid emulsion) = 1020 glucose kcal + 400 protein kcal + 400 lipid kcal = 1820 total kcal/65 kg = 28 kcal/kg/day. Remember, if 10% lipid emulsion is used, caloric intake is 11 kcal/g of lipid emulsion (e.g., propofol), whereas 20% and 30% will provide 10 kcal/g (because of the glycerol and egg phospholipid/emulsifier content of the lipid emulsion). Protein intake is 100 g/65 kg = 1.5 g/kg/day. This caloric and protein intake would be appropriate for this patient because he is only mildly to moderately stressed, and his weight is 90% of IBW. Glucose intake is 3.2 mg/kg/minute and does not exceed 5 mg/kg/minute. Fat intake is reasonable at 0.6 g/kg/day (Answer C is correct). Answers A, B, and D do not represent the correct calculations as described previously.

12. Answer: B

Answers A, C, and D are not correct because an error must have been made in the calculations. Nitrogen balance (NB) is calculated by first determining nitrogen intake by the following: $N_{in} = 100 \text{ g of amino acids} / 6.25 \text{ g of N per gram of protein} = 16 \text{ g}$. Nitrogen loss includes urinary nitrogen and stool loss, which can be estimated by urinary urea nitrogen excretion and an assumption of urinary non-urea nitrogen and stool losses, which is assumed to be about 4 g/day. There are some exceptions to this calculation, but it is considered the classic method for determination of NB that most clinicians use. For patients with renal impairment and an increase in BUN of about 5 mg/dL or greater during the NB determination, these losses must also be undertaken into the calculation. Because the patient case does not represent a patient with renal impairment, we would use the standard calculations for estimation of urinary urea nitrogen loss: $UUN = 600 \text{ mg/dL} = 6 \text{ g/L}$; $9 \text{ g/L} \times 2 \text{ L} = 12 \text{ g}$ and the final NB estimation from intake and loss: $NB = 16 - 12 - 4 = 0 \text{ g/day}$ (Answer B is correct).

13. Answer: D

Most clinicians and nutritional scientists consider an NB of -4 g/day to +4 g/day as nitrogen equilibrium. For a malnourished, unstressed patient, the clinician should strive to achieve an NB of at least +4 to +6 g/day. For highly catabolic or stressed patients, it is impossible to achieve a positive NB unless the patient is being markedly overfed, which can lead to hypercapnia, hyperglycemia, and PN-associated liver disease. Given that

the patient is in nitrogen equilibrium at 1.5 g/kg/day of protein, despite mild to moderate stress from pancreatitis and an infection, the best short-term course of action would be to make no change in the PN regimen (Answer D is correct). Therefore, answers A, B, and C are not necessary and are incorrect given this patient scenario at this time. If the hospital course becomes prolonged with many influencing catabolic factors and worsening NB, an increase in protein intake should be considered. If the protein intake were increased to 2 g/kg/day from 1.5 g/kg/day, the total caloric intake would be increased to 30 kcal/kg/day (0.5 g/kg/day of protein x 4 kcal/g = 2 kcal/kg + 28 kcal/kg from previous PN regimen = 30 kcal/kg/day), which would be reasonable for a highly stressed critically ill patient. If protein intake were to be increased even further, a reduction in non-protein (glucose and fat) energy would be advised.

14. Answer: A

Because the target BG should be within 140–180 mg/dL for this surgical patient being transferred to the floor, a modest improvement in glycemic control is indicated. Thus, answer D (no change) would be incorrect. Ideally, obligatory glucose requirements should be met (e.g., about 130 g/day plus about 80–150 g/day for wound healing) to prevent the use of amino acids for gluconeogenesis. Thus, decreasing the glucose intake to 100 g/day as described in answer B is not desirable, given the mild increases in BG concentration. The easiest method to achieve glycemic control and meet caloric needs is to modestly increase the regular human insulin content in the PN solution. Because 14 units of sliding scale insulin still appears insufficient, a modest increase in insulin appears prudent. The patient is unlikely to experience hypoglycemia with the provision of insulin at 30 units/day when given 200 g of intravenous dextrose concurrently (Answer A is correct). As the stress resolves and glycemic control improves, insulin can be decreased or eliminated from the PN solution. Answer C is incorrect because it would likely provide too much insulin, based on sliding scale coverage and current BG range, and increase the patient's risk for hypoglycemia.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: C

An ileus, usually detected on radiologic examination of the lower abdomen, indicates lack of motility and presence of distention and air within the small bowel. This is usually depicted as “dilated loops of bowel.” Patients cannot be fed safely or efficaciously by the enteral route during an ileus (Answer C is correct). Answer A is incorrect because a feeding tube can be placed for enteral feeding of the patient with anorexia, and PN is not indicated. Answer B is incorrect because presence or absence of bowel sounds is not an accurate marker for assessing bowel function. Answer D is incorrect because a high gastric residual volume during enteral feeding, combined with abdominal distension, bloating, emesis, or regurgitation, can often be efficaciously treated with prokinetic pharmacotherapy or advancement of the feeding tube into the small bowel with resumption of enteral feeding.

2. Answer: B

Answer B, 0.45% sodium chloride and potassium chloride 20 mEq/L, is correct given the average electrolyte composition of gastric fluid (see Table 5 regarding the electrolyte composition of GI fluids). Answers A, C, and D are incorrect because they do not as accurately depict gastric fluid losses.

3. Answer: A

With significant diarrhea, intravenous zinc requirements from GI fluid losses during critical illness increase from the normal requirements of 3–5 mg/day. Data analyses show that most patients with increased intestinal losses can achieve a positive zinc balance on 13 mg of intravenous zinc daily (Gastroenterology 1979;76:458–67). As a result, most clinicians provide additional zinc supplementation for patients with short bowel syndrome, intestinal fistulas, or prolonged and sustained diarrhea (Answer A is correct). Answer B is incorrect as molybdenum is an extremely rare and unlikely deficiency to occur during parenteral nutrition therapy. Answers C, and D are incorrect because intractable diarrhea losses are less likely to cause a deficiency, albeit with the exception of copper (especially with extreme intestinal bypass procedures for obesity).

4. Answer: C

Given the severity of the patient’s condition (recent seizure from severe hyponatremia) and likely diagnosis

of SIADH, the immediate goal should be to achieve a serum sodium concentration of greater than 120 mEq/L by short-term infusion of 3% sodium chloride (Answer C is correct). Conivaptan (Answer D) could then be given to correct the hyponatremia, limiting the increase in serum sodium concentration to less than 10–12 mEq/L/day. Fluid restriction is imperative and is the primary overall management technique for this patient. Answer A is incorrect because a more rapid response is imperative because of the patient’s seizure and severity of the condition. Answer B is incorrect because it would be a potentially life-threatening error by providing more ADH-like substance and because it is used to treat diabetes insipidus (the opposite condition of SIADH).

5. Answer: B

Studies show that increases in mesenteric potassium concentrations detected by potassium sensors in the splanchnic vascular bed evoke increased renal potassium excretion (feed-forward regulation of potassium homeostasis), even before regulation by aldosterone (classic feedback regulation) (Answer B is correct). Some clinicians may have erroneously selected bioavailability (Answer A), but the bioavailability of enteral potassium is 95%–100% in the absence of aberrations in GI motility, function, or anatomy. A primary difference between enteral and parenteral potassium is that the rate of absorption is slower with enteral potassium. Intravenous potassium administration can inadvertently be infused too quickly (it is acceptable to infuse potassium at 10 mEq/hour for patients without a cardiac monitor and up to 20 mEq/hour for those with a monitor). Answer C is incorrect because potassium chloride elixir or solution is an effective means for providing potassium when given intra-gastrically. It generally only causes diarrhea when given in excessive doses or when administered directly into the small bowel through a feeding jejunostomy because it is a hypertonic solution. Answer D is a nonsensible answer.

6. Answer: C

Folic acid deficiency (Answer C) is correct because the patient’s homocysteine concentration is elevated, whereas her methylmalonic acid concentration is normal. If both were elevated, it would likely be a vitamin B12 deficiency (Answer D), although a combined B12-folate deficiency is possible (but less common than a B12

deficiency alone). If her methylmalonic acid concentration were elevated and her homocysteine were normal (rare), she would likely have a vitamin B12 deficiency. If both are normal, the patient's macrocytosis is caused by other factors such as liver disease or alcohol. Answer A is incorrect because iron deficiency causes a hypochromic, microcytic anemia. Answer B is incorrect because thiamine deficiency presents as a neurologic deficit, lactic acidosis, or congestive heart failure and not as a nutritional anemia.

7. Answer: D

Answer D, *additional magnesium therapy should be given daily for the next 4–5 days*, is correct because it takes 48 hours for magnesium to equilibrate after a short-term infusion, thus answer A is incorrect. A normal serum magnesium concentration the following day after a large intravenous dosage (Answer B) is incorrect. Answer C is incorrect because hypocalcemia should autocorrect with magnesium supplementation within 48 hours of magnesium therapy; however, calcium therapy can be given concurrently, if necessary (symptomatic or ionized calcium concentration less than 1 mmol/L).

8. Answer: B

Described are the calculations for determining an NB:

$$NB = N_{in} - UUN - 4$$

$$N_{in} = \text{protein in (g/day)} / 6.25 = 20.8 \text{ g}$$

$$UUN \text{ (g/day): } 900 \text{ mg/dL} = 9000 \text{ mg/L} = 9 \text{ g/L}; 2700 \text{ mL/day} = 2.7 \text{ L/day}$$

$$9 \text{ g/L} \times 2.7 \text{ L/day} = 24.3 \text{ g/day}$$

$$NB = 20.8 - 24.3 - 4 = -7.5 \text{ g/day}$$

If asked "What adjustments would you make to the PN regimen?", the best choice would be to increase the protein intake (to about 2 g/kg/day) because the current regimen provides only around 1.4 g/kg/day. Although the NB is usually negative for a critically ill patient because the anabolic effect of nutrition cannot completely overcome the catabolism of critical illness, most patients can achieve close to nitrogen equilibrium (an NB of around -4 to +4 g/day). Increasing the protein intake by 50 g/day should provide about 8 g of additional nitrogen, which should be sufficient to achieve an NB close to nitrogen equilibrium. Answers A, C, D represent incorrect calculations.

ACUTE KIDNEY INJURY AND RENAL REPLACEMENT THERAPY IN THE CRITICALLY ILL PATIENT

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Learning Objectives

1. Define acute kidney injury (AKI).
2. List common categories and give examples of drug-induced AKI.
3. With respect to renal replacement therapy, define diffusion and convection and describe their role in blood purification.
4. Discuss the role of dialysate and replacement fluids in continuous renal replacement therapy (CRRT).
5. Describe drug-dosing concepts in CRRT and sustained low-efficiency dialysis/extended daily dialysis.

Abbreviations in This Chapter

AIN	Acute interstitial nephritis
AKI	Acute kidney injury
AKIN	Acute Kidney Injury Network
ATN	Acute tubular necrosis
CKD	Chronic kidney disease
CRRT	Continuous renal replacement therapy
CVVH	Continuous venovenous hemofiltration
CVVHD	Continuous venovenous hemodialysis
CVVHDF	Continuous venovenous hemodiafiltration
EDD	Extended daily dialysis
ICU	Intensive care unit
IHD	Intermittent hemodialysis
MW	Molecular weight
RIFLE	Risk, injury, failure, loss, end-stage renal disease
RRT	Renal replacement therapy
SLED	Sustained low-efficiency dialysis
Vd	Volume of distribution

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

Questions 1–5 pertain to the following case.

E.R. is a 67-year-old man admitted to your intensive care unit (ICU) several days ago with acute respiratory failure. He required mechanical ventilation and was placed on empiric antibiotics to cover community-acquired pneumonia. His renal function has worsened over the past 5 days (serum creatinine [SCr] 0.6 mg/dL on admission; today, 2.4 mg/dL), and he now requires

renal replacement therapy (RRT) with continuous venovenous hemofiltration (CVVH). His current medications include ceftriaxone, azithromycin x 2 doses only, enoxaparin, and ranitidine. As a pharmacist, you are asked to evaluate E.R. for a possible cause of drug-induced acute kidney injury (AKI). You determine that the most likely drug is ceftriaxone.

1. Through which mechanism is ceftriaxone most likely to cause AKI?
 - A. Acute tubular necrosis (ATN).
 - B. Acute interstitial nephritis (AIN).
 - C. Glomerulonephritis.
 - D. Tubular precipitation.
2. Using the Acute Kidney Injury Network (AKIN) staging, which best describes E.R.'s stage of AKI?
 - A. Stage 1.
 - B. Stage 2.
 - C. Stage 3.
 - D. Cannot determine because urine output is not provided.
3. Which best describes the principle for clearance used for solute removal during CVVH?
 - A. Convection.
 - B. Diffusion.
 - C. Both convection and diffusion.
 - D. Membrane binding.
4. E.R. continues to worsen. He is now febrile with an increasing white blood cell count (WBC). You are asked to dose his antibiotics while he receives CVVH. Which would be the best place to begin looking for dosing recommendations?
 - A. Intermittent hemodialysis (IHD) guidelines.
 - B. Package insert.
 - C. Primary literature/dosing summaries.
 - D. Estimates using an estimated sieving coefficient.
5. Which drug property is most important to consider when estimating whether a drug will be removed by continuous renal replacement therapy (CRRT)?
 - A. Protein binding.
 - B. Molecular weight (MW).
 - C. Volume of distribution (Vd).
 - D. Drug charge.

I. ACUTE KIDNEY INJURY

A. Introduction

1. AKI was formerly known as acute renal failure.
2. AKI is a decrease in kidney function that occurs over hours to days.
3. AKI results in the accumulation of metabolic waste products and, as urine volume decreases, metabolic disturbances and water retention.
4. AKI has been associated with increased mortality, development of chronic kidney disease (CKD), and development of end-stage renal disease.

B. Epidemiology

1. The incidence of AKI varies and depends on the definition used, its cause, and the patient population.
2. Hospital-acquired AKI occurs infrequently in patients admitted to a general hospital ward (1.9%–20%). In critically ill patients, the risk is greater. In this group, AKI is estimated to occur in 20%–67% of patients.
3. Severe sepsis and septic shock are common causes of ATN, which is a leading cause of AKI in critical illness. Other risk factors for AKI include use of intravenous radiocontrast agents, major surgery (especially cardiothoracic), nephrotoxic medications, and chronic medical conditions (e.g., history of CKD, congestive heart failure, and diabetes mellitus). Most patients have more than one risk factor.
4. Mortality rates in patients with AKI are 10%–80%, with the highest in patients with multisystem organ failure (50%) and those requiring RRT (80%).

C. Definitions (Table 1)

1. During the past several decades, many definitions have been used for acute renal failure, making it difficult to compare patient populations across studies. In 2002, the Acute Dialysis Quality Initiative workgroup developed the RIFLE (risk, injury, failure, loss, end-stage renal disease) definition and staging system.
 - a. RIFLE categorizes acute renal failure into three grades of increasing severity and two clinical outcomes.
 - b. For the acronym RIFLE, risk is defined as oliguria for more than 6 hours or an increase in SCr to 1.5 times baseline or greater. As renal function continues to worsen, the criteria for injury and failure are met. Clinical outcomes (loss and end-stage renal disease) are defined by the need for RRT for more than 4 weeks and more than 3 months.
2. Because of emerging data suggesting that small changes in renal function (SCr of 0.3 mg/dL or greater) lead to worse outcomes, the Acute Dialysis Quality Initiative workgroup formed the AKIN.
 - a. This group defined AKI, using a staging system of 1–3, as a reduction in kidney function that occurs over no more than 48 hours using measures of SCr and urine output.
 - b. Stage 1 is an absolute increase in the SCr concentration of 0.3 mg/dL or greater, a relative increase to 1.5- to 2-fold above baseline, or documented oliguria less than 0.5 mL/kg/hour for more than 6 hours, despite adequate fluid resuscitation.
 - c. Similar to RIFLE, stages 2 and 3 are met with worsening SCr and urine output.
 - d. The main difference between the two staging systems is that the AKIN definition initially includes a lesser degree of SCr elevation to diagnose AKI.
 - e. In patients requiring RRT, AKIN stage 3 is met, regardless of the stage they are in when RRT is initiated.
 - f. Several studies have validated these criteria and show that the more severe the RIFLE class or AKIN stage, the worse the clinical outcome.

3. In 2012, a third consensus definition was introduced, the Kidney Disease: Improving Global Outcomes (KDIGO) classification system.
 - a. This system combines the strengths of both RIFLE and AKIN, retains the AKIN criteria of a rise in SCr of 0.3 mg/dL within 48 hours, and allows 7 days for a 50% increase in SCr from baseline, as seen in RIFLE.
 - b. Because of these strengths, it is considered the preferred definition.

Table 1. Criteria for Establishing AKI

RIFLE Class	SCr Criteria/ GFR	UOP Criteria (for RIFLE, AKIN, KDIGO)	AKIN Stage	SCr Criteria	KDIGO Stage	SCr Criteria
R	Increase to 1.5-fold or GFR decrease > 25% from baseline	< 0.5 mL/kg/hr for 6 hr	1	Increase to 1.5- to 2-fold above baseline or by 0.3 mg/dL	1	Increase to 1.5- to 2-fold above baseline over 7 days or by 0.3 mg/dL within 48 hr
I	Increase to 2-fold or GFR decrease > 50% from baseline	< 0.5 mL/kg/hr for 12 hr	2	Increase to 2- to 3-fold above baseline	2	Increase to 2- to 3-fold above baseline
F	Increase to 3-fold, GFR decrease > 75% from baseline, or SCr $\geq$ 4 mg/dL (acute increase of at least 0.5 mg/dL)	< 0.3 mg/kg/hr for 24 hr or anuria for 12 hr	3	Increase > 3-fold above baseline or $\geq$ 4 mg/dL with an acute rise of $\geq$ 0.5 mg/dL or on RRT	3	Increase > 3-fold above baseline or $\geq$ 4 mg/dL with an acute rise of $\geq$ 0.5 mg/dL or on RRT
L	Complete loss of function for > 4 wk					
E	Complete loss of function for > 3 mo					

AKI = acute kidney injury; AKIN = Acute Kidney Injury Network; GFR = glomerular filtration rate; RIFLE = risk (R), injury (I), failure (F), loss (L), end-stage kidney disease (E); KDIGO = Kidney Disease: Improving Global Outcomes; UOP = urine output; RRT = renal replacement therapy.

4. In AKI and CKD, there are many reasons that changes may occur in the function and structure of the kidney. Moreover, even though changes may occur, it is possible that neither the AKI definition nor the CKD definition is met.
 - a. In its 2012 clinical practice guideline, KDIGO proposed an operational definition for acute kidney disease (AKD). The purpose was to identify patients with AKD in an attempt to offer therapies to restore kidney function and reverse kidney damage.
 - b. An operational definition of “no known kidney disease” (NKD) was also included for those not meeting other criteria.
 - c. Table 2 provides definitions of AKI, CKD, AKD, and NKD.

Table 2. Definitions of AKI, CKD, AKD, and NKD According to Function and Structure

	Functional Criteria (change in SCr, GFR,^a or UOP)	Structural Criteria (damage^b or no damage and duration)
AKI	Change in SCr by 50% within 7 days Or Change in SCr by 0.3 mg/dL within 2 days Or Oliguria	No criteria
CKD	GFR < 60 mL/min per 1.73m ² for > 3 months	Kidney damage for > 3 months
AKD	AKI Or GFR < 60 mL/min/1.73 m ² for < 3 mo Or Change in GFR by ≥ 35% or change in SCr by > 50% for < 3 mo	Kidney damage for < 3 months
NKD	GFR ≥ 60 mL/min per 1.73m ² , stable SCr	No damage

^aAssessed from measured or estimated GFR.

^bKidney damage is assessed by pathology, biomarkers (urine or blood), imaging, and kidney transplantation (for CKD).

AKD = acute kidney disease and disorders; CKD = chronic kidney disease; NKD = no known kidney disease.

D. Differential Diagnosis

1. There is no single specific test for diagnosing AKI.
2. A thorough history and complete examination should be completed, including:
3. Rate of loss, symptoms, and coexisting diseases
4. A comprehensive review of current and recent medications. Drug-related injury is a leading cause of AKI.
5. Chemistries (blood urea nitrogen [BUN], SCr, serum electrolytes, albumin, and a complete blood cell count) and a urinary analysis (microscopy, sodium, SCr, and osmolality) may assist in determining the type of failure (e.g., prerenal, intrinsic, postrenal).
6. If a bladder catheter is not present, one should be inserted; if present, it should be evaluated for obstruction.
7. Abdominal compartment syndrome should be ruled out if clinically suspected. Acute oliguria and AKI are the result of increasing renal outflow pressure and reduced renal perfusion.
8. Routine use of renal ultrasonography is limited because most ICU-related AKI is associated with prerenal azotemia and ATN. However, it may be useful in high-risk patients, those from the community, or after an initial evaluation fails to reveal the cause of AKI.
9. Renal biopsies have limited usefulness but may be necessary. They are most useful in intrinsic renal failure not associated with ATN.

E. Causes of Drug-Induced AKI (Table 3) – Drug-induced AKI can result when medications are given to an otherwise normal, healthy patient, but injury is more common in the setting of several insults (i.e., disease plus drug) to the kidney.

1. Prerenal
 - a. Decreased blood flow to the kidney, which can result in injury, may be caused by several mechanisms. A reduction in intravascular volume from shock, resulting in decreased perfusion pressure, is the most common.

- b. Drugs typically cause prerenal AKI by one of two mechanisms: either by decreasing blood flow to the kidney or influencing intraglomerular hemodynamics. Included among drugs affecting blood flow is the excessive use of loop diuretics and several cardiovascular medications.
 - i. Loop diuretics can alter extracellular volume by causing excess volume depletion or reduced effective circulation.
 - ii. Cardiac medications can decrease cardiac output (e.g., those having a negative inotropic effect, especially in the setting of severe or decompensated heart failure) or alter systemic vascular resistance (e.g., antihypertensive medications that reduce systemic vascular resistance by causing vasodilatation).
 - iii. Normal hemodynamics of the kidney is maintained, in part, by vasodilatation of the afferent arterioles or vasoconstriction of the efferent arterioles. Increased renal vascular resistance or decreased transcapillary pressure can occur after medications that affect these vessels are administered.
 - iv. Vasodilatation of the afferent arteriole is partly caused by the effects of prostaglandins. Medications that decrease prostaglandin synthesis decrease the ability of the afferent arterioles to vasodilate. Common medications known to inhibit this synthesis are the nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 inhibitors.
 - v. Vasoconstriction of the efferent arteriole is mediated through angiotensin II. Drugs that block angiotensin II (e.g., angiotensin-converting enzyme inhibitors and angiotensin receptor blockers) prevent effective efferent vasoconstriction, leading to decreased transcapillary pressure. As a result, the kidney loses its ability to maintain adequate perfusion pressure.
 - vi. Calcineurin inhibitors (e.g., cyclosporine and tacrolimus) have been associated with prerenal AKI, although the exact mechanism has not been well established. Both afferent and efferent vasoconstriction may be involved. These drugs have also been associated with AIN.
- 2. Renal (Intrinsic) – Drug-induced intrinsic AKI can be caused by several mechanisms and is the result of injury to the renal tubules, glomerulus, vascular structures, interstitium, or obstruction of the renal tubules.
 - a. Tubular injury
 - i. ATN is common in critical illness.
 - ii. Tubular injury results most often from prerenal insults (e.g., prolonged hypotension) or from nephrotoxic agents.
 - iii. Intravenous contrast agents, aminoglycosides, amphotericin B, and the antiretroviral agents are usually associated with ATN.
 - b. Interstitial injury
 - i. In the absence of AKI, AIN is uncommon. It occurs in only 1%–3% of all renal biopsy-proven cases. In the presence of AKI, the incidence is higher and accounts for 15%–27% of cases.
 - ii. Interstitial injury is characterized by inflammatory infiltrates and edema within the interstitium. The clinical presentation is nonspecific and may include fever and rash with laboratory evidence of eosinophilia; however, this “classic triad” occurs in only 10%–30% of patients.
 - iii. Drug-induced AIN represents more than 75% of cases. Other causes include infections (5%–10%), idiopathic causes (5%–10%), and causes associated with systemic diseases (10%–15%).
 - iv. Several medications have been associated with AIN, including antimicrobials (e.g., penicillins, cephalosporins, sulfonamides, ciprofloxacin, vancomycin), NSAIDs and cyclooxygenase-2 inhibitors, omeprazole, lansoprazole, phenytoin, valproic acid, cimetidine, ranitidine, diuretics, and cocaine.

- v. Renal recovery is usually complete once the offending agent has been removed; however, it may take weeks to several months. AIN associated with the chronic use of calcineurin inhibitors is often irreversible. In addition to removing the offending agent, steroids may be useful in limiting damage. However, steroid use remains controversial.
- c. Glomerular injury
 - i. Acute glomerulonephritis (GN) is associated with inflammation and proliferation of glomerular tissue that results in damage to the basement membrane, mesangium, or capillary endothelium.
 - ii. Nondrug causes of GN include systemic disorders such as lupus, hepatitis, and vasculitis.
 - iii. Drug-associated GN may include NSAIDs, ampicillin, rifampin, lithium, penicillamine, hydralazine, gold, mercury, and heroin.
 - iv. Fever, malaise, and/or arthralgia may occur.
 - v. Renal indices are non-specific and may mirror prerenal disease.
 - vi. GN can result in irreversible kidney damage.
 - vii. Treatment includes removal of the likely agent and may include the use of immunosuppressant's, which may limit disease.
- d. Vascular injury
 - i. Injury to the renal vascular system is more likely to be caused by either microvascular or macrovascular disease than to be induced by drugs.
 - (a) AKI associated with microvascular disease is usually associated with thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, and HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets). It is often the result of glomerular capillary thrombosis.
 - (b) AKI associated with macrovascular disease is usually associated with renal artery occlusion or major abdominal aortic disease.
 - ii. Injury is often irreversible; it should be considered in patients with recent vascular procedures.
 - (a) Intratubular obstruction
 - iii. Intratubular obstruction is uncommon and can be associated with nondrug or drug causes.
 - iv. Nondrug causes include multiple myeloma and tumor lysis syndrome. Injury results from monoclonal light chains and uric acid that obstructs the tubule.
 - v. Drug-associated intratubular obstruction can result from the calcium oxalate crystals associated with ethylene glycol ingestion.
- 3. Postrenal
 - a. AKI associated with postrenal causes is uncommon in critically ill patients because a bladder catheter is usually in place. If an obstruction is suspected, it should be ruled out by evaluating the catheter or by placing one, if absent.
 - b. The obstruction may be in the luminal wall or extrinsic to the urinary tract. To cause AKI from upper tract obstruction, the blockage must be bilateral or affect a single functioning kidney.
 - c. Medications known to cause tubular obstruction include acyclovir, methotrexate, sulfadiazine, foscarnet, indinavir, tenofovir, and triamterene.
 - d. Risk factors include preexisting renal dysfunction and poor hydration.
 - e. Ultrasonography is the gold standard test for diagnosis.

Table 3. Location, Mechanism of Injury, and Potential Causes of Drug-Induced AKI

Prerenal Hemodynamic alterations • ↓ Cardiac output (e.g., negative inotropic drugs) • ↓ Systemic vascular resistance (e.g., vasodilators) • ↑ Renal vascular resistance (e.g., NSAIDs, COX-2 inhibitors, cyclosporine, tacrolimus) • ↓ Transcapillary pressure (e.g., ACEIs; ARBs) Extracellular volume depletion (e.g., excessive diuretic use)
Renal (intrinsic) • Acute tubular necrosis (e.g., AG, amphotericin B, contrast agents, cocaine, antiretrovirals [adefovir, cidofovir, foscarnet, and tenofovir]) • Acute interstitial nephritis (e.g., antimicrobials [penicillins, cephalosporins, sulfonamides, ciprofloxacin, vancomycin, macrolides, tetracyclines, and rifampin], COX-2 inhibitors, NSAIDs, PPIs [omeprazole, lansoprazole], phenytoin, valproic acid, diuretics, cocaine, H₂RAs [cimetidine, ranitidine]) • Glomerulonephritis (e.g., NSAIDs, antimicrobials [ampicillin, penicillamine, rifampin], lithium, hydralazine, gold, mercury, heroin)
Postrenal Precipitation of drug in renal tubules (e.g., sulfonamides, antiretrovirals [acyclovir, foscarnet, indinavir, tenofovir], methotrexate, sulfadiazine, triamterene, vitamin C at large doses)
Bladder Obstruction Anticholinergics, etc.

ACEI = angiotensin-converting enzyme inhibitor; AG = aminoglycoside; ARB = angiotensin receptor blocker; COX-2 = cyclooxygenase-2; GN = glomerulonephritis; H₂RA = histamine-2 receptor antagonist; NSAID = nonsteroidal anti-inflammatory drug; PPI = proton pump inhibitor.

Patient Case

Questions 1–3 pertain to the following case.

F.B. is a 68-year-old man (weight 70 kg) admitted to your ICU with fever, elevated WBC, respiratory failure requiring mechanical ventilation, and norepinephrine to support his blood pressure. His medical history is significant for chronic back pain, diabetes, and hypertension. He takes acetaminophen as needed and glipizide and enalapril daily. Before this admission, he had otherwise been healthy, seeing his primary care provider about 1 week ago. At that time, his blood pressure was 140/80 mm Hg, and his hemoglobin A1C (A1C) was 5.2. His laboratory workup was also unremarkable: WBC 5.0×10^3 cells/mm³, BUN 7 mg/dL, and SCr 0.9 mg/dL. Today, his WBC is 24×10^3 cells/mm³, BUN is 38 mg/dL, and SCr is 3.2 mg/dL, with about 325 mL of urine output since his admission 24 hours ago.

- Which best describes F.B.'s AKI?
 - RIFLE class R.
 - AKIN stage 1.
 - RIFLE class F or AKIN stage 3.
 - RIFLE class E or AKIN stage 3.

Patient Case (*continued*)

2. Which medication is most likely contributing to his AKI?
 - A. Enalapril.
 - B. Glipizide.
 - C. Acetaminophen.
 - D. Enalapril and glipizide equally.
3. When evaluating F.B.'s potential causes of AKI, which additional information or test would be most important to consider or obtain?
 - A. Rate of loss, symptoms, and coexisting diseases and medications.
 - B. Renal evaluation using ultrasonography because this can determine the cause of AKI in most patients.
 - C. Review of blood chemistries because this will likely determine the cause of injury.
 - D. Renal evaluation using biopsy.

II. RENAL REPLACEMENT THERAPIES**A. General Approaches to Managing AKI**

1. Once injury has occurred, therapy consists of providing supportive care and limiting additional insults, including nephrotoxins.
2. In patients with shock, adequate fluid resuscitation should be initiated to restore effective circulation without producing volume overload.
3. No specific pharmacologic therapy is effective in treating or reversing AKI.
4. Metabolic control and patient volume should be followed closely, and RRT should be initiated when other approaches have failed.
5. Few data exist to suggest the timing or modality of therapy. Historically, RRT has been offered when severe acidosis (A) or electrolyte abnormalities – hyperkalemia (E) are present, in the setting of certain intoxicants (I), refractory volume overload (O), or symptomatic uremia (U): the AEIOUs of initiating RRT. Whether RRT is initiated largely depends on the treating physician, but recent evidence suggests that early initiation is associated with decreased mortality.

B. Mode of Renal Replacement for AKI

1. Differing modes of RRT include IHD, peritoneal dialysis, CRRTs, and extended daily dialysis (EDD) or sustained low-efficiency dialysis (SLED).
2. Solute and water transport through a semipermeable membrane, which assists in defining the mode of RRT.
3. Solute removal requires diffusion, convection, or both.

C. IHD

1. IHD has historically been used to treat critically ill patients with AKI.
2. However, hypotension can occur in about 20%–30% of patients treated with IHD.
3. IHD may also be problematic in patients with head trauma or hepatic encephalopathy because of rapid solute removal from the intravascular space, causing cerebral edema and increased intracranial pressure.

D. CRRTs

1. CRRT is the most commonly used modality of RRT in hemodynamically unstable ICU patients.
2. CRRT modalities include CVVH, continuous venovenous hemodialysis (CVVHD), and continuous venovenous hemodiafiltration (CVVHDF).
3. SCUF, or slow continuous ultrafiltration, is another type of CRRT that removes fluid without the need for replacement solutions. It does not affect the removal of waste products (e.g., BUN) or electrolytes and cannot correct acid-base abnormalities.
4. Solute clearance during CVVHD occurs by diffusion. Diffusion is the movement of solutes from an area of higher solute concentration to an area of lower concentration. A concentration gradient is produced by running an electrolyte solution (i.e., dialysis fluid with a flow rate of 17–40 mL/minute) countercurrent to the flow of blood. Small-molecular-weight solutes are cleared efficiently.
5. Solute clearance during CVVH occurs by convection, and the ultrafiltration rate determines the clearance rate for most solutes. Convection uses the concept of “solute drag” and is capable of removing both small- and large-molecular-weight solutes. Solute removal occurs when the transmembrane pressure drives water and solute across a semipermeable membrane. This process involves adding replacement fluid to replace the excess volume that is being removed and replenish the desired electrolytes.
6. For CVVHDF, solute removal is by convection (i.e., CVVH) and diffusion (i.e., CVVHD).

E. Prolonged Intermittent RRT

1. An alternative to both CRRT and IHD
2. Includes several forms of daily renal replacement; examples include sustained low-efficiency daily dialysis (SLEDD), sustained low-efficiency daily diafiltration (SLEDD-f), EDD, and accelerated venovenous hemofiltration
3. These therapies are provided using conventional hemodialysis machines with low blood-pump speeds (around 200 mL/minute) and low dialysate flow rates (around 300 mL/minute) for extended periods: 6–12 hours a day versus 3–4 hours for IHD or 24 hours for CRRT.
4. Similar to CRRT, they allow for improved hemodynamic stability by producing gradual solute and volume removal compared with IHD.
5. These therapies have certain advantages over CRRT. They produce high solute clearances using existing IHD machines, eliminating the need for external solutions, and allow “time away” when various diagnostic and therapeutic procedures are needed. Disadvantages include limited data on drug clearance.

F. Choosing a Mode

1. Data are conflicting regarding the renal replacement mode of choice for critically ill patients.
2. Outcomes such as mortality and renal recovery appear to be no different between IHD and CRRT; however, most studies are limited by design, patient characteristics, and crossover between different modalities.

G. CRRT and Drug-Dosing Concepts

1. Drug properties that influence removal during CRRT include protein binding, MW, and Vd. Drug charge is less important.
 - a. The ability of a drug to bind to plasma protein (i.e., albumin) greatly influences how it is removed by CRRT. Removal is inversely proportional to the percent bound (i.e., the higher the percent bound, the less removed). Protein binding affects removal for both convection and diffusion.
 - b. In the absence of significant protein binding, the MW of most drugs has little impact on its overall clearance. Removal can be significant during CVVH because this therapy effectively removes drugs with an MW less than 15,000 kDa, and the pore sizes of most membranes are 20,000–30,000 kDa, allowing drugs to pass freely. During CVVHD, the greatest impact on drug clearance occurs with

drugs having an MW less than 500 kDa. As MW increases, clearance is reduced. Given that most drugs have an MW of less than 500 kDa, CVVH, CVVHD, and CVVHDF result in significant drug removal if protein binding is low.

- c. Vd is less of an issue with CRRT than with other RRTs. Because CRRT uses slower flow rates, time is allowed for drugs to equilibrate between body compartments. Drugs with a Vd less than 0.6 L/kg have a greater potential for removal.
2. CRRT modalities and their influence during therapy

a. CVVH

- i. Solute removal during CVVH is by convection. Convection is influenced by the membrane pore size; the free fraction of drug, as discussed earlier; and the ultrafiltration rate.
- ii. The ability of a substance to pass through a membrane by convection is termed *sieving coefficient* (SC). The SC ranges from 0 to 1. An SC of 1 represents free movement, whereas an SC of 0 represents no movement across a filter.
- iii. SC can be calculated using a ratio of measured drug or other solute in the ultrafiltrate to its concentration in the plasma, $SC = CUF/C_p$, where CUF is concentration in the ultrafiltrate and C_p is concentration in the plasma.
- iv. If a measured SC is not available, it can be estimated using the percent unbound to albumin, $SC = 1 - fb$, where fb is fraction bound.

If replacement fluids are administered postfilter, the clearance rate can be estimated using the following equation:

$$CVVH_{\text{post-dilution}} = Q_{UF} \times SC \text{ (mL/min)}$$

If pre-dilution (i.e., before the filter) fluids are used, clearance across the membrane is reduced. Clearance can be estimated using the following equation:

$$CVVH_{\text{pre-dilution}} = Q_{UF} \times SC \times Q_b / (Q_b + Q_{rf})$$

where Q_{UF} is ultrafiltration flow rate, Q_b is blood flow rate, and Q_{rf} is pre-dilution replacement fluid flow rate. For pre-dilution fluid replacement to affect overall clearance, the rate must be high. Increased clearance can also occur if both pre- and post-dilution fluids are used.

b. CVVHD

- i. Solute removal during CVVHD occurs by passive diffusion. The flow of dialysate is countercurrent to that of the blood. Movement of solute across the semipermeable membrane occurs because of a concentration gradient, with movement from an area of higher concentration (blood) to an area of lower concentration (dialysate). This process occurs until equilibrium is established.
- ii. Small substances (e.g., urea with an MW of 60 kDa) are cleared more rapidly than large substances (e.g., drugs with an MW approaching 500 kDa).
- iii. The ability of a drug to cross the dialysis filter during CVVHD is called the saturation coefficient (SA). Equations exist for estimating the SA when published data are unavailable. It can be calculated as $SA = CE/C_p$, where CE is the concentration in the effluent (spent dialysate) fluid and C_p is the concentration in plasma. C_p can be calculated as $C_p = (CA + CV)/2$, where CA is the concentration obtained from the prefilter port and CV is the concentration obtained from the postfilter port. This equation can be simplified to $SA \sim CE/C_p$, but this is slightly less accurate. $CVVHD \sim Q_d \times SA$, where Q_d is the dialysate flow rate.

c. CVVHDF

- i. Solute removal during CVVHDF is by diffusion and convection (i.e., both dialysate and replacement fluids are used).

- ii. Clearances of small substances are about equal to the sum of the clearance from CVVH and CVVHD separately. However, as MW increases, this correlation no longer holds true.
- iii. Clearance is estimated as $CVVHDF = (Q_{UF} + Q_d) \times SA$.
- d. SLED and EDD
 - i. As with IHD and CRRT, the most important factor influencing drug removal during SLED/EDD is protein binding.
 - ii. Other factors include blood and dialysis flow rates and membrane surface area and flux.
 - iii. Solute removal during SLED/EDD is greater than that during CVVHD when estimated over the same time interval because higher dialysis flow rates are used during SLED/EDD treatments.
- e. Drug-dosing concepts
 - i. Drug dosing during CRRT and SLED is often unclear because this information is not included in product labeling. Manufacturers are not required to study how these therapies alter clearance.
 - ii. General dosing considerations for CRRT
 - (a) For most medications, loading doses require no adjustment.
 - (b) If a drug is normally cleared by the kidneys or is removed by other RRT modalities, CRRT will likely have a significant impact on its removal.
 - (c) When available, drug-specific literature should be used in determining dose and frequency to minimize the likelihood of dosing errors. Although CRRT is meant to be a continuous therapy, it is often interrupted. If therapy is held for an extended period, dose adjustment may be required.
 - iii. General dosing considerations for SLED
 - (a) The duration of SLED and its flow rates (dialysate, blood) vary between studies and institutions, making a general approach to dosing problematic.
 - (b) In addition, little information is available to guide drug dosing.
 - (c) Like IHD and CRRT, the most important factors determining drug removal are protein binding, water solubility, MW (less than 500 kDa), and Vd (less than 0.8–1 L/kg).

Patient Case

Questions 4–6 pertain to the previous case.

F.B. is a 68-year-old man (weight 70 kg) admitted to your ICU with fever, elevated WBC, respiratory failure requiring mechanical ventilation, and norepinephrine to support his blood pressure. His medical history is significant for chronic back pain, diabetes, and hypertension. He takes acetaminophen as needed and glipizide and enalapril daily. Before this admission, he had otherwise been healthy, seeing his primary care provider about 1 week ago. At that time, his blood pressure was 140/80 mm Hg, and his A1C was 5.2. His laboratory workup was also unremarkable: WBC 5.0×10^3 cells/mm³, BUN 7 mg/dL, and SCr 0.9 mg/dL. Today, his WBC is 24×10^3 cells/mm³, BUN 38 mg/dL, and SCr 3.2 mg/dL, with about 325 mL of urine output since his admission 24-hours ago.

It is determined that F.B. needs RRT to manage his volume and control his metabolic derangements. He is currently receiving norepinephrine with a mean arterial pressure of 65 mm Hg.

4. Which renal replacement mode will most likely be chosen?
- A. IHD.
 - B. Slow-low EDD.
 - C. CRRT.
 - D. Peritoneal dialysis.

Patient Case (*continued*)

5. You are asked to dose F.B.'s medications while he receives CRRT. Which propriety has the greatest influence on drug removal?
 - A. Protein binding.
 - B. MW.
 - C. Vd.
 - D. Drug charge.

6. F.B. is to start antimicrobial therapy, and you are asked to dose his medications. Which is the most reasonable approach to determining the appropriate dose and frequency?
 - A. Look up recommendations for IHD therapy because they are the same as for CRRT.
 - B. Perform a drug-specific literature search to determine the most appropriate IHD dose, and then use it to recommend dosing during CRRT.
 - C. Use only CRRT-based recommendations because drug removal is different between IHD and CRRT.
 - D. Once a dose and frequency are determined, they can be continued until the patient recovers his renal function.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES**1. Answer: C**

Both RIFLE class “F” and AKIN stage 3 are met using similar SCr and urine output criteria. For this case, the SCr increased by at least 3-fold above baseline, and the patient’s urine output was less than 0.3 mL/kg/hour for 24 hours. Although A and B are true, the worse values in the RIFLE class and AKIN staging systems should be chosen when determining the class and stage of AKI. Answer D is incorrect because his renal indices have not been present for at least 3 months.

2. Answer: A

This patient has severe sepsis that led to decreased renal perfusion, causing AKI. Enalapril likely contributed to the injury by altering renal hemodynamics (Answer A is correct). Neither glipizide nor acetaminophen is likely to cause AKI (Answers B–D are incorrect).

3. Answer: A

Acute kidney injury cannot be diagnosed with a specific test or study. The patient’s rate of kidney loss, symptoms, and coexisting diseases are very important because these may lead to the cause of injury. Drug-induced AKI is most common in the setting of additional insults and may occur even after the drug is discontinued.

4. Answer: C

Intermittent hemodialysis is often used in critically ill patients because many physicians are familiar with this therapy; however, about 20%–30% of patients receiving IHD become hypotensive and require discontinuation or a switch to an alternative therapy. Although slow-low EDD is an option, some form of CRRT would likely be chosen because of this patient’s unfavorable hemodynamics. Continuous renal replacement therapies such as CVVH, CVVHD, and CVVHDF are often used because they allow for slower flow rates and improved hemodynamics. However, there is no clear benefit with one therapy over another.

5. Answer: A

The greatest influence of drug removal during CRRT is binding to albumin (i.e., the higher the percent bound, the less drug removed). The MW of most drugs has little impact on the drug’s overall clearance because most drugs are less than 500 kDa. Continuous venovenous

hemofiltration can effectively remove drugs with an MW less than 15,000 kDa, whereas the greatest impact of removal during CVVHD occurs with drugs having an MW less than 500 kDa. Because CRRT is performed using slower flow rates, time is allowed for the drugs to equilibrate between body compartments, making Vd less of an issue. Although not well studied, binding to the filter is not important for most drugs.

6. Answer: C

Continuous renal replacement therapy presents unique challenges, and dosing considerations are not interchangeable between intermittent and continuous therapies. In general, if a drug is normally cleared by the kidneys or removed by other RRT modalities, CRRT will likely affect its clearance significantly. In the absence of significant protein binding, removal can be expected. Drug-specific guidance can be obtained from the primary literature or from summary charts, but it should be reviewed with caution because flow rates during CRRT may vary. Although CRRT is meant to be a continuous therapy, it is often interrupted, and drug dose and frequency may need adjustment.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS**1. Answer: B**

Although AIN is an uncommon occurrence, drugs are associated with more than 75% of cases if it occurs. Several medications have been associated with AIN, including antimicrobials (e.g., penicillins, cephalosporins, sulfonamides, ciprofloxacin, vancomycin, macrolides) and histamine-2 receptor antagonists. ATN is more common with sepsis (Answer A is incorrect). GN is associated with ampicillin and penicillamine but uncommon with cephalosporins and ceftriaxone does not precipitate in renal tubules (Answers C and D are incorrect).

2. Answer: C

Stage 3 of AKIN is met, regardless of the patient's change in SCr or urine output, because he is receiving RRT. Since E.R is receiving RRT, Answers A, B, and D are all incorrect.

3. Answer: A

Solute removal during CVVH is by convection, which is primarily influenced by membrane pore size, free fraction of drug, and ultrafiltration rate. Diffusion is the process of clearance during CVVHD making Answers B and C incorrect. Membrane binding does occur but is not the primary route of clearance during CVVH (Answer D is incorrect).

4. Answer: C

Drug-dosing recommendations for IHD can be found in many resources. However, dosing during CRRT and SLED is less clear. Primary literature and/or summary tables for CRRT and SLED should be referenced because these recommendations are not usually found in other sources. Use caution to ensure that identical modes of CRRT are referenced with similar flow rates (Answers A and B are incorrect). Drug dosing using a sieving coefficient should only be used when a review of the literature fails to provide specific drug adjustment recommendations (Answer D is incorrect).

5. Answer: A

Although protein binding, MW, Vd, and drug charge may influence drug removal during CRRT, binding to plasma protein has the greatest impact because only unbound drugs can be cleared through the filter (Answer A is correct).

PHARMACOKINETICS/ PHARMACODYNAMICS

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Learning Objectives

1. Describe the changes in critically ill patients that alter drug absorption.
2. Explain how critical illness affects the distribution of drugs.
3. Depict the effects of changing hepatic blood flow, intrinsic activity, and protein binding on drug metabolism.
4. Differentiate between different critically ill patient populations and the expected pharmacokinetic (PK) changes.
5. Incorporate the PK changes in a critically ill patient into the design and evaluation of an appropriate drug regimen.
6. Identify the desired pharmacodynamic variables associated with efficacy in select drugs.

Abbreviations in This Chapter

AAG	α_1 -Acid Glycoprotein
AKI	Acute kidney injury
aPTT	Activated partial thromboplastin time
ARC	Augmented renal clearance
AUC	Area under the curve
AUC/MIC	Ratio of area under the curve to the minimum inhibitory concentration for the bacterial pathogen
AUC ₀₋₂₄ /MIC	Ratio of area under the curve for 24 hours to the minimum inhibitory concentration for the bacterial pathogen
CKD	Chronic kidney disease
C _{max} /MIC	Ratio between the maximum drug concentration and the minimum inhibitory concentration for the bacterial pathogen
f _T >MIC	Free drug concentration time above the minimum inhibitory concentration for the bacterial pathogen
GFR	Glomerular filtration rate
ICU	Intensive care unit
KDIGO	Kidney Disease Improving Global Outcomes
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
SIRS	Systemic inflammatory response syndrome
TBI	Traumatic brain injury
Vd	Volume of distribution

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

1. J.H. is a 30-year-old man admitted to the intensive care unit (ICU) for septic shock. He initially received 30 mL/kg of normal saline for intravenous fluid resuscitation. He required further fluid administration to achieve a central venous pressure greater than 8 mm Hg. Despite prophylaxis with enoxaparin 30 mg subcutaneously every 12 hours, J.H. has a proximal deep venous thrombosis. Which is the most likely pharmacokinetic (PK) alteration contributing to this therapeutic failure?
 - A. Decreased antifactor Xa (anti-Xa) activity secondary to decreased volume of distribution (Vd)
 - B. Decreased anti-Xa activity secondary to decreased absorption
 - C. Increased anti-Xa activity secondary to decreased hepatic metabolism
 - D. Increased anti-Xa activity secondary to decreased renal elimination

Questions 2–4 pertain to the following case.

E.W. is a 48-year-old man (height 70 inches, weight 85 kg) admitted to the trauma ICU after a motorcycle collision. E.W. presents with a traumatic brain injury (TBI; head computed tomography [CT] reveals a depressed skull fracture, frontal subarachnoid hemorrhage, and right intraparenchymal hemorrhage), right acetabulum fracture, bilateral rib fractures, and abdominal trauma. According to his abdominal CT, E.W. must go to the operating room for an exploratory laparotomy to undergo repair of several serosal tears. After surgery, E.W. requires significant resuscitation in his first 24 hours of admission (12 L of normal saline). He is made NPO (nothing by mouth) to allow bowel rest.

E.W.'s laboratory values are as follows: serum creatinine (SCr) 1.1 mg/dL, blood urea nitrogen (BUN) 17 mg/dL, and white blood cell count (WBC) 19×10^3 cells/mm³. Pulmonary artery catheterization values are cardiac index 4.2 L/minute/m² (normal 2.8–3.6 L/minute/m²) and central venous pressure 9 mm Hg. His medication therapy includes a fentanyl continuous infusion of 75 mcg/hour, a propofol continuous infusion of 15 mcg/kg/minute, pantoprazole 40 mg intravenously every 24 hours, enoxaparin 30 mg subcutaneously every 12 hours, and phenytoin 150 mg intravenously every 8 hours.

2. Which is the most accurate assessment of risk factors for the decreased absorption of enterally administered drugs?
 - A. Intestinal atrophy, pantoprazole therapy, abdominal surgery
 - B. TBI, fentanyl therapy, cardiac output
 - C. Abdominal surgery, pantoprazole therapy, TBI
 - D. Intestinal atrophy, cardiac output, fentanyl therapy
3. Before E.W.'s admission to the ICU, his albumin concentration was 3.8 g/dL, but after surgery, it declines to 2.1 g/dL. Given this change in albumin, which change in total concentration and unbound concentration of propofol would be most likely?
 - A. Increased total concentration, decreased unbound concentration
 - B. No change in total concentration, increased unbound concentration
 - C. Increased total concentration, no change in unbound concentration
 - D. Decreased total concentration, increased unbound concentration
4. On postoperative day 3, E.W.'s serum creatinine (SCr) increases to 3 mg/dL. On postoperative day 4, his SCr is 3.2 mg/dL. Which variable for assessing kidney function would be most important for determining dosing adjustments in E.W.?
 - A. BUN/SCr ratio
 - B. Total daily urine output
 - C. Estimation of glomerular filtration rate (GFR)
 - D. History of chronic kidney disease (CKD)
5. According to the known PK changes in S.H., which would be the most appropriate intravenous loading dose of vancomycin?
 - A. 1500 mg
 - B. 2000 mg
 - C. 2500 mg
 - D. 3000 mg
6. S.H. is given a diagnosis of methicillin-resistant *Staphylococcus aureus* health care–associated pneumonia. On day 10 of vancomycin therapy, he has a vancomycin trough of 25 mcg/mL. On his current vancomycin dosing, he was previously therapeutic (trough of 19 mcg/mL). Which most likely explains what transpired?
 - A. Augmented renal excretion returned to normal.
 - B. Vd increased to larger than normal.
 - C. Tissue penetration decreased to below normal.
 - D. Liver blood flow returned to normal.
7. B.B. is 40-year-old woman with a surgical site infection caused by *Pseudomonas aeruginosa*. She is initiated on a piperacillin/tazobactam 3.375 g intravenous infusion for 4 hours every 8 hours. Which is the most likely benefit of this approach with piperacillin/tazobactam?
 - A. Decreased mortality supported by prospective controlled studies
 - B. Decreased neurotoxicity supported by prospective controlled studies
 - C. Decreased mortality supported by retrospective reviews
 - D. Decreased neurotoxicity supported by retrospective reviews
8. C.W. is a 52-year-old man admitted to the ICU for acute respiratory failure. He is given scheduled morphine for pain control. Which PK variable would most likely affect the hepatic metabolism of morphine?
 - A. Increased α_1 -Acid Glycoprotein (AAG)
 - B. Decreased albumin
 - C. Increased hepatic blood flow
 - D. Increased intrinsic clearance

Questions 5 and 6 pertain to the following case.

S.H. is a 35-year-old man (height 70 inches, weight 85 kg) admitted to the medical ICU because of sepsis caused by health care–associated pneumonia. He is empirically treated with vancomycin, piperacillin/tazobactam, and ciprofloxacin. His laboratory values are as follows: SCr 1 mg/dL, BUN 12 mg/dL, and WBC 18×10^3 cells/mm³.

I. INTRODUCTION

Pharmacokinetics (PK) refers to the movement of a drug through the body, particularly the absorption, distribution, metabolism, and excretion of a drug, whereas pharmacodynamics (PD) addresses the biochemical and physiologic effects of a drug on the body according to the concentration. Physiologic changes in critically ill patients cause alterations that affect the PK and PD of drugs. Although few studies evaluate the effect of these changes, clinicians must consider the general principles when making decisions about drug dosing in the critically ill. The most important consideration in critically ill patients is that changes can occur rapidly. A patient may have an altered PK variable on one day, only to experience changes that alter that variable in a completely different way on the following day. The best example is of a critically ill patient with augmented renal clearance who then experiences acute kidney injury (AKI). In this example, the patient may have increased renal elimination of a specific drug, followed by decreased elimination when AKI occurs. Therefore, it is important for the critical care pharmacist to know how the principles can be altered and to continually anticipate changes during a patient's stay in the ICU.

II. ROUTES OF ADMINISTRATION

A. Intravenous

1. The intravenous route is the most widely used method of drug administration in the critically ill population. The bioavailability of an intravenously administered drug is 100%, thus ensuring the entire dose reaches the systemic circulation.
2. Although intravenous drug administration is the most popular method used in the ICU, it still poses several potential problems. The intravenous route does not guarantee penetration of the drug into sites outside the circulatory system. Examples of this include poor penetration of drugs into various tissues such as the meninges, pulmonary tissue, and bone. In conditions such as septic shock, drug penetration into muscle and subcutaneous tissue is lower than expected. Finally, reports of inadvertent extravascular administration of a drug contain documented severe adverse effects. Several reports of drug (cytotoxic and noncytotoxic) extravasation highlight this potential complication of intravenous administration.

B. Enteral/Oral – Using the enteral or oral route of administration in critically ill patients results in variable drug bioavailability. The predominant concern for this route of administration in critically ill patients pertains to alterations in drug absorption. The issues pertaining to altered drug absorption are discussed in the next section. Of note, not all drugs show reduced absorption when administered enterally/orally to critically ill patients. One example comes from a study investigating the PK of atorvastatin. Compared with healthy volunteers, patients in the ICU had a significantly higher area under the curve (AUC) (110.5 ng/mL vs. 5.9 ng/mL, $p < 0.01$) after a single dose of atorvastatin 20 mg. The increased AUC could only partly be explained by altered hepatic metabolism (Intensive Care Med 2009;35:717-21). As such, critical care clinicians often question use of the enteral/oral route.

C. Subcutaneous/Intramuscular – Subcutaneous and intramuscular drug administration avoids first-pass metabolism by the liver and has the potential to increase the bioavailability of a drug. However, these routes still require the drug to be absorbed into the blood. Therefore, these routes are potentially affected by changes in absorption. Unlike the enteral or oral route, clinicians do not routinely abandon the use of subcutaneously or intramuscularly administered medications. Examples include the continued use of low-molecular-weight heparins and the antipsychotic haloperidol in patients for whom the absorption may be altered.

- D. Inhalation – Administration of drugs directly into the lungs of critically ill patients is generally used for the local effect and not intended for systemic distribution. In fact, this route is often chosen to reduce systemic exposure of a drug. Ideally, an inhaled drug will achieve a high concentration in the pulmonary tissue, with little systemic exposure. The high local concentration is intended to maximize the therapeutic effect while reducing any adverse or unwanted effects. For example, the use of inhaled bronchodilators reduces unwanted systemic effects such as tachycardia. Antibiotics such as colistin and aminoglycosides are administered to improve the antibiotic concentrations in the lungs and reduce exposure to the kidneys. Drug particles between 1 and 5 micrometers have the best opportunity to be delivered to all areas of the lungs. Smaller particles will be exhaled without being deposited in the lower airways, whereas larger particles will be deposited in the large bronchi or the oropharynx. Several models of nebulizers are on the market that use different methods to achieve the desired particle sizes.
- E. Intrathecal/Intraventricular – The intraventricular route is used with the same goal as the inhalation route. Increased local concentrations and reduced systemic concentrations are the desired effect. Data evaluating the efficacy of this route of administration are lacking in the general population and mostly limited to case series. Despite the lack of data, clinicians use this route when treating multidrug-resistant meningitis.

Patient Case

1. M.J. is a 70-year-old man admitted to the neurosurgical ICU for an aneurysmal subarachnoid hemorrhage. His initial management included placement of an external ventricular drain. Subsequently, he had a maximum temperature of 101.5°F, a WBC of 15×10^3 cells/mm³, and a cerebrospinal fluid culture positive for methicillin-resistant *S. aureus*. Intraventricular vancomycin 20 mg is used for therapy. Which is the best rationale for this approach?
 - A. Demonstrated superiority to intravenous antibiotics
 - B. Maximizing localized antibiotic concentrations
 - C. Reducing the nephrotoxicity of vancomycin
 - D. Reducing the ototoxicity of vancomycin

III. ABSORPTION

- A. Bioavailability refers to the percentage of an administered dose of drug that reaches the systemic circulation. Bioavailability from subcutaneous, intramuscular, or enteral administration is affected by absorption and first-pass metabolism (enterally administered drugs). Few studies directly assess the enteral absorption of drugs in critically ill patients, and the results vary. In addition, studies of enterally administered drugs do not differentiate whether plasma concentrations are altered because of changes in absorption or first-pass metabolism. Although data on absorption in critically ill patients are limited, clinicians must consider several factors if a route of administration other than intravenous is desired.

- B. Gastrointestinal (GI) Perfusion – Hypotension and/or shock are known to cause the shunting of blood toward the vital organs (brain, heart, lungs) and away from the less vital organs (muscles, skin, splanchnic organs).
1. GI absorption: No studies clearly show the effect of hypotension or shock on the oral or enteral absorption of drugs. Clinicians extrapolate changes in splanchnic blood flow to the likelihood that GI absorption is altered. Redistribution of blood away from the splanchnic circulation is thought to decrease drug absorption from the GI tract. The hyperdynamic phase of sepsis or septic shock can increase cardiac output, and studies have shown an increase in hepatosplanchnic (portal vein and hepatic artery) blood flow. In late-stage (decompensated) sepsis, it is thought that splanchnic blood flow is decreased, but no studies have verified this. This uncertainty in splanchnic blood flow and GI absorption leads many clinicians to forgo the enteral route for drug administration.
 2. Transdermal, subcutaneous, and intramuscular absorption: There are no studies evaluating the effect of hypotension or shock on transdermal, subcutaneous, or intramuscular absorption. Similar to splanchnic circulation, the shunting of blood to vital organs reduces blood flow to the skin and muscles, which is thought to reduce absorption from these sites. This assumption is supported by the observation that critically injured trauma patients with edema have significantly lower anti-Xa and antithrombin activity after treatment with subcutaneous enoxaparin (J Trauma 2005;59:1336-43). It is believed that altered absorption is a contributing factor to these results. However, this may not be generalized to all critically ill patients because anti-Xa activity was not significantly different in edematous compared with non-edematous medical-surgical ICU patients after dalteparin administration (Crit Care 2006;10:R93).
 3. Vasopressor effect: Vasopressors may contribute to regional hypoperfusion, which could result in decreased absorption of drugs. Vasopressin reduces splanchnic blood flow in patients with distributive shock. In septic shock, use of epinephrine results in reduced splanchnic blood flow. Dopamine is not as effective as norepinephrine in maintaining splanchnic blood flow in patients with stable distributive shock. Conversely, when gut perfusion is compared between cardiac surgery patients with and without vasodilatory shock, norepinephrine use results in higher intestinal perfusion. However, this is countered by a worse splanchnic oxygen demand versus supply. The variable effect of vasopressors on splanchnic perfusion creates enough concern that most clinicians abandon the use of orally or enterally administered drugs when vasopressors are being used. In addition, absorption from other sites could be impaired. One study investigated the anti-Xa activity of the low-molecular-weight heparin certoparin in critically ill patients, of which 40.3% were receiving vasopressors. Less than 50% of patients receiving standard doses of certoparin had anti-Xa activity in the antithrombotic range (0.1–0.3 IU/mL) (Crit Care 2005;9:R541-8).
- C. Intestinal Atrophy – After 3–5 days of fasting, gut mucosal crypt depth and villus height can be decreased. This correlates with an abnormal lactulose-mannitol test, indicating increased gut permeability. Splanchnic hypoperfusion can further worsen gut hypoxia, exacerbating gut permeability. However, the effect of intestinal atrophy on drug absorption has not been systematically evaluated. Atrophy and the corresponding loss of integrity of the tight junctions could lead to an increased absorption of drugs that are absorbed through passive diffusion. Conversely, cellular dysfunction caused by atrophy might decrease the absorption of drugs that require active transport for absorption. Currently, no studies can clarify this quandary.
- D. GI Dysmotility – GI dysmotility has been clearly established in critically ill patients, with an incidence as high as 60%. Table 1 shows the conditions in critically ill patients that are associated with delayed gastric emptying caused by dysmotility. Acetaminophen kinetics show that GI dysmotility causes a delay in absorption and a reduced peak concentration in most studies. Concern regarding PK changes in the presence of delayed gastric emptying is a major factor contributing to the avoidance of orally or enterally administered drugs in critically ill patients. GI dysmotility is generally treated using prokinetic agents such as metoclopramide or erythromycin. There are no data regarding the effect of prokinetics on drug absorption in critically ill patients with dysmotility. Therefore, the effect of prokinetics on the PK of orally or enterally administered drugs in critically ill patients is unclear.
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Table 1. Reasons for Delayed Gastric Emptying

Surgery	Postoperative ileus	Trauma
Traumatic brain injury	Burns	Sepsis
Opioid analgesics	Mechanical ventilation	Electrolyte abnormalities
Hyperglycemia	Shock	Ileus

- E. **Intestinal Drug Transporters** – Transmembrane proteins such as P-Glycoprotein (PGP) and cytochrome P450 (CYP) enzymes play an integral role in the absorption of drugs. In general, these transporters serve to reduce the absorption of drug substrates. Therefore, decreased activity of these enzymes will theoretically increase the absorption of drugs that are substrates. Conversely, several intestinal transporters facilitate drug absorption and may thus decrease drug absorption. Unfortunately, there are no PK studies evaluating changes in drug absorption caused by changes in intestinal transporters that are specifically related to critical illness or conditions often present in these patients. As such, clinicians must understand the conditions that may affect transporter activity. Increased inflammatory cytokines in patients with conditions that precipitate inflammation, previously referred to as systemic inflammatory response syndrome (SIRS), and sepsis affect PGP activity. Therefore, enteral drug absorption has the potential to be altered in these states. Unfortunately, no studies have directly investigated the effects of inflammatory states, or SIRS, on drug absorption changes mediated by changes in PGP activity.
- F. **Physical Incompatibilities** – Drugs administered through enteral feeding tubes come in contact with gastric secretions, intestinal secretions, and enteral nutrition formulas. All of these pose a problem for drug absorption.
1. **Drug enteral nutrition binding:** Some drugs potentially interact with enteral nutrition. The degree of interaction and clinical significance varies.
 - a. Ciprofloxacin bioavailability is reduced when it is administered with enteral nutrition, but most studies suggest that serum concentrations remain above the minimum inhibitory concentration (MIC) for most bacterial pathogens.
 - b. Enteral nutrition has been reported to significantly reduce the absorption of levothyroxine, phenytoin, and warfarin. One case report showed a reduction in voriconazole serum concentrations when enteral nutrition was initiated (J Oncol Pharm Pract 2012;18:128-31).
 - c. A suggested solution to this interaction is to hold the enteral nutrition 1–2 hours before and after drug administration. However, this poses two problems. First, interruption of enteral nutrition may contribute to inadequate nutrition support. Second, this increases the difficulty of administering the medications appropriately. Increasing the workload of nursing has the potential to cause administration delays or, even worse, errors. This is very important, because failure to withhold the enteral nutrition could result in suboptimal dosing and effects of the interacting drug.
 2. **pH changes:** The state of ionization of a drug generally affects the lipophilicity and potentially the absorption. Examples from noncritically ill patients include increased gastric pH caused by histamine-2 receptor antagonists or proton pump inhibitors, resulting in decreased absorption of ketoconazole, itraconazole, atazanavir, cefpodoxime, and dipyridamole. Acid-suppressive drugs increased nifedipine and digoxin absorption, and alendronate had a 2-fold increase in bioavailability in the presence of these agents (Aliment Pharmacol Ther 2009;29:1219-29).
- G. **Important Considerations for Absorption**
1. The overall uncertainty of a patient's ability to absorb drugs from the GI tract often results in the clinician's avoidance of enterally administered drugs. The decision to use the GI route of administration is arbitrary. Many clinicians will anecdotally use tolerance of enteral feedings as a surrogate marker for normal drug absorption. If certain drugs are administered enterally, withholding the nutrition to avoid physical incompatibilities is warranted.

2. Subcutaneous and intramuscular routes of administration present similar problems with absorption, but clinical practice has not abandoned these routes of administration. Some clinicians advocate for using larger doses of drugs being administered subcutaneously, but no studies have verified the safety or efficacy of this practice.

Patient Case

2. I.L. is a 32-year-old man receiving stress ulcer prophylaxis with esomeprazole 40 mg intravenously every day. Which drug will most likely have an increased absorption secondary to the increased gastric pH?
- A. Carvedilol
 - B. Ciprofloxacin
 - C. Diazepam
 - D. Digoxin

IV. DISTRIBUTION

- A. The V_d of a drug is a PK variable that relates the dose with the resultant serum concentration of said drug. A simple mathematical representation of this relationship is the following equation:

$$C = \frac{\text{dose}}{V_d}$$

where C is the initial serum concentration of an intravenously administered drug and V_d is the volume of distribution. However, the distribution of most drugs is more complex and is affected by several factors, such as perfusion, degree of protein binding, tissue permeability, drug lipid solubility, drug pK_a , and pH of the environment. Critically ill patients may be subjected to changes in the previously stated factors that could result in an altered V_d for some drugs.

- B. Tissue Perfusion – As noted in the previous section, shock states cause the redistribution of blood flow. This results in decreased perfusion of the muscle, skin, and splanchnic organs. Hydrophilic drugs with a smaller V_d (ones that remain in the plasma water volume) may have decreased distribution to parts of the body with decreased blood flow. This is highlighted by animal studies of septic shock showing lower gentamicin concentrations in the microcirculation compared with the central vessels.
- C. Fluid Shifts and Tissue Membrane Permeability – Critically ill patients can receive significant volumes of intravenous fluid for resuscitation purposes. This often results in increased volumes of total body water and interstitial fluid. In addition to fluid administration, disease states such as sepsis, thermal injury, acute respiratory distress syndrome, AKI, heart failure, and cirrhosis can cause increases in interstitial fluid volumes. In addition, surgery increases extracellular volume postoperatively. In this setting, the V_d for hydrophilic drugs is increased, whereas the V_d for lipophilic drugs is often unchanged. The increased interstitial water provides a larger compartment for hydrophilic drugs to distribute, thus decreasing the serum concentrations. In addition, because distribution is into a larger interstitial space, the drug concentration can be decreased in this space. This has been shown in microdialysis studies evaluating subcutaneous tissue concentrations for piperacillin. Compared with healthy volunteers, patients with septic shock had reduced

piperacillin tissue concentrations. Unfortunately, increased Vd of drugs is not universally noted. Although one study found increases in aminoglycoside Vd, another study was unable to correlate fluid shifts with changes in the aminoglycoside Vd (Crit Care Med 1988;16:327-30).

- D. **Protein Binding** – Drugs can bind to plasma proteins such as albumin, AAG, lipoproteins, and cortisol-binding protein. Albumin and AAG are important in critically ill patients. Albumin generally binds to acidic drugs (e.g., diazepam, phenytoin), whereas AAG binds to basic drugs (e.g., lidocaine, diltiazem). Of importance, their concentrations change during various states of critical illness. Albumin concentrations generally decrease under stress, whereas AAG concentrations increase. The following equation represents the calculation of Vd:

$$Vd = \left(\frac{f_u}{f_{ut}} \right) Vt + Vp$$

where f_u is the fraction unbound in the plasma, f_{ut} is the fraction unbound in the tissues, Vt is the volume of tissue, and Vp is the volume of plasma. When the plasma concentration of albumin decreases, the f_u of a drug increases. This increase results in an increased Vd. The converse is true for drugs bound to AAG.

1. The clinical relevance of this was noted when a decrease in the Vd of lidocaine correlated with an increase in AAG in post-cardiac surgery patients. It was suspected that arrhythmias were caused by these PK changes (Clin Pharmacol Ther 1984;35:617-26).
2. Table 2 provides examples of drugs used in critically ill patients that bind to albumin and AAG.

Table 2. ER and Protein Binding of Select Drugs Used in Critically Ill Patients

Protein Binding	High ER Drugs*	Intermediate ER Drugs*	Low ER Drugs*
Albumin	Propofol Morphine Propranolol Verapamil	Aspirin Carvedilol Omeprazole Midazolam	Carbamazepine Ceftriaxone Dexamethasone Diazepam Itraconazole Phenytoin Valproic acid Warfarin Diltiazem
AAG	Lidocaine Fentanyl Propranolol Verapamil	Midazolam	Carbamazepine Diltiazem

AAG = α_1 -Acid Glycoprotein; ER = extraction ratio. * Extraction ratio is addressed in section V. Metabolism.

- E. **pH** – Acid-base disorders are common among the critically ill. Although these disorders are treatable, they create plasma pH changes that could affect drug distribution. Most drugs are either weak acids or bases and exist in either the ionized or the nonionized state, depending on the surrounding environment. Nonionized drugs penetrate cell membranes more easily than do ionized drugs. Therefore, it would be expected that a drug in the ionized state would have a smaller Vd than when in the nonionized state. Theoretically, a drug that is a weak acid in a patient experiencing acidemia would be expected to have a larger Vd, and the converse would be true for a basic drug. Although the potential exists to correlate plasma pH changes with changes in drug Vd, evidence in humans is lacking.

Patient Cases

3. R.H. is 20-year-old man who presents to the emergency department with nausea and vomiting. His vital signs are significant for a heart rate of 130 beats/minute, blood pressure of 98/62 mm Hg, and respiratory rate of 28 breaths/minute. Laboratory tests reveal an arterial blood gas significant for a pH of 7.11, PCO_2 of 18 mm Hg, and sodium bicarbonate of 5.2 mEq/L. His basic metabolic panel is significant for a potassium concentration of 5 mEq/L, BUN of 22 mg/dL, SCr of 1.4 mg/dL, and blood glucose of 400 mg/dL. Which describes what would most likely happen to the V_d of a weak acid like ciprofloxacin in this patient?
- A. Increased because of decreased ionization.
 - B. Decreased because of increased ionization.
 - C. No change because of no change in ionization.
 - D. Decreased because of decreased ionization.
4. B.B. is a 62-year-old woman admitted to the ICU for septic shock. She required 25 L of crystalloids during her resuscitation. Which antibiotic would be most likely to have a V_d similar to that in normal individuals?
- A. Tobramycin
 - B. Linezolid
 - C. Levofloxacin
 - D. Cefepime

V. METABOLISM

- A. Introduction – The predominant location for drug metabolism is the liver, but it can include tissues such as the GI tract, kidneys, lung, and brain. The greatest extent of knowledge regarding drug metabolism and, more importantly, changes in critically ill patients relates to hepatic metabolism. Therefore, this section will focus largely on changes in the hepatic metabolism of drugs.
- B. Renal Metabolism – There is evidence that the kidneys express the CYP isoenzymes 2B6 and 3A5. Data suggest that CYP 2C8, 2C9, and 3A4 are also expressed in the kidneys. In addition, UGT (UDP-glucuronosyltransferase) enzymes 1A9 and 2B7 are abundantly expressed in the kidneys, and they play a role in the glucuronidation of drugs. Unfortunately, there are no data describing how changes in critically ill patients affect drug metabolism in the kidneys by these enzymes. Critically ill patients with AKI have clinically relevant changes in insulin metabolism, as evidenced by increased hypoglycemic events and lower insulin requirements upon developing AKI (Nutrition 2011;27:766-72).
- C. Hepatic Metabolism – Hepatic clearance refers to the volume of blood that is completely cleared of drug by the liver per unit of time. The ability of the liver to metabolize drugs depends on three physiologic variables: hepatic blood flow, drug protein binding, and the intrinsic activity of hepatic enzymes. When evaluating an intravenously administered drug (bioavailability of 1), clearance by the liver can be simply represented by the following equation:

$$CL_H = Q \times E$$

where CL_H is the hepatic clearance, Q is the hepatic blood flow, and E is the hepatic extraction ratio. The hepatic extraction ratio can be further described by the following equation:

$$E = \frac{f_u \times CL_{int}}{Q + f_u \times CL_{int}}$$

where f_u is the fraction unbound in the plasma, CL_{int} is the intrinsic hepatic clearance, and Q is hepatic blood flow. The hepatic extraction ratio is classified by the fraction of drug removed during one pass through the liver and can range from 0 to 1. It can be separated into high (greater than 0.7), intermediate (0.3–0.7), and low (less than 0.3) categories. The extraction ratio would be zero when the liver does not metabolize a drug and 1 when CL_H is entirely dependent on hepatic blood flow. The effect of changes in critical illness depends on the extraction ratio of the drug. Table 2 provides a list of select high extraction ratio and low extraction ratio drugs.

D. High Extraction Ratio Drugs

1. Drugs with a high hepatic extraction ratio are highly metabolized by hepatic enzymes and are thus extensively cleared by the liver. In drugs with high extraction ratios, clearance does not vary with changes in hepatic enzymatic activity and is primarily dependent on hepatic blood flow. Mathematically, this can be represented by:

$$f_u \times CL_{int} \gg Q$$

Given the previously stated relationship, CL_H can be simplified to:

$$CL_H = Q$$

As previously noted, clearance of a drug pertains to removal of the drug from the blood. Therefore, the effect on plasma drug concentration will affect the efficacy of the drug. Because only the free drug is available to produce a clinical effect, the unbound steady-state concentration (C_{ssu}) is extremely important. The steady-state concentration (C_{ss}) of hepatically metabolized drugs can be represented by the following equation:

$$C_{ss} = \frac{\text{dose}}{CL_H}$$

where C_{ss} is the steady-state concentration and dose is the rate of drug input. Because $CL_H = Q$ for high extraction ratio drugs, the equation can be modified to:

$$C_{ss} = \frac{\text{dose}}{Q}$$

The unbound steady-state concentration for a high extraction ratio is represented by the following equation:

$$C_{ssu} = \frac{f_u \times \text{dose}}{Q}$$

Figure 1 shows how a change in each variable of CL_H affects the C_{ss} and C_{ssu} . For high extraction ratio drugs, altered hepatic blood flow affects both the C_{ss} and the C_{ssu} , whereas changes in f_u affect only the C_{ssu} .

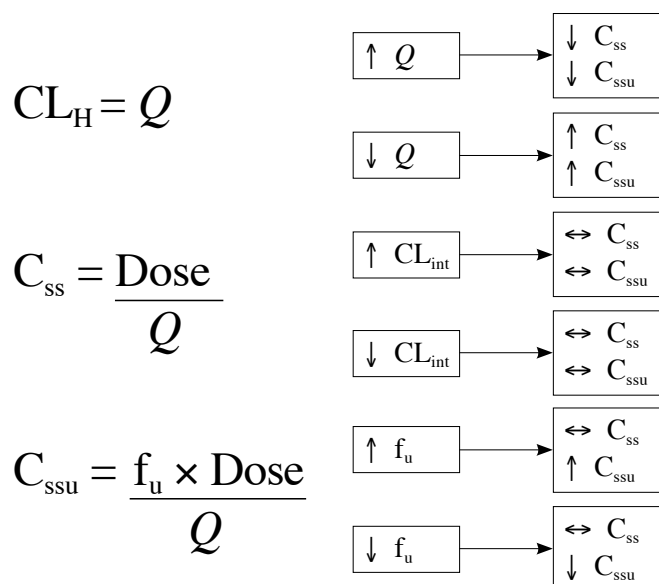


Figure 1. Effect of variable changes on steady-state and unbound steady-state concentrations of a high extraction ratio drug.

2. Effect of increased hepatic blood flow: Animal models have shown a clear increase in splanchnic perfusion during the hyperdynamic phase of sepsis. Critically ill patients in the hyperdynamic phase of sepsis or septic shock have an increased cardiac output and increased hepatosplanchnic blood flow. Unfortunately, a correlation directly relating cardiac output (or an increase in cardiac output) to an increase in splanchnic blood flow could not be established in some studies. Therefore, quantification of the increase in blood flow and the resultant increase in hepatic metabolism cannot be established. The clinician is left to assume the potential for increased metabolism of high extraction ratio drugs and the expected decrease in unbound steady-state concentration and possibly a reduced clinical efficacy.
3. Effect of decreased hepatic blood flow
 - a. Conditions with a low cardiac output such as hypovolemic or hemorrhagic shock, late (hypodynamic) sepsis, myocardial infarction with or without cardiogenic shock, and acute heart failure exacerbation would be expected to cause a decrease in hepatic blood flow. Human studies to verify this assertion are lacking. Animal models of hypodynamic sepsis and cardiogenic shock show a reduction in hepatic blood flow.
 - b. Mechanical ventilation produces an increased intrathoracic pressure. This pressure causes a decrease in venous return to the heart, compresses the ventricles, and reduces ventricular filling. The result is a decrease in cardiac output (N Engl J Med 1981;304:387-92) and hepatic blood flow (Crit Care Med 1982;10:703-5).
 - c. Adding an inotrope would likely improve hepatic blood flow. Although data in humans are lacking, an animal model of endotoxemia found improvement in hepatic blood flow after the administration of dobutamine.
- E. Low Extraction Ratio Drugs – Drugs with a low hepatic extraction ratio undergo a lower degree of hepatic enzyme metabolism; thus, they are not extracted from hepatic blood flow as high extraction ratio drugs. In drugs with low extraction ratios, clearance varies with changes in hepatic enzymatic activity, and clearance is independent of hepatic blood flow. Mathematically, this can be represented by:

$$f_u \times CL_{int} \lll Q$$

According to this relationship, CL_H can be simplified to:

$$CL_H = f_u \times CL_{int}$$

Again, the C_{ss} for hepatically metabolized drugs can be represented by the following equation:

$$C_{ss} = \frac{\text{dose}}{CL_H}$$

where C_{ss} is the steady-state concentration and dose is the rate of drug input. Because $CL_H = f_u \times CL_{int}$ for low extraction ratio drugs, the equation can be modified to:

$$C_{ss} = \frac{\text{dose}}{f_u \times CL_{int}}$$

The unbound steady-state concentration for a low extraction ratio drug is represented by the following equation:

$$C_{ssu} = \frac{\text{dose}}{CL_{int}}$$

Figure 2 shows how a change in each variable of CL_H affects the C_{ss} and the C_{ssu} . For low extraction ratio drugs, altered CL_{int} affects both the C_{ss} and the C_{ssu} , whereas changes in the f_u affect only the C_{ss} .

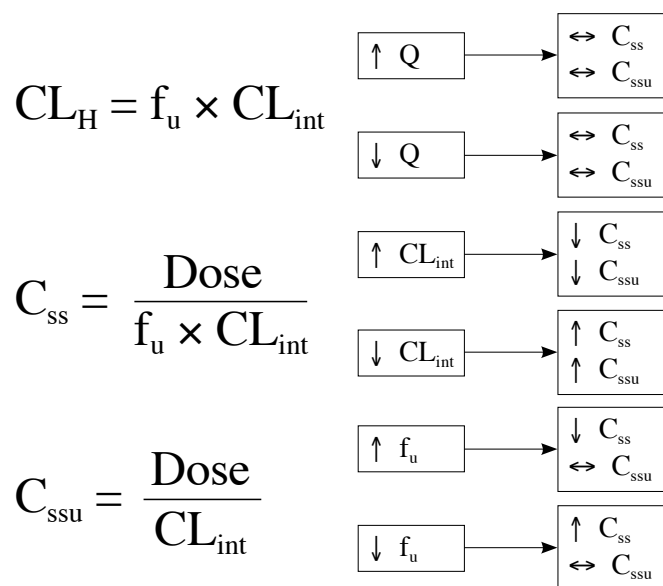


Figure 2. Effect of variable changes on steady-state and unbound steady-state concentrations of a low extraction ratio drug.

F. Effect of Changes in Intrinsic Clearance

1. Drug interactions – A major mechanism for altered intrinsic clearance is not caused by changes in critically ill patients, but it still poses a significant threat to altered metabolism of drugs. The CYP enzymes play an important role in phase I metabolism. Many drugs used in critically ill patients are substrates, inducers, inhibitors, or combinations of these. Critically ill patients often have complex pharmacotherapeutic regimens that create the potential for drug interactions through the CYP system. As in other patient populations, drug concentrations are increased when substrates are coadministered with inhibitors of the same CYP and decreased when substrates are coadministered with inducers.
2. Inflammation – Inflammatory states play an important role in altering CYP activity. The inflammatory cytokines interleukin (IL)-1 α , IL-6, and tumor necrosis factor alpha (TNF α) decrease the expression and activity of CYP enzymes. Similarly, patients in early sepsis would have increased inflammatory cytokines with the resultant depressed CYP activity. This is supported by studies showing that endotoxin administration results in decreased CYP-mediated drug metabolism in healthy volunteers. Unfortunately, studies have not characterized a time course for the cytokine-mediated changes. Clinicians are left to use patient response and monitoring for toxicity to determine whether drug metabolism is altered or has returned to normal.
3. Hypothermia – Animal models have shown that hypothermia affects drugs metabolized through the CYP system. Drugs studied in animal models include fentanyl, pentobarbital, propranolol, and morphine. Human studies have investigated the effect of hypothermia on low extraction ratio drug kinetics. One example showed changes in phenytoin PK during mild hypothermia. Specifically, increased concentrations and reduced metabolism, but no changes in protein binding, were noted during hypothermia (Ther Drug Monit 2001;23:192-7). Other drugs noted to have decreased hepatic clearance during hypothermia are midazolam, fentanyl, remifentanyl, phenobarbital, and vecuronium.
4. AKI – One study investigated the effects of AKI on the hepatic metabolism of midazolam. Patients with worsening AKI, as determined using the RIFLE (risk, injury, failure, loss) criteria, had increasing midazolam concentrations. The authors hypothesized that the increased concentrations were caused by impaired CYP3A activity (Intensive Care Med 2012;38:76-84).

- G. Intermediate Extraction Ratio Drugs – Metabolism of an intermediate extraction ratio drug is dependent on hepatic blood flow, intrinsic clearance, and fraction of unbound drug. Essentially, intermediate extraction ratio drugs are dependent on the same variables as both the low extraction ratio and high extraction ratio drugs. As such, they are the most complex drugs for determining how hepatic clearance will be affected in critically ill patients. This is important because critically ill patients generally have more than one change occurring at the same time. For example, patients with septic shock may have increased hepatic blood flow secondary to increased cardiac output while having a decreased intrinsic clearance secondary to increased circulating inflammatory cytokines. Quantifying the overall effect is difficult in the ever-changing critically ill patient. The clinician is often left to monitor for the expected therapeutic outcome while being aware of the potential toxicities.

H. Other Factors

1. TBI increases the hepatic clearance of some drugs.
 - a. One study found that patients with TBI had increased hepatic clearance of phenytoin during the first 7–14 days. The authors alluded to the possibility that the increased clearance was associated with changes in protein binding, induction of metabolism, or stress on hepatic metabolic capacity (Clin Pharmacol Ther 1988;44:675-83).
 - b. Another study noted a correlation between nutritional protein intake and increased phenytoin metabolism in patients with TBI.
 - c. Phase II enzymatic activity may also be enhanced in patients with TBI, as evidenced by increased lorazepam clearance. Similar data for lorazepam were noted in thermally injured patients. These data suggest that phase II metabolism can be affected by critical illness.

2. Hepatic failure – Hepatic failure will significantly affect drug dosing in the critically ill patient. See the Hepatic Failure/GI/Endocrine Emergencies chapter for more information regarding drug dosing in hepatic failure.

Patient Cases

5. A.P. is a 35-year-old woman admitted to the ICU for an acute asthma exacerbation. She was intubated and required mechanical ventilation. She is prescribed morphine for pain control. Which statement best describes the effect of mechanical ventilation on morphine unbound concentrations?
 - A. Increases oxygenation delivery to the liver and increases the unbound concentration.
 - B. Decreases hepatic blood flow and increases the unbound concentration.
 - C. Increases cytokine production and decreases the unbound concentration.
 - D. Cannot affect the unbound concentration.
6. J.M. is a 65-year-old woman in the ICU who develops atrial fibrillation. Her rate is controlled using a diltiazem infusion of 10 mg/hour. J.M. develops a fever and leukocytosis. She is empirically initiated on vancomycin 1 g intravenously every 12 hours, piperacillin/tazobactam 2.25 g intravenously every 6 hours, and fluconazole 400 mg intravenously every 24 hours. Which PD response would you most expect to see in J.M.?
 - A. Increased heart rate caused by an increased intrinsic clearance of diltiazem
 - B. Decreased heart rate caused by a decreased intrinsic clearance of diltiazem
 - C. Increased heart rate caused by a decreased unbound fraction of diltiazem
 - D. Decreased heart rate caused by an increased unbound fraction of diltiazem
7. P.M. is receiving phenytoin for the treatment of posttraumatic seizures. You measure a total phenytoin concentration, which is 8 mcg/mL. You calculate the adjusted concentration according to P.M.'s hypoalbuminemia (albumin of 2.5 g/dL) and determine the concentration to be around 13 mcg/mL. Which best depicts why this adjustment was needed?
 - A. The unbound phenytoin concentration increased because of an increased unbound fraction of phenytoin.
 - B. The total phenytoin concentration increased because of an increased unbound fraction of phenytoin.
 - C. The unbound phenytoin concentration decreased because of an increased unbound fraction of phenytoin.
 - D. The total phenytoin concentration decreased because of an increased unbound fraction of phenytoin.
8. C.P. is a 50-year-old man admitted to the medical ICU for diabetic ketoacidosis. His medical history is significant for hypertension, type 1 diabetes mellitus, and a myocardial infarction 2 years ago. He quit smoking last year and only drinks alcohol occasionally. His vital signs are significant for a heart rate of 125 beats/minute, blood pressure of 95/65 mm Hg, and respiratory rate of 22 breaths/minute. His significant dehydration contributed to the development of AKI. His current SCr is 2.8 mg/dL. His blood glucose is significantly elevated at 350 mg/dL. He will be initiated on a continuous intravenous infusion of insulin to correct his blood glucose. Which factor is most important to consider when dosing insulin in C.P.?
 - A. Decreased renal metabolism of insulin
 - B. Increased Vd of insulin
 - C. Increased hepatic metabolism of insulin
 - D. Decreased receptor binding of insulin

VI. EXCRETION

A. Renal Excretion

1. For most drugs, the kidneys are the primary site for excretion of the parent drug, metabolites, or both. Urinary excretion of a drug is dependent on filtration, secretion, and reabsorption. Patients in the ICU may experience increased, decreased, or normal renal excretion of drugs. The state of renal excretion depends on many variables and can change rapidly. This is especially true in ICU patients, where a clinical condition can contribute to both increased and decreased excretion, depending on how that condition progresses.
2. Filtration
 - a. GFR is the variable most widely used to describe kidney function. The National Kidney Foundation defines normal kidney function as 140 ± 30 mL/minute/1.73 m² for healthy young men and 126 ± 22 mL/minute/1.73 m² for healthy young women. Although there is no standard definition for increased GFR (augmented renal clearance [ARC]), an increase of 10% above the upper end of normal (greater than 160 mL/minute/1.73 m² in men and greater than 150 mL/minute/1.73 m² in women) has been proposed (Crit Care 2013;17:R35).
 - b. ARC – Conditions such as surgery, trauma, burns, and sepsis have been associated with increased renal blood flow. This is generally believed to be caused by an increased cardiac output coupled with vasodilation. The resulting ARC is believed to be a response to an inflammatory insult (previously referred to as SIRS).
 - i. One study found glomerular hyperfiltration present in 17.9% of patients admitted to the ICU. Most of these patients were younger and admitted for multi-trauma or surgery (Anaesth Intensive Care 2008;36:674-80). These data are supported by a study showing young, postoperative trauma patients with peak creatinine clearance (CrCl) values as high as 190 mL/minute/1.73 m². A more recent study found significant risk factors for the ARC to be age 50 years or younger, trauma, and a modified sequential organ failure score of 4 or less.
 - ii. A study of burn patients found an increase in iothexol clearance with a median value of 155 mL/minute/1.73 m² on day 1 of admission. In this small study, clearance had returned to the expected baseline of 122 mL/minute/1.73 m² by day 7 (Burns 2010;36:1271-6). In addition, several studies have shown increased excretion of renally eliminated drugs in burn patients. Examples include vancomycin, ciprofloxacin, imipenem, fluconazole, and aminoglycosides.
 - iii. Fluid administration would be expected to improve cardiac output and thus renal blood flow. Animal studies have confirmed that the administration of crystalloids can increase CrCl. Sheep administered normal saline and 3% hypertonic saline have a significantly higher calculated CrCl compared with controls. However, no human studies have verified ARC in critically ill patients after fluid administration.
 - iv. Vasoactive drugs would be expected to improve cardiac output and thus renal blood flow. Unfortunately, human studies did not corroborate this expectation and, instead, were only able to establish an improvement in CrCl in a subset of patients with impaired CrCl before norepinephrine administration. Although studies were unable to show development of ARC, patients receiving vasopressors for shock states might be expected to have normal renal blood flow and CrCl, assuming they are not experiencing AKI.
 - The duration of ARC is not well established, but the peak CrCl appears to occur at about days 4–5 in most studies, with CrCl returning to normal by day 7 in one study.
 - c. Impaired renal clearance
 - i. Decreased renal excretion of drugs during AKI is the most widely applicable change occurring in critically ill patients. Depending on the patient population and definition used, the incidence of AKI in ICU patients can be as high as 78%. AKI significantly affects the excretion of renally eliminated drugs, and dosing modifications must be made in these situations.

- ii. The guidelines recommend that staging of AKI be done using the Kidney Disease Improving Global Outcomes (KDIGO) AKI criteria. However, these guidelines do not make specific recommendations regarding drug dosing.
- iii. A clinical update to the 2010 guidelines does provide recommendations on how to approach drug dosing in critically ill patients with AKI. Because of the complicated picture of AKI in critically ill patients, however, the recommendations are not as precise as recommendations for drug dosing in CKD. In fact, the authors note that most renal dose adjustment recommendations in the literature and from the FDA (U.S. Food and Drug Administration) are based on data from patients with CKD (Kidney Int 2011;80:1122-37).
- iv. The update recommends a stepwise approach to adjusting drug-dosing regimens in patients with AKI (Box 1).

Box 1. Recommended Steps for Assessing and Adjusting Drug Regimens in Patients with AKI

Step 1 – Assess the following Demographic information Past medical history (including history of renal disease) Current clinical information Current laboratory information DNA polymorphisms
Step 2 – Estimate eGFR or CrCl using: Age Body size Ethnicity Concomitant diseases
Step 3 – Review current medications Identify drugs needing individualized dosing
Step 4 – Calculate individualized treatment regimen Determine treatment goals (PK or PD values) Calculate dosage regimen (based on drug PK and changes noted in the patient)
Step 5 – Monitor regimen Drug response Signs or symptoms of toxicity Drug levels (if available)
Step 6 – Revise regimen Adjust regimen according to patient response Adjust regimen according to changes in patient status

- v. The recommendations include using the estimated GFR (eGFR) or CrCl to assess renal function for drug dosing. The estimated GFR equation is described as follows:

$$\text{GFR} = 175.6 \times \text{SCr}^{-1.154} \times \text{age}^{-0.212} \times 1.212 \text{ (if black)} \times 0.742 \text{ (if female)}$$

where GFR is in milliliters per minute/1.73 m², SCr is measured in the laboratory using isotope dilution mass spectroscopy (IDMS), and age is in years. If the laboratory measuring the SCr does not use IDMS, the following equation should be used:

$$\text{GFR} = 186.3 \times \text{SCr}^{-1.154} \times \text{age}^{-0.203} \times 1.212 \text{ (if black)} \times 0.742 \text{ (if female)}$$

- vi. The Cockcroft-Gault equation is used to estimate the CrCl as follows:

$$\text{CrCl} = \frac{(140 - \text{age}) \text{ weight}}{\text{SCr} \times 72} \times 0.85 \text{ (if female)}$$

where CrCl is in milliliters per minute, weight is in kilograms, and SCr is in milligrams per deciliter.

- vii. The update also notes that the most important factor when determining kidney function is having at least one GFR estimate for all patients.
3. Secretion and reabsorption: Unfortunately, it is difficult to study changes in drug secretion and reabsorption in patients. Therefore, data are not available to describe the clinically important changes in these two variables in critically ill patients.
4. Renal replacement therapies:
- Patients having a diagnosis of AKI may require hemodialysis. The choice of dialytic technique depends on the institution, expertise of the clinician, patient hemodynamic stability, and access to various types of dialysis machines. Drug removal by dialysis depends on the method of dialysis used.
 - Acute intermittent hemodialysis
 - Intermittent hemodialysis can significantly contribute to the excretion of drugs, whereas other drugs are not appreciably removed by hemodialysis. Removal of drugs during hemodialysis depends on the size of the molecule, Vd, protein binding, and type of dialysis filter (specifically the membrane size).
 - Continuous renal replacement therapies (CRRTs)
 - CRRT refers to several methods of renal replacement. Many studies have investigated the effect of CRRT on drug removal. Considerable variability exists in the type of CRRT used. The 2010 clinical update to the KDIGO guidelines suggests the following equation as one option to determine the appropriate dose of a drug in CRRT:

$$\text{dose} = \text{dose}_n \left(\frac{\text{CL}_{\text{nonrenal}} + (\text{Q}_{\text{eff}} \times \text{SC})}{\text{CL}_{\text{norm}}} \right)$$

where dose is the desired dose for CRRT, dose_n is the normal dose of a drug, CL_{nonrenal} is the nonrenal clearance of a drug, Q_{eff} is the effluent rate, SC is the sieving coefficient, and CL_{norm} is the normal clearance of the drug.

- B. Hepatic Excretion – Hepatic excretion of drugs is less important for most drugs than renal excretion. However, excretion of drug in the bile can potentially be affected by critical illness. This is evidenced by changes in the clearance of some neuromuscular blocking agents.
- A study of nine patients undergoing surgery for total biliary obstruction showed a significant increase in pancuronium half-life compared with normal patients (270 minutes vs. 132 minutes, $p < 0.001$). The urinary excretion of pancuronium and its metabolites did not change. This suggests that the increased half-life was caused by the decreased hepatic excretion of pancuronium (Br J Anaesth 1977;49:1103-8).
 - Similar results were found for vecuronium in patients with cholestasis, where the mean half-life was 98 minutes in patients with cholestasis and 58 minutes in normal patients (Br J Anaesth 1986;58:983-7).

- C. Pulmonary Excretion – Pulmonary excretion is important for volatile gases such as anesthetics. It can be hypothesized that impaired gas exchange (e.g., acute respiratory distress syndrome) has an effect on the body's ability to remove volatile gases. However, data are lacking regarding changes in critically ill patients that affect their ability to excrete anesthetics.

VII. PHARMACODYNAMICS

- A. *Pharmacodynamics* refers to the biochemical and physiologic effects of a drug, specifically those related to the mechanism of action.
- B. This term also pertains to drug/receptor binding and clinical effect. Most clinicians use the term to refer to the physically identifiable effect of a drug in a patient. For example, the PD effect of an opioid is the relief of pain reported by the patient. However, the PD effect of some drugs is not readily observable. For example, the PD effect of proton pump inhibitors is an increase in gastric pH. Few PD studies of critically ill patients are reported in the medical literature, and most pertain to antibiotic therapy.
1. Antibiotics general information: PD studies of antibiotics use models to estimate the combined effects of the patient population PK of specific antibiotics and the MIC for select bacteria. These techniques generally allow a calculation of the desired PD outcome. Antibiotics generally fall into three PD categories, which correlate with efficacy: (1) time-dependent killing ($T > MIC$), (2) concentration-dependent killing (C_{max}/MIC), and (3) a combination of time- and concentration-dependent killing (AUC/MIC).
 2. β -Lactam antibiotics: For β -Lactam antibiotics, the PD parameter of the free drug concentration time above the MIC ($fT > MIC$) is used to predict treatment success. This is reported as a percentage of time the free drug concentration remains above the MIC. The ideal $fT > MIC$ is 100%. However, PD studies of β -Lactam antibiotic use in critically ill patients have found that a very low percentage of patients will achieve the desired PD targets (Crit Care 2011;15:R206). These failures are often attributed to clinically important changes that can occur rapidly in critically ill patients (e.g., ARC). As such, epidemiologic studies have tried to determine a breakpoint at which clinical success is achieved. Studies vary, and the suggested breakpoint ranges from 50% to 100% ($fT > MIC$) (Br J Clin Pharmacol 2012;73:27-36), with others suggesting cutoffs of about 40% for carbapenems, 50% for penicillins, and 50-75% for cephalosporins (Clin Infect Dis 1008;26:1-10). Modeling generally suggests improved PD of β -Lactams when using prolonged or continuous infusions. Many institutions have adopted the practice of prolonged infusions. This is supported by quasi-experimental and retrospective studies showing improved outcomes such as improved clinical cure, improved microbiological cure, and reduced morbidity and mortality. Unfortunately, prospective controlled clinical trials have produced mixed results (J Crit Care 2014;29:1089-95, Am J Respir Crit Care Med 2015;192:1298–1305). There are many reasons why there appears to be a discrepancy between PD modeling studies and controlled clinical trials; patient variability, dosing variability, and disease severity seem to be important factors (Ann Intensive Care 2012;2:37).
 3. Aminoglycosides: Aminoglycoside bacterial killing is based on the ratio between the maximum drug concentration and the MIC for the bacterial pathogen (C_{max}/MIC), or concentration-dependent killing. Efficacy was noted when patients were pooled from four controlled clinical trials and peak concentrations, MIC values, and clinical response were evaluated. Peak-to-MIC ratios of 8–10 resulted in around 90% clinical response (J Infect Dis 1987;155:93-9). In patients with gram-negative bacteremia, early therapeutic peak concentrations were a significant discriminating factor for mortality. According to these and other data, once-daily aminoglycoside dosing has been used. Taking advantage of high peak concentrations maximizes the PD of aminoglycosides. Variability in the Vd of aminoglycosides in

- critically ill patients, together with concern for ARC in this population, raises issues about appropriately dosing these agents, especially in critically injured trauma patients, whose drug levels can be undetectable for more than 12 hours (J Trauma 2000;49:869-87).
4. Vancomycin: The PD parameter that best describes vancomycin efficacy is the AUC/MIC. Several studies have evaluated the free 24-hour AUC/MIC ($fAUC_{0-24}/MIC$), or the AUC $\times$ 50% protein binding/MIC. Current guidelines use the available literature to recommend an AUC/MIC of 400 or greater (Am J Health Syst Pharm 2009;66:82-98). The guidelines suggest that continuous-infusion regimens are unlikely to improve patient outcomes and that standard intermittent infusions should be sufficient to achieve the desired PD end points. Of interest is a retrospective study of vancomycin-associated nephrotoxicity in critically ill patients. In this study, intermittent dosing was associated with a significantly higher risk of nephrotoxicity compared with continuous infusion (odds ratio 8.2; $p \leq 0.001$) (Crit Care Med 2014;42:2527-36). Of note, more aggressive dosing may be required in critically ill patients. Doses as high as 20 mg/kg administered as often as every 6 hours were needed to optimize PK variables in critically injured trauma patients being treated for ventilator-associated pneumonia (J Trauma Acute Care Surg 2012;72:1478-83).
 5. Fluoroquinolones: Similar to the efficacy of aminoglycosides, efficacy of the fluoroquinolones is based on a C_{max}/MIC (10 or greater), and the fluoroquinolones have a post-antibiotic effect against gram-negative and gram-positive bacteria. PD studies have shown that the $fAUC_{0-24}/MIC$ is associated with bacterial eradication. In one study of lower respiratory tract infections treated with ciprofloxacin, an AUC_{0-24}/MIC of 125 was associated with the percent probability of 80% for clinical cure (Antimicrob Agents Chemother 1993;37:1073-81). Unfortunately, it is difficult to incorporate these PD variables into fluoroquinolone dosing in individual critically ill patients.
 6. Nonantibiotic drugs: PD studies of other drugs in critically ill patients are sparse.
 - a. The PD parameter for continuous infusions of many anticoagulants is change in the activated partial thromboplastin time (aPTT). Unfractionated heparin infusions are generally predictable in most patient populations. However, in critically ill patients, just under one-half (44%) did not reach a therapeutic aPTT within 24 hours of starting a heparin continuous infusion (Neth J Med 2013;71:466-71). Concern for a variable response in critically ill patients has led to the development of dosing nomograms/protocols. Researchers have found a shortened time to therapeutic aPTTs in critically ill patients receiving unfractionated heparin and direct thrombin inhibitors (argatroban and bivalirudin).
 - b. As with antibiotic PD studies, most PD studies of other drugs have shown a decreased response in critically ill patients. For example, critically ill patients in septic shock had a reduced response to dobutamine compared with critically ill patients without septic shock and with normal volunteers (Crit Care Med 1993;21:31-9). Trauma patients with edema have lower AUCs for anti-Xa activity compared with non-edematous patients (J Trauma 2005;59:1336-43). Mechanically ventilated patients with chronic obstructive pulmonary disease were studied for covariates affecting acetazolamide therapy. Mixed-effects modeling found the Simplified Acute Physiology Score II, serum chloride concentrations, and concomitant corticosteroids to be the main covariates interacting with acetazolamide PD.

VIII. THERAPEUTIC DRUG MONITORING

- A. Therapeutic drug monitoring (TDM) refers to the measurement of medication concentrations in the blood. The focus of TDM is on drugs with a narrow therapeutic index and aims to achieve two things: (1) maximize efficacy and (2) reduce toxicity. Use of TDM in critically ill patients is extremely important because changes in the PK variables previously described can result in less-than-desirable drug concentrations. Table 3 highlights some commonly used medications in the ICU and their therapeutic ranges. One of the main limitations of TDM is the lack of clinically available assays. In addition, assays for some drugs may not be cost-effective to routinely conduct in certain institutions. These issues generally result in TDM for a very limited spectrum of drugs.
1. Monitoring of blood concentrations is dependent on the intended use and interpretation of those concentrations. Most TDM occurs as a method to confirm a therapeutic concentration in a patient with signs and/or symptoms of toxicity or decreased efficacy. In this case, a concentration is measured during the appropriate time frame (Table 3), and a clinician interprets the concentration. If needed, the clinician modifies the drug dosing according to clinical experience. This method may produce variable results. The critically ill patient requires important considerations. For example, if extended-interval dosing is being used, the likelihood of an increased V_d must be considered. Patients with ARC have the potential to have a prolonged drug-free period. Finally, the status of a critically ill patient can change rapidly. Monitoring for decreased kidney function is essential to avoid accumulation.

Table 3. Therapeutic Drug Monitoring Ranges for Select Drugs Used in Critically Ill Patients

Drug	Timing of Blood Sample	Therapeutic Range
Amikacin	Trough Peak (traditional)	< 8 mg/L 20–30 mg/L
Phenobarbital	Trough	10–40 mg/L
Carbamazepine	Trough	4–12 mg/L
Cyclosporin	Trough	50–500 mcg/L
Digoxin	Trough (8–24 hours postdose)	0.6–2 mcg/L
Gentamicin	Trough (traditional) Trough (extended interval) Peak	< 2 mg/L Undetectable 5–10 mg/L
Lidocaine	Peak	1.5–5 mg/L
Phenytoin	Trough	10–20 mg/L
Tobramycin	Trough (traditional) Trough (extended interval) Peak	< 2 mg/L Undetectable 5–10 mg/L
Vancomycin	Trough (complicated infections) Trough (uncomplicated infections)	15–20 mg/L 10–15 mg/L

2. For certain intravenously administered drugs (e.g., aminoglycosides, vancomycin), several concentrations can be measured when the drug is at steady state. The patient's specific PK can be determined and used to tailor the drug-dosing regimen. The following PK equations can be used to calculate the various kinetic variables.

Determination of the elimination rate constant:

$$k_e = \frac{\ln \frac{C_1}{C_2}}{\Delta \text{ in time}}$$

where k_e is the elimination rate constant, C_1 is the measured peak concentration, C_2 is the measured trough concentration, and Δ in time is the elapsed time from C_1 to C_2 .

Determination of the drug half-life:

$$t_{1/2} = \frac{0.693}{k_e}$$

where $t_{1/2}$ is the calculated half-life.

Determination of the calculated peak concentration:

$$C_{\max} = C_1 (e^{k_e(t')})$$

where $C_{\max}$ is the calculated peak concentration and t' is the time between the C_1 and the end of the intravenous infusion.

Determination of the calculated trough concentration:

$$C_{\min} = C_2 (e^{-k_e(t')})$$

where $C_{\min}$ is the calculated trough concentration and t' is the time between C_2 and the beginning of the next dose.

Determination of the drug Vd:

$$Vd = \frac{\text{dose}}{t_{\text{inf}} \times k_e} \times \frac{(1 - e^{-k_e(t_{\text{inf}})})}{C_{\max} - C_{\min} \times e^{-k_e(t_{\text{inf}})}}$$

where t_{inf} is the duration of the drug infusion.

Determination of the new dosing interval:

$$\tau = \frac{\ln \left(\frac{C_{\max, \text{desired}}}{C_{\min, \text{desired}}} \right)}{k_e} + t_{\text{inf}}$$

where τ (tau) is the new dosing interval, $C_{\max, \text{desired}}$ is the desired peak concentration for the new dosing regimen, and $C_{\min, \text{desired}}$ is the desired trough concentration for the new dosing regimen.

Determination of the new dose:

$$\text{dose} = C_{\max, \text{desired}} \times k_e \times Vd \times t_{\text{inf}} \times \frac{(1 - e^{-k_e(\tau)})}{(1 - e^{-k_e(t_{\text{inf}})})}$$

3. One drawback of this method is that it assumes the PK variables obtained (e.g., vancomycin trough) correlate with PD variables (AUC/MIC). Although this may be true in many cases, some advocate for the incorporation of PD into individualized drug dosing. Alternative methods use PK variables from previous patients (population PK) to estimate the PK in an individual patient. These methods generally require complicated mathematical calculations, many of which are not practical for clinical use. However, with the development of PK software, clinicians can carry out complex calculations. Many software programs are available for clinician use in patient care. More advanced modeling using the Bayesian method has also been proposed to address the issues posed by using population PK in patient groups that may not be well represented in the population. Using software with population PK variables from noncritically ill patients in the interpretation of PK in critically ill patients could result in errors in designing the appropriate drug-dosing regimen.
- B. Drug Nomograms/Protocols – A nomogram is a diagram representing the relationship between three or more variables using scales arranged in a manner such that one variable can be determined if the other variables are known. A classic drug-dosing example is the once-daily aminoglycoside nomogram (Antimicrob Agents Chemother 1995;39:650-5). The nomogram itself allows the user to determine only one variable (generally, the dosing interval) using other variables (time from infusion to drug concentration and the measured drug concentration). Many institutions incorporate nomograms into drug-dosing protocols or pathways but still call them drug-dosing nomograms. One of the most commonly used drug-dosing nomograms was developed for continuous infusions of unfractionated heparin. As previously noted, a heparin nomogram can improve time to therapeutic aPTT when developed specifically for critically ill patients. It is important to consider the patient population used to develop a nomogram because the variables may not apply to all patient populations. An example of this occurs with protocols for insulin infusions in critically ill patients. As previously noted, patients with AKI are at a greater risk of hypoglycemia if treated with an insulin infusion protocol developed in critically ill patients without kidney impairment.

IX. CONCLUSION

There are marked differences in the ways in which critically ill patients respond to drugs. Research in this area has noted significant changes in the PK and PD of certain medications in select critically ill populations. Although these studies have highlighted important issues, considerable work is still needed to better define these changes in different critically ill populations. As research continues to advance, together with our knowledge of how patients respond to drugs differently, critical care clinicians must stay abreast of new information and the ways in which it will affect the care of their patients.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: B

Increasing the concentration of an antibiotic at the site of an infection is most important (Answer B is correct). Although there are case reports describing the use of intraventricular antibiotics in the treatment of meningitis, they have not shown superiority (Answer A is incorrect). Although there is the potential to reduce vancomycin-induced nephrotoxicity, no studies have compared the nephrotoxicity of intraventricular antibiotics with that of intravenous antibiotics, likely because this is not the rationale for their use (Answer C is incorrect). Ototoxicity could also be reduced, but this was not the intent of the locally instilled antibiotics (Answer D is incorrect).

2. Answer: D

Three studies have documented an increase in digoxin absorption when the gastric pH is increased, with two studies noting the cause of increased gastric pH from a proton pump inhibitor (Answer D is correct). However, no studies have shown a decreased absorption of carvedilol (Answer A is incorrect), ciprofloxacin (Answer B is incorrect), or diazepam (Answer C is incorrect).

3. Answer: A

A decrease in the ionization of a drug allows the drug to pass more easily through membranes. Increasing the ionization would decrease the V_d by decreasing its ability to pass through membranes. A weak acid would be less ionized in a more acidic environment. The patient is likely in diabetic ketoacidosis with a definite acidosis. Aspirin (a weak acid) is less likely to be ionized and would have an increased V_d (Answer A is correct; Answers B–D are incorrect).

4. Answer: C

Levofloxacin has a large V_d . The increase in interstitial fluid volume caused by 25 L of crystalloids would increase the V_d of hydrophilic drugs but would have no appreciable effect on the V_d of a drug like levofloxacin, which already has a large V_d (Answer C is correct). Tobramycin, linezolid, and cefepime have relatively small volumes of distribution and are increased in patients with increased interstitial volumes (Answers A, B, and D are incorrect).

5. Answer: B

Morphine is a high extraction ratio drug. Mechanical ventilation can decrease cardiac output and thus decrease liver blood flow. The decrease in liver blood flow is inversely proportional to the unbound steady-state concentration. Therefore, it both decreases the hepatic blood flow and increases the unbound concentration (Answer B is correct). The effects of mechanical ventilation on cardiac output would likely decrease oxygen delivery (Answer A is incorrect). Cytokines affect intrinsic clearance but would not affect the concentration of a high extraction ratio drug (Answer C is incorrect). Mechanical ventilation can indirectly affect the unbound concentration (Answer D is incorrect).

6. Answer: B

This patient has sepsis, which is associated with an increased production of inflammatory cytokines. These cytokines can decrease the activity of the CYP enzymes and decrease intrinsic clearance. In addition, fluconazole inhibits the activity of CYP3A4. Diltiazem is a low extraction ratio drug. The hepatic clearance of diltiazem is affected by changes in intrinsic clearance (including CYP3A4 activity). The unbound steady-state concentration would be increased, with a decrease in intrinsic clearance caused by the inflammatory cytokines. The increased unbound steady-state concentrations would cause a decrease in the heart rate (Answer B is correct). There is no cause for an increase in intrinsic clearance and a corresponding increase in heart rate (Answer A is incorrect). There is no reason for this patient to have a decrease in the unbound fraction of diltiazem (Answer C is incorrect). A decrease in albumin could occur with sepsis and would result in an increase in the unbound fraction of diltiazem. The increase in unbound fraction would not affect the unbound steady-state concentration, nor would it affect the heart rate (Answer D is incorrect).

7. Answer: D

Using the equations for low extraction drugs like phenytoin, it is clear that the unbound fraction is inversely proportional to the steady-state concentration and has no effect on the unbound steady-state concentration (Answer D is correct; Answers A and C are incorrect). An increase in the unbound fraction of phenytoin would not result in an increase in the total concentration (Answer B is incorrect).

8. Answer: A

The kidney plays a role in the excretion and metabolism of insulin. Acute kidney injury will decrease the ability of the kidney to metabolize insulin. This will increase circulating insulin and contribute to hypoglycemia (Answer A is correct). The Vd of insulin in AKI is not well studied and has not been tied to episodes of hypoglycemia (Answer B is incorrect). Hepatic impairment may increase the risk of hypoglycemia with insulin, but an increase in hepatic metabolism is unlikely to affect the risk of hypoglycemia in AKI (Answer C is incorrect). There have been reports of insulin resistance in patients with AKI, but this would not contribute to hypoglycemia (Answer D is incorrect).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: B

Decreased anti-Xa activity occurs in critically ill patients receiving several different low-molecular-weight heparins. This patient received the standard fluid bolus and then required more fluid to raise his central venous pressure. This suggests that the patient has redistributed the fluids to the extravascular space. The data showing that edematous patients have lower anti-Xa activity compared with non-edematous patients supports the connection between anti-Xa activity and absorption (Answer B is correct). Given the patient's fluid distribution, the Vd of enoxaparin would likely be increased, not decreased (Answer A is incorrect). Enoxaparin is not hepatically metabolized (Answer C is incorrect). Although a patient could have an increased anti-Xa activity secondary to decreased renal elimination, this would require a CrCl of less than 30 mL/minute. That the patient experienced a deep venous thrombosis does not correlate with increased activity (Answer D is incorrect).

2. Answer: C

Abdominal surgery has been identified as a risk factor for ileus. Antisecretory agents such as pantoprazole alter the absorption of drugs. Traumatic brain injury is significantly associated with intolerance of enteral nutrition, as indicated by increased gastric residuals. This indicates delayed gastric emptying and the risk of altered absorption. Therefore, the combination of abdominal surgery, pantoprazole therapy, and TBI contains the three variables identified in the literature to alter absorption (Answer C is correct). Theoretically, intestinal atrophy could cause changes in absorption, but no data are available to confirm this theory (Answers A and D are incorrect). Changes in cardiac output have been correlated with changes in hepatosplanchnic blood flow. These changes in blood flow are thought to affect absorption, but, again, no data have correlated increased cardiac output with increased absorption of drugs (Answer B is incorrect).

3. Answer: B

Propofol is a high extraction ratio drug that is bound to albumin. When the albumin concentration decreases, there is an expected increase in the free fraction of propofol. Using the equations describing the total and unbound concentrations of a high extraction ratio drug, the total concentration is not affected by changes in the

free fraction, but unbound concentrations are increased when the free fraction increases (Answer B is correct; Answers A, C, and D are incorrect).

4. Answer: C

The update to the KDIGO guidelines notes that the most important factor in determining kidney function is having at least one estimate of GFR. The update recommends that the GFR or the creatinine clearance (CrCl) be estimated to make this determination (Answer C is correct). The BUN value can be used to help identify the BUN/SCr ratio indicating intravascular volume contraction and, potentially, a prerenal cause to the patient's AKI, but it is not helpful in drug dosing (Answer A is incorrect). Total daily urine output is helpful in the diagnosis of AKI (oliguric vs. non-oliguric AKI) and in the staging of AKI (using a urine output of less than 0.5 mL/kg/hour) but not in the dosing of drugs (Answer B is incorrect). A history of CKD is helpful in determining a baseline kidney function, but the GFR is still needed for changes in drug dosing (Answer D is incorrect).

5. Answer: C

The ASHP (American Society of Health-System Pharmacists) vancomycin dosing guidelines recommend a 25- to 30-mg/kg loading dose of vancomycin for serious infections. Given the patient's sepsis, he is likely to have more interstitial fluid. This fluid will increase the Vd of hydrophilic drugs like vancomycin. The 2500-mg dose is near the top end of the recommended 25- to 30-mg/kg loading dose (Answer C is correct). The other doses are outside the recommended 25- to 30-mg/kg loading dose range (Answers A, B, and D are incorrect).

6. Answer: A

Critically ill patients younger than 50 years are more likely to have augmented renal excretion. Vancomycin is excreted unchanged in the urine. The initial dosing would result in a therapeutic trough concentration, given the increased (augmented) renal excretion of vancomycin. Augmented renal excretion usually returns to normal around day 7. An increased vancomycin trough after a previously therapeutic trough is most likely associated with a decline in renal excretion at day 10 of therapy (Answer A is correct). There is no indication that the Vd has changed, which would likely result in lower or unchanged concentrations (Answer

B is incorrect). Vancomycin tissue penetration may be better if inflammation is present, but there are no documented studies correlating decreased inflammation with increased serum concentrations (Answer C is incorrect). The liver does not appreciably metabolize vancomycin, and liver blood flow would not be a factor in the vancomycin concentration (Answer D is incorrect).

7. Answer: C

Prospective controlled studies of prolonged infusions of piperacillin/tazobactam have not shown an improvement in mortality (Answer A is incorrect). No studies have reported neurotoxicity as an outcome (Answers B and D are incorrect). Only retrospective studies have shown improvements in mortality with the use of prolonged or continuous infusions of piperacillin/tazobactam (Answer C is correct).

8. Answer: C

Morphine is a high extraction ratio drug. As such, its hepatic metabolism or hepatic clearance depends only on hepatic blood flow. Hepatic clearance equals hepatic blood flow (Answer C is correct). Morphine does not bind to AAG (Answer A is incorrect). Because hepatic blood flow is the major determinant of hepatic metabolism of morphine, changes in protein binding do not affect metabolism (Answer B is incorrect). Changes in intrinsic clearance do not affect the metabolism of morphine as significantly as does hepatic blood flow (Answer D is incorrect).

POLICY, PRACTICE, AND REGULATORY ISSUES

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Learning Objectives

1. List the congressional committees and government agencies that regulate health care in the United States.
 2. Identify the regulatory and oversight bodies with jurisdiction over health system delivery of care.
 3. Explain recent federal legislative and regulatory activity that affects the delivery of health care.
 4. Describe the regulatory actions that govern the prescription drug approval process and the conduct of human subjects' research.
 5. Describe national quality initiatives aimed at improving health care delivery and patient health outcomes.
 6. Explain medication policy implications at an institutional level.
- A. Must be provided when a drug is dispensed in an outpatient setting and will be used without direct supervision by a health care professional.
 - B. Need not be provided to a hospital inpatient receiving that drug.
 - C. Cannot be removed from that REMS program in the future.
 - D. Need not be provided when a drug is dispensed to a health care professional for administering to a patient in an outpatient setting.
3. Which option is best to correctly state when an IND application should be submitted to the FDA?
 - A. Before preclinical studies.
 - B. After preclinical studies, before phase I clinical trials.
 - C. During phase II studies.
 - D. After phase III studies, before market approval.

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

1. With respect to reporting for adverse drug experiences, which is the best option to correctly describe the purpose of MedWatch Form FDA 3500A?
 - A. Is for voluntary reporting by health care professionals of a serious adverse event, product quality problem, or product use error with a U.S. Food and Drug Administration (FDA)-regulated drug, biologic, medical device, or dietary supplement.
 - B. Is for consumer reporting of adverse drug experiences.
 - C. May contain patient identifiers and still comply with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule.
 - D. Is the mandatory form to be submitted by investigational new drug (IND) reporters, manufacturers, distributors, importers, and facility personnel.
2. Which is most accurate with respect to the provision of medication guides when they are included as an element to ensure safe use within a Risk Evaluation and Mitigation Strategies (REMS) program?
 - A. Must be provided when a drug is dispensed in an outpatient setting and will be used without direct supervision by a health care professional.
 - B. Need not be provided to a hospital inpatient receiving that drug.
 - C. Cannot be removed from that REMS program in the future.
 - D. Need not be provided when a drug is dispensed to a health care professional for administering to a patient in an outpatient setting.
3. Which option is best to correctly state when an IND application should be submitted to the FDA?
 - A. Before preclinical studies.
 - B. After preclinical studies, before phase I clinical trials.
 - C. During phase II studies.
 - D. After phase III studies, before market approval.
4. Which option is best to correctly name the legislative act that created an abbreviated FDA approval pathway for generic drugs?
 - A. Kefauver-Harris Amendments of 1992.
 - B. Hatch-Waxman Act of 1984.
 - C. Durham-Humphrey Amendment of 1951.
 - D. Biologics Price Competition and Innovation (BPCI) Act of 2009.
5. Which description most accurately represents the use of quality measures?
 - A. The ORYX initiative reimburses health plans using HEDIS measures.
 - B. The Centers for Medicare & Medicaid Services (CMS) Hospital Value-Based Purchasing (VBP) Program reimburses hospitals using quality measures endorsed by the National Quality Forum (NQF) as well as the Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS).
 - C. The Health Insurance Marketplace Quality Rating System (QRS) for health plans uses National Hospital Quality Measures to display "star" quality ratings.
 - D. The Quality Compass is a tool comparing hospital systems using measures shared by the Joint Commission and CMS.

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6. Which is most accurate regarding patient safety organizations (PSOs)?
- A. The creation of PSOs was authorized under the Data Security Act of 2015.
 - B. The Patient Safety Organization Privacy Protection Center ensures patient safety events submitted to the network are non-identifiable.
 - C. The National Committee for Quality Assurance coordinates the endorsement of the Common Formats developed by the Agency for Healthcare Research and Quality (AHRQ).
 - D. Use of Common Formats is required by PSOs for CMS conditions of participation.
7. Which best describes the management of an Investigational Drug Service (IDS)?
- A. United States Pharmacopoeia standards require policies for the use of investigational drugs that specifically address their storage, dispensing, labeling, and distribution.
 - B. The Joint Commission standards regulate the disposal of investigational drugs.
 - C. The purpose of the IDS is to obtain and manage investigational drugs according to protocol and in compliance with state and federal requirements.
 - D. The institutional review board (IRB) maintains a study-specific notebook that includes IRB approval records, consent forms, and drug accountability records.
8. Which best depicts the final rule that has been promulgated by Department of Health and Human Services (DHHS) agencies, as authorized under the Administration Procedure Act of 1946?
- A. The Pregnancy and Lactation Labeling Final Rule requires that medications be labeled with pregnancy categories A, B, C, D, or X, according to risk of harm to the fetus.
 - B. The Disposal of Controlled Substances Final Rule governs the secure disposal of controlled substances by Drug Enforcement Administration (DEA) registrants and ultimate users.
 - C. The Provider and Supplier Enrollment, Ordering and Referring, and Documentation Requirements; and Changes in Provider Agreements Final Rule expanded hospital, non-physician practitioners to include pharmacists.
 - D. The Federal Policy for the Protection of Human Subjects protects the rights of patients of federally qualified health centers.
9. Which best describes the Safe and Secure Drug Disposal Act of 2010?
- A. Authorizes hospitals and clinics with on-site pharmacies and retail pharmacies to become collectors.
 - B. Authorizes the DHHS to promulgate rules for patient disposal of unused controlled substances.
 - C. Requires all collectors to register as reverse distributors.
 - D. Requires current DEA registrants to become collectors.
10. Which best reflects the safety and/or quality rules that were created as result of the FDA Safety and Innovation Act of 2012?
- A. State that a manufacturer of a drug that is life supporting must notify the DHHS of a permanent discontinuation at least 9 months prior.
 - B. Authorize hospitals to repackage drugs without registering as an establishment if distributing within a health system.
 - C. State that compounding facilities participating in outsourcing must report to the secretary every 6 months and undergo inspection by the FDA.
 - D. Institute “track-and-trace” requirements for manufacturers, repackagers, and dispensers to provide transaction details when products change ownership.
11. Which is most accurate regarding the differences in the approval process for generic small molecules (drugs) versus biosimilars?
- A. Biosimilars require a biologics license application (BLA) to be submitted to the Center for Biologics Evaluation and Research (CBER) for approval.
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- B. Generic drugs receive 180 days of market exclusivity after investigational new drug (IND) approval by the Center for Drug Evaluation and Research (CDER).
 - C. Biosimilars use an abbreviated licensure pathway after 12 years of patent exclusivity.
 - D. Biosimilar manufacturers are not required to pay fees for product applications, supplements, and other services.
12. When evaluating medications for interchange in the FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book), which statement is most accurate?
- A. Products with an "A" rating are pharmaceutical equivalents only and cannot be interchanged.
 - B. Interchangeable products may vary in dosage form and route of administration.
 - C. Products with an "A" rating are pharmaceutical equivalents and bioequivalents and can be interchanged.
 - D. Interchangeable products may vary in release mechanism or excipients.
13. Which situation best represents an adverse drug reaction?
- A. A patient with no known allergies develops hives with amoxicillin.
 - B. A patient is dispensed hydralazine instead of hydroxyzine and experiences hypotension.
 - C. A patient is given 325 mg of acetaminophen by nursing staff but is prescribed 500 mg.
 - D. A patient reports a hypoglycemic episode when self-titrating insulin.

OVERVIEW

The purpose of this review of policy, practice, and regulatory issues is to highlight areas of importance for clinical pharmacists as they pertain to policies governing patient care delivery and clinical research activity. Specifically, this chapter addresses rules, regulations, and quality initiatives at the institutional and national levels.

I. CONGRESSIONAL OVERVIEW, COMMITTEES WITH JURISDICTION OVER HEALTH-RELATED POLICY, AND THE LEGISLATIVE PROCESS

1. Congress is bicameral, with two legislative chambers: the Senate and the House of Representatives.
2. The Senate is composed of 100 elected, voting members. Legislation and tasks are divided into 20 standing committees, 68 subcommittees, and 4 joint committees. The committees that have jurisdiction over health-related policy include the following:
 - a. Appropriations Committee writes the legislation that allocates federal funds to the many government agencies, departments, and organizations on an annual basis and, in particular, funds discretionary programs.
 - b. Finance Committee has jurisdiction over issues that pertain to taxation and health programs under the Social Security Act including Medicare, Medicaid, and the Children's Health Insurance Program.
 - c. Health, Education, Labor and Pensions (HELP) Committee, as it pertains to health, authorizes agencies, institutes, and programs under the Department of Health and Human Services (DHHS), which includes the U.S. Food and Drug Administration (FDA), National Institutes of Health (NIH), and Centers for Disease Control and Prevention (CDC).
 - d. Committee on Veterans' Affairs oversees issues related to veterans' affairs (VA), including the VA health system.
 - e. Aging Committee was initially established as a temporary committee but transitioned to a permanent, special committee without legislative authority for matters relating to older Americans.
 - f. Legislation is reviewed by the committee with the most jurisdiction over the provisions in the bill. For example, the Pharmacy and Medically Underserved Areas Enhancement Act (S. 314) introduced in the Senate in 2015 was referred to the Committee on Finance because it amends the Medicare program.
3. The House of Representatives is composed of 435 elected, voting members and six delegates from the U.S. territories or from Washington, D.C., with nonvoting privileges. Legislation and tasks are divided into 20 standing committees, 4 joint committees, and 1 select committee. The committees with jurisdiction over health-related policy include the following:
 - a. Appropriations has jurisdiction similar to that listed above.
 - b. Ways and Means has jurisdiction over taxation and most programs authorized by the Social Security Act, similar to the Senate Finance Committee.
 - c. Energy and Commerce is the oldest standing committee of the House of Representatives. It has oversight of the DHHS and is similar to the Senate HELP committee.
 - d. Veterans' Affairs oversees issues related to VA.
 - e. Legislation is sent to any committee that has jurisdiction over any of the provisions in the bill. For example, the companion bill to S. 314, the Pharmacy and Medically Underserved Areas Enhancement Act (H.R. 592) introduced in the House in 2015, was referred to the Subcommittees on Health in both the Energy and Commerce and Ways and Means committees.

4. Legislative Process (Figure 1)

- a. Legislation is drafted by a member of Congress, a congressional committee, a constituent, a state legislature, or an executive communication from the president or an administrative agency.
- b. Types of legislation:
 - i. Bills are introduced into either the House or the Senate (prefixed either H.R. or S.) as one of two types:
 - (a) Authorization bills grant authority for a program or agency to exist or promulgate regulations. A program must still receive an appropriation in order to receive funding.
 - (b) Appropriation bills designate and commit a sum of money designated for a particular purpose by an act or bill.
 - (c) Companion bills, such as the Pharmacy and Medically Underserved Areas Enhancement Act, may be introduced separately or simultaneously into the House and Senate.
 - ii. Joint resolutions are similar to bills. They are designated by H.J. Res. or S.J. Res. and are often used for continuing or emergency appropriations.
 - iii. Concurrent resolutions are designated H.Con. Res. or S.Con. Res. They are used for internal affairs such as setting congressional hours and do not require presidential approval because they are not laws.
 - iv. A simple resolution, designated H.Res. or S.Res., is used for internal affairs of one chamber and does not require presidential approval.
- c. Once introduced, the legislation is generally referred to the relevant committees for consideration, markup, and approval.
- d. Action, debate, and voting on legislation, which are dictated by rules, differ greatly between the Senate and the House of Representatives.
- e. Because identical versions of a bill have to be approved by both chambers before they can go to the president, conference committees work to draft a compromise bill acceptable to both chambers.

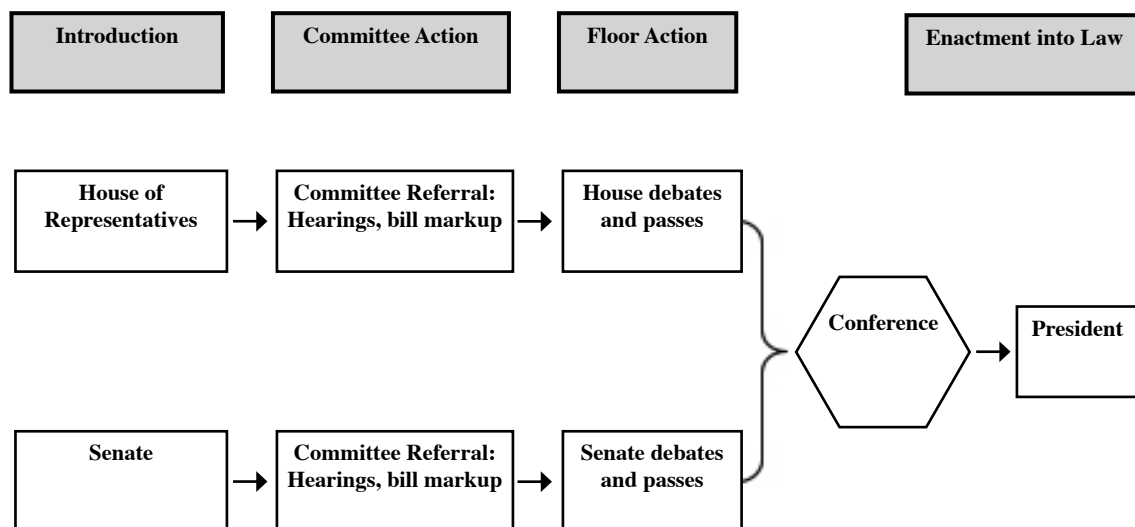


Figure 1. Legislative process.

5. Creation and codification of regulation by the authorized U.S. government department or agency is discussed in the next section.
6. Types of Appropriations, or Funding:
 - a. Entitlement spending for programs such as Medicare, Medicaid, and Social Security is automatically set according to eligible recipients. Levels of spending can be changed only by eligibility criteria changes.
 - b. Discretionary spending represents annual spending levels determined by Congress; such spending is optional.
 - c. Continuing resolution continues funding for a program if the congressional fiscal year, ending September 30, ends without a new appropriation in place.

II. U.S. GOVERNMENT DEPARTMENTS AND AGENCIES WITH PRIMARY REGULATORY IMPACT ON THE PRACTICE OF PHARMACY

1. DHHS is the agency charged with protecting the health of Americans. Appropriations to the DHHS represent the largest share of nondefense discretionary funding at 32% of federal monies appropriated. The following agencies are located within the DHHS:
 - a. The FDA is responsible for the safety of most foods (human and animal) and cosmetics, and it regulates both the safety and effectiveness of human drugs, biologics (e.g., vaccines, blood products, therapeutic proteins), medical devices, and animal drugs.
 - b. The Centers for Medicare & Medicaid Services (CMS) administers Medicare, Medicaid, and the State Children's Health Insurance Program (CHIP). It is driving the Value-Based Purchasing (VBP) Program, the Medicare Shared Savings Program, and the EHR Meaningful Use Incentive Program, and it develops Conditions of Participation (CoP) and Conditions for Coverage (CfC) that health care organizations are required to meet in order to participate in Medicare and Medicaid programs.
 - c. The Agency for Healthcare Research and Quality (AHRQ) supports research that helps people make better-informed decisions and improves the quality of health care services. The Public Health Service Act of 1998 authorized AHRQ to convene the U.S. Preventive Services Task Force (USPSTF). The USPSTF is an independent panel of experts on evidenced-based practices for preventive health care who develop clinical recommendations for preventive services.
 - d. The CDC provides programs that reduce the health and economic consequences of the leading causes of death and disability. An example is Healthy People, which provides science-based national goals and objectives with 10-year targets designed to guide national health promotion and disease prevention efforts.
 - e. The Health Resources and Services Administration (HRSA) improves access to health care through programs that strengthen the health care workforce, build healthy communities, and achieve health equity for people who are geographically isolated and/or economically or medically vulnerable. HRSA houses the National Center for Health Workforce Analysis charged with estimating the supply and demand for health care workers and designating shortage criteria in order to establish Health Professional Shortage Areas or Medically Underserved Areas or Populations.
2. U.S. Department of Justice (DOJ): Has jurisdiction over the Drug Enforcement Administration (DEA), which prevents, detects, and investigates the diversion of controlled substances and monitored chemicals
3. U.S. Environmental Protection Agency (EPA) seeks to protect human health and the environment.
 - a. Through the Resource Conservation and Recovery Act of 1976, the EPA has jurisdiction over rules governing the disposal of solid and hazardous waste.

- b. The Management Standards for Hazardous Waste Pharmaceuticals Rule proposes new regulations for health care facilities (including pharmacies) and reverse distributors in the handling of hazardous waste pharmaceuticals in order to improve environmental protection.
- 4. Departments and agencies of the U.S. government make rules and adjudicate (enforce) them within areas of delegated authority.
 - a. The Administrative Procedure Act of 1946 granted agencies of the DHHS the power to promulgate rules and regulations that have the effect of substantive law.
 - b. Proposed codification of general and permanent rules is published in the Federal Register, and the public is allowed to provide feedback within a prespecified time limit.
 - c. Final rules are published in the Code of Federal Regulations (CFR), which has 50 titles that are updated every year on a staggered basis.
 - i. Title 21: Food and Drugs
 - (a) Contains rules related to the FDA, DEA, DOJ, and Office of National Drug Control Policy
 - (b) Pregnancy and Lactation Labeling Rule (21 FDA CFR Part 201) requires changes to the content and format for drug labeling to assist in the risk-benefit assessment for medication use related to pregnancy and lactation and includes the removal of pregnancy letter categories.
 - (c) Institutional Review Boards (21 FDA CFR Part 56) contains standards for the composition, operation, and responsibility of an institutional review board (IRB) that reviews and approves of studies for products regulated by the FDA. This rule includes clinical investigations designed for submission to the FDA in support of an application or marketing permit. Exemptions from an IRB requirement are outlined in the text of this rule. Differences exist between this regulation and that of the Common Rule for the definitions of research, human subjects, and IRB (discussed later). Both need to be considered when conducting research.
 - (d) Disposal of Controlled Substances (21 CFR DOJ DEA Parts 1300, 1301, 1304, et al.) governs the secure disposal of controlled substances by DEA registrants and ultimate users.
 - ii. Title 42: Public Health
 - (a) Contains rules related to HHS, CMS, and the Office of Inspector General (OIG)-Healthcare
 - (b) Federally qualified health centers, organizations that receive grants for enhanced reimbursement from Medicare and Medicaid for offering health care services to all patients regardless of their ability to pay, are regulated by rules outlined in Medicare CMS regulations in Title 42.
 - (c) Changes in Provider and Supplier Enrollment, Ordering and Referring, and Documentation Requirements; and Changes in Provider Agreements for CMS (42 CFR DHHS CMS parts 424 and 31). This final rule expanded the definition of non-physician practitioners on hospital staffs to include pharmacists.
 - iii. Title 45: Public Welfare
 - (a) Common Rule (45 CFR Part 46): Federal Policy for the Protection of Human Subjects (revisions proposed in 2015 with finalization planned for 2016) protects human subjects involved in research (discussed later). Defines an IRB in the context of the rule and is different from that of 21 CFR 56
 - (b) Health Insurance Portability and Accountability Act (HIPAA) (45 CFR Parts 160, 162, and 164) protects personal health information (PHI).
 - (c) Enacted through HIPAA and enforced by the DHHS Office for Civil Rights
 - (d) The suite of HIPAA regulations for patient privacy and security is outlined in the Transactions and Code Set Standards, Identifier Standards, Privacy Rule, Security Rule, Enforcement Rule, and Breach Notification Rule.

III. RECENT LEGISLATIVE ACTIVITY WITH REGULATORY AND HEALTH POLICY IMPLICATIONS

1. The American Recovery and Reinvestment Act (ARRA) of 2009 included the Health Information Technology for Economic and Clinical Health (HITECH) Act.
 - a. HITECH authorizes the DHHS to create programs to improve health care quality, safety, and efficiency through the promotion of health information technology, including electronic health records (EHRs) and health information exchanges (HIEs) to facilitate and expand the secure, electronic movement and use of health information among organizations according to nationally recognized standards.
 - i. Created the Office of the National Coordinator for Health Information Technology (ONC) to coordinate nationwide standards and implementation efforts
 - ii. The Standards and Certification Criteria Final Rule is the initial approach to adopting standards, implementing specifications, and providing certification criteria to increase the interoperability, functionality, utility, and security of health information technology and to support its meaningful use.
 - iii. An HIE is defined as a process for exchanging health information through one of three forms:
 - (a) Directed exchange – Ability to send and receive secure information electronically between care providers to support coordinated care
 - (b) Query-based exchange – Ability for providers to find and/or request information on a patient from other providers
 - (c) Consumer mediated exchange – Ability for patients to aggregate and control the use of their health information among providers
 - iv. A health information organization (HIO) is a model for exchanging information at local, regional (known as RHIO [regional health information organization]), or state levels.
 - b. “Meaningful use” is part of the Electronic Health Records Incentive Programs issued by CMS to provide a financial incentive to eligible professionals, eligible hospitals and critical access hospitals, and Medicare Advantage Organizations that are “meaningful users” of EHRs.
 - i. Meaningful use consists of three stages:
 - (a) Stage 1 targets data capture and sharing (completed in 2014).
 - (b) Stage 2 targets advancement in clinical practices (through 2017).
 - (c) Stage 3 targets improvement in outcomes (by 2018).
 - ii. Meaningful users meet several objectives that demonstrate the use of certified EHRs in a meaningful manner (e.g., e-Prescribing), several objectives that demonstrate the use of certified EHR technology for electronic exchange of health information to improve the quality of public health and health care
 - (a) Opportunities for pharmacists include the provision of medication reconciliation for a minimum of 50% of patients at transitions of care, as included in the HIE objective.
 - (b) Each stage requires an increasing number of provider-generated prescriptions to be queried against a drug formulary and submitted to pharmacies electronically.
 - c. HITECH also imposes new penalties for breaches in HIPAA and PHI; the Office for Civil Rights within the DHHS will audit for compliance.
2. The Patient Protection and Affordable Care Act of 2010 (ACA) contains several provisions, ranging from protecting consumers to improving health care quality and lowering costs to increasing access to care. As the law translates into regulation, unique opportunities exist for pharmacists to become engaged.
 - a. Mandates that new health plans cover USPSTF recommendations receiving a grade of A or B at no cost to patients
 - b. The Medicare Shared Savings Program offers providers and systems the opportunity to participate in accountable care organizations (ACOs). ACOs are a set of providers associated with a defined population of patients accountable for the quality and cost of care delivered to that population. Pharmacists may aid ACOs in achieving these quality goals.

- c. Provides opportunities for pharmacists to participate in the Medicare Annual Wellness Visit
- d. Created the CMS Innovation Center to pioneer novel care delivery and payment models in which opportunities for pharmacists may exist
 - i. Comprehensive Primary Care (CPC) initiative explores whether reimbursable comprehensive primary care can result in better outcomes at reduced costs.
 - ii. Community-Based Care Transitions Program (CCTP) explores models for reducing readmissions in high-risk patients and is led by the Partnership for Patients, a nationwide partnership to reduce preventable errors in hospitals and readmissions.
 - iii. The Independence at Home Demonstration Program promotes the interdisciplinary collaboration of clinicians to provide home-based medical care for Medicare beneficiaries and test the effectiveness of delivering comprehensive primary care services at home and if doing so improves care for Medicare beneficiaries with multiple chronic conditions.
- e. Created an optional Medicaid State Plan benefit that allows states to establish Health Homes to provide comprehensive care for Medicaid patients with chronic conditions
- 3. The Biologics Price Competition and Innovation (BPCI) Act of 2009 is a provision in the ACA that creates an abbreviated approval pathway for follow-on biologic products, known as “biosimilars.”
- 4. The Physician Payments Sunshine Act (i.e., Sunshine Act) authorized CMS to require manufacturers of drugs, medical devices, and biologicals that participate in federal health care programs to report payments and items of value given to physicians and teaching hospitals. It also requires manufacturers and group purchasing organizations to report physician ownership or investments as part of the Open Payments Program.
- 5. The Safe and Secure Drug Disposal Act of 2010
 - a. Authorized the DEA to promulgate rules for patient disposal of unused controlled substances and controlled substance disposal by long-term care facilities
 - b. The Disposal of Controlled Substances Final Rule allows the transfer of unwanted and unused controlled substances from an ultimate user (i.e., patient) to an authorized collector for safe, secure, and responsible disposal.
 - i. Authorized collectors include manufacturers, distributors, reverse distributors, narcotic treatment programs, hospitals and clinics with on-site pharmacies, and retail pharmacies, including long-term care facilities and specialty pharmacies.
 - ii. Allows ultimate users to voluntarily dispose of controlled substances through take-back events, mail-back events, and collection receptacles
 - iii. Regulates each element of the disposal process, including transfer, deliver, collection, return, and recall of controlled substances
- 6. The FDA Safety and Innovation Act of 2012
 - a. Amends the federal Food, Drug, and Cosmetic (FD&C) Act to reauthorize PDUFA through 2017
 - b. Addresses drug shortages and states that the manufacturer of a drug that is life supporting, life sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition, including use in emergency medical care or during surgery, must notify the Secretary of the DHHS of a permanent discontinuation in the manufacturing of the drug that may disrupt supply in the United States, together with the reasons for discontinuation, at least 6 months before the date of discontinuation
 - c. Additional provisions include responding to those failing to report a shortage, expediting manufacturer inspections, publishing a drug shortage list, authorizing hospitals to repackage drugs without registering as an establishment if distributing within a health system, and requiring the Comptroller General to conduct a study on the impact of medication shortages.

7. The Drug Quality and Security Act (DQSA) of 2013
 - a. Establishes a new section (503B) in the FD&C Act to allow a compounding facility to voluntarily register as an outsourcing facility with the FDA (Table 1).
 - i. The outsourcing facility must give a licensed pharmacist direct oversight over compounded drugs.
 - ii. Other requirements include the following: only drugs with bulk ingredients listed as approved by the secretary can be compounded, the facility must report to the secretary every 6 months and undergo inspection by the FDA, the facility must report serious adverse events, and the facility must label products identifying them as a compounded drug.
 - b. Adds a new section (582) to the FD&C Act with product-tracing requirements (“track-and-trace”) for drug manufacturers, repackagers, wholesale distributors, and dispensers to provide transaction details when pharmaceutical products change ownership. Entities will also need to respond promptly in the event of a recall or an illegitimate product suspicion or investigation.

Table 1. Basic Comparison of the Compounding of Drug Products Under Section 503A and 503B

	503A: Traditional Compounder	503B: Outsourcing Facility
FDC Act exemptions	• Good manufacturing practices • Specific labeling requirements • FDA approval before marketing	• Specific labeling requirements • FDA approval before marketing
Compounding practice	• Compounded for identified individual patient • Must follow USP guidance for compounding	• Sterile compounding • May or may not obtain prescriptions for individual patients • Must follow good manufacturing practices for compounding
Reporting and registration	• No reporting or registration • Must follow track-and-trace requirements	• FDA registration required • Reports of compounded products and bulk ingredients every 6 months • Exempt from track-and-trace requirements
Fees	• None	• Establishment and inspection fees
Shipping restrictions	• Under state regulations	• None

FDA = U.S. Food and Drug Administration; USP = United States Pharmacopoeia.

8. Medicare Access and CHIP Reauthorization Act (MACRA) of 2015
 - a. Legislation repealed the sustainable growth rate (SGR) physician reimbursement methodology that threatened to reduce Medicare physician payments for more than a decade.
 - b. Represents a shift in reimbursement from fee-for-service to pay-for-performance or pay-for-value
 - i. Establishes the alternative payment model for physicians participating in patient-centered medical homes, ACOs, and Medicare shared-savings programs
 - ii. Establishes the merit-based incentive payment system (MIPS) that reimburses on the basis of quality, resource use, clinical practice improvement activities, and meaningful use of HER
 - iii. Sunsets three existing value-based payment adjustments: the EHR incentive program and the Physician Quality Reporting System and Value-Based Payment Modifier (discussed later) and combines them into MIPS
 - iv. Promises to revise and replace the EHR incentive program known as meaningful use
 - v. Reauthorized the State Children’s Health Insurance Program through fiscal year 2017. Final rule published in the Federal Register November 4, 2016. It works to broaden physician involvement in alternative payment models, to reduce administrative burden, and to ease providers into the transition.

9. Introduction of the Pharmacy and Medically Underserved Areas Enhancement Act (S. 314 and H.R. 592)
 - a. The companion bills were introduced in January 2015 and were referred to committee and subcommittee shortly thereafter.
 - b. The bills would enable pharmacists to provide reimbursable services to eligible Medicare Part B beneficiaries residing in medically underserved communities.
 - c. The bipartisan bill was a result of the combined efforts of pharmacy organizations and advocates, receiving wide support in the House and Senate, with 293 co-sponsors in the House and 51 co-sponsors in the Senate.
 - d. After referral to committee and subcommittee, there has been no further action on this bill.

IV. THE U.S. FOOD AND DRUG ADMINISTRATION AND THE PRESCRIPTION DRUG APPROVAL PROCESS

1. The Basics of the FDA and the Prescription Drug Approval Process
 - a. Most federal laws that authorize the FDA to promulgate rules are enacted by amendments to the FD&C Act, and they are organized in Title 21 of the CFR.
 - b. The FDA is funded through discretionary spending every fall in Congress's appropriations bill written by the Senate and House appropriations committees, but the Senate HELP and the House Energy and Commerce committees have jurisdiction over its reauthorization.
 - c. Organized by the Office of the Commissioner, Medical Products and Tobacco, Foods and Veterinary Medicine, and Global Regulatory Operations and Policy. The following offices and centers affect medication use:
 - i. Office of the Commissioner conducts overall agency coordination; the FDA's top official, the commissioner, requires Senate confirmation.
 - ii. Office of Regulatory Affairs, the largest office, regulates all inspection and enforcement activities.
 - iii. National Center for Toxicological Research supports the six product centers with scientific technology, training, and technical expertise.
 - iv. Center for Drug Evaluation and Research (CDER) regulates prescription and nonprescription drugs.
 - v. Center for Biologics Evaluation and Research (CBER) regulates biologic products, including vaccines, blood products, and gene therapy.
 - vi. Center for Devices and Radiological Health regulates medical devices.
 - vii. Center for Food Safety and Applied Nutrition regulates most foods, food additives, infant formulas, dietary supplements, and cosmetics.
 - viii. Center for Tobacco Products regulates tobacco-containing products.
 - ix. Center for Veterinary Medicine regulates feed, drugs, and devices used for pets, farm animals, and other animals.
 - d. Definitions
 - i. A clinical trial is a research study of humans conducted to answer specific questions about vaccines, new therapies, or new ways of using known treatments. Clinical trials are required by the FDA to determine whether new drugs or treatments are both safe and effective.
 - ii. An Investigational New Drug Application (INDA) is used for a new drug, a new indication, or an off-label use that will be used in a clinical investigation's preclinical development for that new drug to be distributed across state lines before full FDA review.
 - iii. A New Drug Application (NDA) is the vehicle through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing in the United States.

- iv. The Abbreviated New Drug Application (ANDA) contains data that, when submitted to the FDA's CDER, Office of Generic Drugs, allow the review and ultimate approval of a generic drug product.
 - v. An authorized generic drug is a listed drug that is marketed, sold, or distributed directly or indirectly to the retail class of trade. Its labeling, packaging (other than repackaging as the listed drug in blister packs, unit doses, or similar packaging for use in institutions), product code, labeler code, trade name, or trademark differs from that of the listed drug.
 - vi. A biologics license application is a submission that contains specific information on the manufacturing processes, chemistry, pharmacology, clinical pharmacology, and medical effects of a biologic product (monoclonal antibodies, enzymes, immunomodulators, growth factors, and cytokines) seeking approval to market in the United States.
 - vii. The interchangeability of a biosimilar product may allow it to be substituted for the legend (brand) biologic with an expectation that the same clinical outcome will occur and without the requirement of notification or intervention of a prescriber.
2. History of the Regulation of Drugs and Human Subjects' Research
- a. The Drug Importation Act of 1848: Prohibited the importation of unsafe or adulterated drugs at key ports of entry
 - b. The Biologics Control Act of 1902
 - i. Mandated annual licensing of establishments to manufacture and sell vaccines, sera, antitoxins, and similar products in interstate commerce
 - ii. Authorized Hygienic Laboratory, precursor of the NIH, to conduct regular inspections for purity and potency
 - c. The Pure Food and Drug Act of 1906
 - i. Prohibited interstate commerce of adulterated or misbranded drugs
 - ii. Required labeling of selected dangerous and addictive substances
 - iii. Identified the United States Pharmacopoeia and the National Formulary (USP/NF) as official standards for drugs
 - d. The FD&C Act of 1938
 - i. Required that firms prove evidence of safety to the FDA before marketing
 - ii. Placed drug advertising under the jurisdiction of the Federal Trade Commission
 - iii. Recognized the USP/NF as the official compendia of drug standards
 - e. The Durham-Humphrey Amendment of 1951: Amended the FD&C Act of 1938 to statutorily differentiate prescription and nonprescription drugs
 - f. The Kefauver-Harris Amendments of 1962
 - i. Established the requirement for drug firms to demonstrate efficacy as well as safety
 - ii. Statutory requirement to obtain informed consent for research subjects
 - iii. Authorized the FDA to regulate advertising of prescription drugs and establish good manufacturing practices
 - g. The Comprehensive Drug Abuse Prevention and Control Act of 1970 (i.e., Controlled Substance Act) authorized the DEA and FDA to regulate the manufacture, classification (schedule), importation, possession, use, and distribution of controlled substances.
 - h. The Orphan Drug Act of 1983: Established grants, federal assistance for research, and tax incentives to develop drugs targeted for a patient population of less than 200,000 or for medications with no expectation of cost recovery.
 - i. Grants a period of market exclusivity to new medications (7 years) for these rare diseases (Box 1)
 - ii. This timeline is independent of patent life (20 years), which begins when a new molecule is invented, not when it gains approval.

Box 1. Suboxone Orphan Drug Status Timeline

- The first patent for Suboxone was filed in 1990.
- While being investigated under an IND, the manufacturer filed for Orphan Drug Status in 1993. The application reflected that, despite the high rates of opioid addiction, less than 200,000 patients would be using the medication for opiate detoxification and maintenance. In addition, the application noted that market projections found no reasonable expectation that the costs of developing the drug would be recovered from sales. The drug was granted Orphan Drug Status in 1994.
- Suboxone was FDA approved in 2002, and the market exclusivity of 7 years began.
- Market exclusivity lapsed for this product in 2009. The FDA began accepting applications for generic products. The product patent for this formulation expired in 2010.
- The first generic formulations were brought to market in 2013.
- Controversy exists over the original estimates and approval of the product as an orphan drug.

- i. The Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Act): Authorized the FDA to create an abbreviated regulatory pathway through the ANDA for generic drugs
 - i. Grants a period of market exclusivity to new medications (4–5 years) or new indications (3 years) from approval until the acceptance of applications for generic drugs
 - ii. Grants the first approved generic drug 180 days of market exclusivity before other generic drugs can be approved
 - iii. This timeline is independent of patent life.
- j. The Food and Drug Administration Act of 1988: Officially established the FDA as an agency in the DHHS
- k. The Prescription Drug User Fee Act of 1992 (PDUFA)
 - i. Requires drug, biologics, and medical device (Medical Device User Fee Amendments) manufacturers to pay fees for product applications, supplements, and other services
 - ii. Reauthorized every 5 years (1997, 2002, 2007, 2012, expected 2017)
- l. The Dietary Supplement Health and Education Act of 1994: Allows nutritional supplements and vitamins to be regulated
- m. The FDA Modernization Act of 1997
 - i. Streamlines clinical research on drugs and devices
 - ii. Has exclusivity provisions for pediatric drugs
 - iii. Authorizes the creation of a databank (ClinicalTrials.gov) to provide easy access to information on federally and privately supported clinical trials for a wide range of diseases and conditions
 - iv. Provides abstracts of clinical study protocols that investigators are required to submit
 1. Summary and purpose of study
 2. Recruiting status
 3. Criteria for patient participation
 4. Location for trial and specific contact information
 5. Research study design
 6. Phase of trial
 7. Disease or condition and drug or therapy under study
 - v. More than 200,000 clinical trials have been listed with locations in all 50 states and in 191 countries.
 - vi. Reauthorized PDUFA through 2002
- n. The FDA Amendments Act (FDAAA) of 2007
 - i. Statutory authority to require Risk Evaluation and Mitigation Strategies (REMS) for the safe use of medications (discussed later)

- ii. Expanded the requirements for the types of drugs that must be registered on ClinicalTrials.gov; requires the submission of results for certain clinical trials
 - iii. Reauthorized the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act. Both were designed to encourage more research into, and more development of, treatments for children
 - iv. Reauthorized PDUFA through 2012
 - o. The Family Smoking Prevention and Tobacco Control Act of 2009: Gave the FDA authority to regulate tobacco products
 - p. The BPCI Act of 2009 passed as a provision within the Patient Protection and Affordable Care Act of 2010 (ACA),
 - i. Established a regulatory approval pathway for biosimilars
 - ii. Created FDA-administered periods of regulatory exclusivity for certain brand-name drugs and follow-on products
 - iii. Created a patent dispute resolution procedure for use by brand-name biosimilar manufacturers
 - q. The Reducing Prescription Drug Shortages Executive Order was signed by President Barack Obama on October 31, 2011. It requires the FDA to:
 - i. Broaden the reporting of manufacturing discontinuances that may lead to shortages of drugs that are life supporting or life sustaining or that prevent debilitating disease
 - ii. Expedite regulatory reviews to avoid or mitigate existing or potential drug shortages. Reviews may include new drug suppliers, manufacturing sites, and manufacturing changes.
 - iii. Communicate to the DOJ any evidence of or behaviors by market participants that have contributed to stockpiling or exorbitant prices
 - r. The FDA Safety and Innovation Act of 2012 (reviewed earlier)
 - i. Established the Biosimilar User Fee Act of 2012 to assess and collect fees for biosimilar biological products
 - ii. Established the “breakthrough therapy” drug approval pathway
 - iii. Increased stakeholder involvement in FDA processes by providing for the establishment of a patient-focused drug development initiative
 - iv. Reauthorized PDUFA through 2017
 - s. The DQSA of 2013 (reviewed earlier)
3. New Prescription Drug Approval Path
- a. The 1962 Kefauver-Harris Amendments included a provision requiring manufacturers of drug products to establish a drug’s effectiveness by “substantial evidence.”
 - i. It has been the FDA’s position, based on the language of the statute and the legislative history of the 1962 amendments, that Congress generally intended to require at least two adequate and well-controlled trials, each convincing on its own, to establish effectiveness.
 - ii. In 1997 under the FDA Modernization Act, section 505(d) was amended to make it clear that the agency may consider “data from one adequate and well-controlled clinical investigation and confirmatory evidence” to constitute substantial evidence if the FDA determines that such data and evidence are sufficient to establish effectiveness.
 - b. Preclinical studies
 - i. Laboratory and animal studies that assess safety and biologic activity in various model systems
 - ii. Toxicologic studies completed
 - 1. Effects on the fetus in pregnant mice, rats, rabbits, or baboons
 - 2. May or may not translate into human fetal adverse effects
 - 3. Fetal effects in humans may occur that were not observed in animal studies.
 - 4. Basis for pregnancy categorization

- c. An IND is drafted and submitted to the FDA. It must contain a general plan of investigation, drug information (i.e., chemistry, pharmacology, toxicology, pharmacokinetics, biologic disposition, laboratory and animal testing data, and existing human data), protocol, manufacturing, and control of the drug.
- d. Phase I drug trial
 - i. Initial introduction of an IND into humans, typically 20–80 healthy volunteers
 - ii. Goal is to garner information on the pharmacokinetic and pharmacodynamic properties and safety profile of the investigational drug to design a well-controlled and robust phase II trial.
- e. Phase II drug trial
 - i. Controlled clinical studies conducted in no more than several hundred subjects
 - ii. Goal is to evaluate the drug's effectiveness for a particular indication in patients with the disease or condition under investigation and to determine the common short-term adverse effects and risks associated with the drug.
- f. Phase III drug trial
 - i. Involves administering the investigational drug to a range of several hundred to several thousand patient subjects in different clinical settings to confirm its safety, efficacy, and appropriate dosage
 - ii. Goal is to gather necessary additional information about effectiveness and safety for evaluating the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling.
 - iii. The step before the sponsor's submission of an NDA to the FDA for approval to market the drug (Box 2)
- g. An NDA is submitted to the FDA and classified with a code that reflects both the type of drug being submitted and its intended uses.
 - i. The numbers 1–7 are used to describe the type of drug:
 1. New molecular entity (1)
 2. New salt of previously approved drug (2)
 3. New formulation of previously approved drug (3)
 4. New combination of two or more drugs (4)
 5. Already marketed drug product (i.e., new manufacturer) (5)
 6. New indication for currently marketed drug or switch from prescription to over the counter (6)
 7. Already marketed drug product without a previously approved NDA (7)
 - ii. Letter code describes the review priority of the drug.
 1. S = standard review for drug similar to currently available drugs.
 2. P = priority review for drugs that represent significant advances over existing treatments.
 - iii. Not all phase III drugs are approved, and the FDA can impose a clinical hold at any stage.

Box 2. Components of the New Drug Application

Index	Nonclinical pharmacology and toxicology
Summary	Human pharmacokinetics and bioavailability
Chemistry, manufacturing, and control	Microbiology (for antimicrobial drugs only)
Samples, methods, and labeling	Clinical data
Safety update report	Case report forms
Statistical analysis	Patent information
Case report tabulations	Patent certification
Other pertinent information	

- h. Phase IV drug trial
 - i. Also called postmarketing studies
 - ii. May be required by the FDA to identify additional information about the drug's risks, benefits, and optimal use
 - iii. Verify effectiveness or focus treatment on special populations
- 4. Generic Drug Approval
 - a. A generic drug product is identical to an innovator drug product in bioequivalence and pharmaceutical equivalence. Demonstrations of bioequivalence indicate that there are no significant differences in the bioavailability (e.g., rate and extent of absorption of the active ingredient) under experimental conditions, such as through in vivo or in vitro studies. The Drug Price Competition and Patent Term Restoration Act of 1984, also known as the Hatch-Waxman Act, defined bioequivalence statutorily as a means to approve a generic drug.
 - b. An ANDA must be submitted to CDER's Office of Generic Drugs.
 - i. ANDAs generally do not require preclinical or clinical data; rather, they must demonstrate pharmaceutical equivalence and bioequivalence.
 - ii. Once an ANDA is submitted to and approved by, the applicant can manufacture and market the generic drug as a safe, effective, and low-cost option to the public.
 - c. Pharmaceutical equivalents share the same active ingredient, dosage form and strength, route of administration, quality, and intended use (Box 3).

Box 3. Criteria for Medications to Be Pharmaceutical Equivalents

Three criteria:
☐ Must contain the same active ingredient
☐ Must be the same dosage form and route of administration
☐ Must be of identical strength or concentration, quality, and purity
Differences allowed:
☐ Shape
☐ Releasing mechanism
☐ Labeling (limited differences)
☐ Scoring
☐ Excipients (colors, flavors, preservatives)

- d. Therapeutic equivalence of generic drugs
 - i. All approved multisource products are listed in the FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book). The therapeutic equivalence coding system, using A or B, helps health care providers determine whether the FDA evaluated a product to be therapeutically equivalent to other pharmaceutically equivalent products.
 - (a) A code: An approved generic product considered therapeutically equivalent to other pharmaceutical equivalents
 - (b) B code: An approved generic product that is not considered therapeutically equivalent to other pharmaceutical equivalents
 - ii. Therapeutic equivalents can be substituted with the expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product.
 - (a) Criteria
 - (1) Pharmaceutical equivalent
 - (2) Therapeutic equivalence codes rated "A" by the FDA

- (3) Designates a brand-name drug or a generic drug as the reference-listed drug
 - (4) Demonstrates bioequivalence
 - (b) Assigns therapeutic equivalence code according to data submitted in an ANDA to demonstrate bioequivalence. Products deemed by the FDA not therapeutically equivalent are rated “B.”
 - e. An authorized generic is a drug that is produced by the brand company under the NDA but marketed as a generic. It is identical to the brand alternative in both active and inactive ingredients. The federal FD&C Act establishes a 180-day exclusivity period after approval of an ANDA. In this period, the FDA cannot approve other ANDAs for the same drug product.
 - f. At-risk launch of a generic occurs when a generic drug manufacturer challenges the validity of the existing patent of a brand drug.
5. Biosimilars and Interchangeable Biologic Products
- a. A biologic product is a drug or vaccine that has been produced in living cells.
 - b. The ACA amends the PHS Act through part of the legislation known as the BPCI Act. This legislation created an abbreviated licensure pathway for biological products found to be biosimilar or interchangeable with an FDA-approved reference biological product after 12 years of patent exclusivity.
 - i. A biosimilar product is a biological product that is highly similar in safety and efficacy to an FDA-approved reference biological product with only minor differences in clinically inactive components.
 - ii. An interchangeable biological product is biosimilar to an FDA-approved reference biological product that meets additional standards. An interchangeable biological product may be substituted for the reference product by a pharmacist without the intervention of the health care provider who prescribed the reference product. Because this interchange is also subject to state regulation, the statewide policy may override federal policy if it is more restrictive.
 - iii. The Biosimilar Implementation Committee, staffed by CDER, CBER, the Office of Chief Counsel, and the Office of the Commissioner, has developed several guidances for industry that describe the current thinking relating to quality and scientific considerations in demonstrating biosimilarity, clinical pharmacology data required to demonstrate biosimilarity, reference product exclusivity for biological products, and nonproprietary naming of biological products. These guidances do not establish legally enforceable responsibilities of the FDA. As of this writing, final naming guidance and draft interchangeability guidances are awaited.
 - iv. Table 2 compares the regulatory pathway differences between traditional small molecules and biologics for FDA approval.

Table 2. Regulatory Approval Pathway Comparison for Small Molecule and Biologic Products

Product	Regulatory Pathway	Nonproprietary Name	Indications	Interchangeability	Clinical and Trial Data Requirement
Small Molecule (Food, Drug, and Cosmetic Act)	New Drug Application (505(b)1 and 2)	N/A; Legend (Brand) drug	N/A; Legend (Brand) drug	N/A; Legend (Brand) drug	Clinical data required; safety and efficacy data requirement
	Abbreviated New Drug Application (505(j))	Same as originator	Same as originator	Granted with initial approval (e.g., Orange Book rating)	Clinical data not required; bioequivalence data requirement
Biologic (Biologics Price Competition and Innovation Act)	Biologics License Application (351(a))	N/A; Innovator (Reference) drug	N/A; Legend (Brand) drug	N/A; Legend (Brand) drug	Clinical data required; purity, safety, and potency data requirement
	Biosimilar Application (351(k))	Uncertain, may be different	May or may not have all indications, extrapolation allowed	Not automatically granted at initial approval – Requires additional review (e.g., Purple Book rating)	Clinical data required; abbreviated data requirement with purity, safety, and potency (i.e., totality of the evidence)

N/A = not applicable.

6. Medical Devices

- a. An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory that is:
 - i. Recognized in the official NF, or the USP, or any supplement to them
 - ii. Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in humans or other animals
 - iii. Intended to affect the structure or any function of the body of humans or other animals that does not achieve any of its primary intended purposes through chemical action within or on the body of human beings or other animals and that does not depend on being metabolized for the achievement of any of its primary intended purposes
- b. Regulated by the Center for Devices and Radiological Health
 - i. To be approved, a manufacturer of a class 3 (high-risk) medical device must submit a premarket approval application ensuring the device's safety and efficacy.
 - ii. If a medical device is essentially equivalent to an existing, legally marketed device, a 510(k) is submitted for premarket notification.
 - iii. An investigational device exemption allows an investigational device to be used in a clinical study to collect the safety and effectiveness data required to support a premarket approval application or a premarket notification 510(k) submission to the FDA.
- c. Classified according to the risks associated with the device:
 - i. Class I: Deemed low risk and therefore subject to the least regulatory control
 - ii. Class II: Higher-risk devices than class I that require greater regulatory controls to ensure reasonable safety and efficacy
 - iii. Class III: Highest-risk devices, subject to the greatest regulatory control; must be approved by the FDA before marketing

7. REMS

- a. The FDAAA of 2007 authorized the FDA to require REMS to ensure benefits outweigh risks before or after drug approval, if necessary. Examples of drug risks and possible actions include patient education on signs and symptoms or monitoring of laboratory values to avoid serious adverse effects, negative pregnancy tests before dispensing medications linked to serious birth defects, or administration by health care professionals in the presence of high administration-related risks.
- b. Is separate from the FDA's Risk Minimization Action Plans, which is a voluntary program for industry for drugs that have unusual risks but also unusual benefits
- c. Requires that a drug be prescribed and dispensed with one of the following:
 - i. Medication guide or patient package inserts. Medication guides are not usually required as part of a REMS unless the REMS includes Elements To Assure Safe Use (ETASU). If listed as an ETASU, a medication guide must be provided in all settings, including inpatient settings, outpatient settings but administered by a health care professional, and outpatient settings but dispensed to a patient.
 - ii. Communication plan to health care providers (for NDAs or biologics license applications only, not ANDAs)
 - iii. Elements To Assure Safe Use (ETASU) (Box 4)

Box 4. Risk Evaluation and Mitigation Strategies' Requirements of ETASU

ETASU may include one or more of the following:
☐ Health care providers who prescribe the drug have particular training or experience or are specially certified
☐ Pharmacies, practitioners, or health care settings that dispense the drug are specially certified
☐ Drug is dispensed only in certain health care settings
☐ Drug is dispensed to patients with evidence of safe use conditions such as laboratory test results
☐ Each patient using the drug is subject to monitoring
☐ Each patient using the drug is enrolled in a registry

ETASU = Elements To Assure Safe Use.

- d. The FDA does not have the authority to impose penalties on pharmacies and pharmacists not in compliance with REMS requirements, but there may be legal implications such as misbranding violations or civil liability issues.

Box 5. Suboxone® REMS Program

REMS elements include:
• Medication guide • ETASU: • Documentation of several safe use conditions by the prescriber: • Patient meets diagnostic criteria • Risks have been explained • Safe storage has been reviewed • Limited quantity prescribed at first visit • REMS Instruction Letter to Prescribers will be mailed annually to all physicians certified to treat opioid dependence under the Drug Addiction Treatment Act of 2000 and all retail pharmacies authorized by the DEA to handle schedule 3 controlled substances by manufacturer • Documented patient monitoring: regular visits, adherence assessments, appropriate prescribing, psychosocial support assessment, progress toward treatment goals

DEA = Drug Enforcement Administration.

- e. Critical Path Initiative
 - i. Created in response to a significant decline in NDAs, biologics license applications, and medical device applications because of the widening gap between basic science discovery and the challenging, inefficient, and costly development of medical products
 - ii. Prioritizes the most pressing developmental problems and identifies areas that provide the greatest opportunities for rapid improvement and public health benefit through three dimensions: safety assessment, evaluation of medical utility, and product industrialization
- f. The Clinical Trials Transformation Initiative (CTTI) is a public-private partnership that includes government agencies, industry representatives, patient advocacy groups, professional societies, investigator groups, academic institutions, and other stakeholders. It aims to improve the quality and efficiency of clinical trials.

V. ACCREDITING ORGANIZATIONS AND QUALITY IMPROVEMENT EFFORTS

- 1. Accreditation: The Joint Commission
 - a. Not-for-profit, independent organization that sets standards for accrediting health care facilities through its mission “to continuously improve health care for the public, in collaboration with other stakeholders, by evaluating health care organizations and inspiring them to excel in providing safe and effective care of the highest quality and value”
 - b. Accredits and certifies almost 21,000 health care organizations in the United States. Accreditation is reassessed every 3 years according to adherence to Hospital Standards, as assessed during on-site surveys, and quality reporting of performance indicators.
 - i. Standards address performance in functional areas of patient rights, patient treatment, medication safety, and infection control. National Patient Safety Goals were established to help accredited organizations address specific areas of concern in patient safety. Goals differ by health care setting and can change on the basis of recommendations from the Patient Safety Advisory Group.
 - ii. On-site surveys are unannounced and use tracer methodology to evaluate a patient’s medical record as a road map through a health care organization to evaluate its compliance with standards and systems to provide care and services. First-generation tracers follow a patient through care areas, whereas second-generation tracers focus on major organizational areas, such as high-alert medications or medication shortages.
 - iii. Performance measurement: The ORYX is a Joint Commission initiative to integrate outcomes with accountability in core measures: acute myocardial infarction, pneumonia, surgical care improvement project, children’s asthma care, perinatal, hospital outpatient measures, venous thromboembolism, substance abuse, tobacco treatment, emergency department care, immunization, hospital-based inpatient psychiatric services, and stroke in its accreditation process.
 - 1. Included accountability measures and processes are those that result in the greatest improvement in patient outcomes as identified by the Joint Commission. These measures and processes must be of sound scientific evidence, be in proximity between process and outcome, accurately measure the process, and minimize adverse effects without inducing unintended consequences. Measures are updated semiannually.
 - 2. National Hospital Quality Measures include common standardized measures between the Joint Commission and CMS, designed to share a single set of documentation (Box 6).

Box 6. National Hospital Quality Measure for Substance Abuse (SUB) -3

Measure: Alcohol and Other Drug Use Disorder Treatment Provided or Offered at Discharge

Type of Measure: Process

Description: Patients who are identified with alcohol or drug use disorder who receive or refuse at discharge a prescription for FDA-approved medications for alcohol or drug use disorder OR who receive or refuse a referral for addictions treatment out of hospitalized inpatients 18 years and older identified with an alcohol or drug use disorder

Rationale: Excessive alcohol and substance abuse negatively affects health and society. Brief interventions have been found improve health and reduce costs

3. National Quality Measures contain measures not common to CMS.
4. The Targeted Solutions Tool, created by the Joint Commission Center for Transforming Healthcare, provides a process for accredited hospitals to measure performance, identify barriers to excellent performance, and implement proven solutions.
2. Accreditation and Certification: The National Committee for Quality Assurance (NCQA)
 - a. Private, not-for-profit organization with a mission to improve the quality of health care through measurement, transparency, and accountability
 - b. Responsible for the development and maintenance of the Healthcare Effectiveness Data and Information Set (HEDIS)
 - i. Consists of more than 83 measures across five domains of care that health plans use to measure performance and focus improvement efforts. Domains include effectiveness of care, access of care, experience of care, utilization and relative resource use, and health plan descriptive information.
 - ii. Several measures are included in CMS's Quality Rating System for health plans participating in federally facilitated marketplaces for consumers to view in 2016.
 - c. Voluntary accreditation programs, certification programs, physician recognition programs, and distinctions are directed at health plans (e.g., health maintenance organizations, preferred provider organizations, and consumer-directed health plans), physician networks, medical groups, and individual physicians.
 - i. Notably accredits ACOs and certifies and recognizes patient-centered medical homes (PCMHs)
 - ii. Assessments may include on-site clinical and administrative processes, through data collection for the HEDIS, and measuring member satisfaction through the Consumer Assessment of Healthcare Providers and Systems survey.
 - d. The Quality Compass: A comparison tool that allows users to view measure results and benchmark information that ranks health plans using the HEDIS measures
 - e. Public reporting: "The State of Health Care Quality," which is an annual, overall assessment of the performance of the American health care system; "America's Best Health Plans" in collaboration with *U.S. News & World Report*; and the online Health Plan Report Card with a searchable database detailing health plans' accreditation and performance ratings
3. The Center for Pharmacy Practice Accreditation: Established by the American Pharmacists Association, the National Association of Boards of Pharmacy, and ASHP, offers accreditation for pharmacy practice sites on the basis of adherence to comprehensive and patient-centered medication use performance measures. Accreditation includes community, specialty, and telehealth pharmacy practice programs.

4. Quality Improvement Efforts
 - a. The National Quality Forum (NQF)
 - i. Nonprofit organization that aims to improve quality through a three-part mission:
 - (a) Build consensus on national priorities and goals for performance improvement and work in partnership to achieve them.
 - (1) Medicare Improvements for Patients and Providers Act of 2008: The DHHS entered into a contract with the NQF to establish a portfolio of quality and efficiency measures for use in reporting on and improving health care quality for the federal government to determine a return on investment in health care spending. The NQF is tasked with the formulation of a national strategy and priorities for health care performance measurement based on evidence related to 20 high-priority conditions identified by CMS that account for more than 95% of their costs.
 - (b) Endorse national consensus standards for measuring and publicly reporting on performance. Assess evidence to support and endorse quality measures proposed by other organizations (NCQA, American Medical Association, etc.) through a transparent, consensus-based practice
 - (c) Promote the attainment of national goals through education and outreach programs
 - ii. Membership includes stakeholders from consumer organizations, public and private purchasers, physicians, nurses, accrediting and certifying bodies, supporting industries, and health care research and quality improvement organizations.
 - b. AHRQ
 - i. The agency within the DHHS that supports research that helps people make more informed decisions and improves the quality of health care services through its mission to improve the quality, safety, and effectiveness of health care for all Americans
 - ii. Health service research provides clinical, health care system, and public policy decision-makers evidence-based information on health outcomes, quality, cost, use, and access to improve the quality of health care services.
 - iii. The Consumer Assessment of Healthcare Providers and Systems (CAHPS) program is an initiative to support and promote the assessment of consumer experiences with health care. The surveys assess the patient experience with a broad range of health care services and at multiple levels of delivery (e.g., health plans, hospitals [the Hospital Consumer Assessment of Healthcare Providers and Systems; HCAHPS] and dialysis centers) and can be used to make quality assessments for programs such as value-based purchasing.
 - iv. Funding opportunities, toolkits, and resources are available for researchers, clinicians, policy-makers, and consumers.
 - c. The Patient-Centered Outcomes Research Institute (PCORI): Nonprofit authorized by Congress in 2010 charged with improving the quality and relevance of evidence available to help patients, caregivers, clinicians, employers, insurers, and policy-makers make informed health decisions through the support and funding of comparative clinical effectiveness research (CER)
 - d. The Pharmacy Quality Alliance (PQA)
 - i. The mission of the PQA is to improve the quality of medication use across health care settings through a collaborative process in which key stakeholders agree on a strategy for measuring and reporting performance information related to medications.
 - ii. Develops medication-related performance measures, including proportion of days covered, gap in medication therapy, diabetes medication dosing, suboptimal treatment of hypertension in patients with diabetes, use of high-risk medications in older adults, drug-drug interactions, and medication therapy for people with asthma

- e. CMS Initiatives
 - i. Hospital VBP Program was established by the ACA in 2010 and uses quality measures endorsed by NQF as well as HCAHPS to establish and apply criteria for reimbursement and incentive payments starting in 2013. Performance data are public on the Hospital Compare website.
 - ii. Physician Quality Reporting System ties quality measures to physician reimbursement and makes some data public on the Physician Compare website.
 - iii. Health Insurance Marketplace Quality Rating System (QRS) aims to:
 - (a) Provide useful information to consumers using the Health Insurance Marketplace. Plans will be required to display their QRS star ratings (5-star scale) on their website before the 2018 Open Enrollment Period (limited pilot for 2017), and ratings will be displayed through the federally facilitated marketplaces. These ratings incorporate quality measures such as HEDIS and PQA measures.
 - (b) Provide actionable information that plans can use for performance improvement
 - (1) Quality Bonus Payment Demonstration Project was designed to drive quality improvement by extending bonus payments for improvements to low-performing plans.
 - (2) Potential opportunity for community pharmacy to improve plan ratings. EQuIPP is a performance information management system that makes performance data available to both health plans and pharmacy organizations.
 - (c) Facilitate oversight of qualified plans
- f. The Leapfrog Group is a voluntary program that works with employers to enable and direct purchasing power toward health care decisions focused on safety, quality, and value. It compares hospital performance on the metrics most important to consumers and purchasers of care. A Hospital Safety Score of A, B, C, D, or F has been applied to more than 2500 hospitals on the basis of prevention of errors, accidents, injuries, and infections.

VI. INSTITUTIONAL MEDICATION USE POLICY CONSIDERATIONS

- 1. Formulary Management
 - a. Basics
 - i. Formulary management is an ongoing process for a health care organization to establish medication use policies on drugs, therapies, and drug-related products that are evidence based and cost-effective for certain patient populations.
 - ii. The Joint Commission Medication Management Standard Chapter requires the hospital to develop and approve criteria for selecting medications that include indications for use, effectiveness, drug interactions, potential for errors and abuse, adverse drug events, sentinel event advisories, populations served, other risks, and costs.
 - iii. The CMS CoP require that medical staff establish a formulary system.
 - iv. A pharmacy and therapeutics (P&T) committee develops consensus on medication use policies and formulary management.
 - v. Evidence-based evaluation of medications for inclusion on a formulary includes a drug use review or drug use evaluation (DUE) (Box 7) and will be affected by CER.

Box 7. Elements of a Drug Use Evaluation Monograph

Brand and nonproprietary names	Use in special populations (e.g., pediatric, geriatric, hepatic, or renal insufficiency)
FDA approval information, including date and FDA rating	Pregnancy category and use in breastfeeding mothers
For biosimilars, interchangeability status	Clinical trial analysis and critique
Pharmacology and mechanism of action	Comparison of efficacy, safety, and cost-effectiveness
FDA-approved indications	Medication safety assessment and considerations
Potential off-label uses	Financial analysis based on use within a health system
Dosage forms and strengths	Recommendation for inclusion or exclusion
Pharmacokinetic considerations	

FDA = U.S. Food and Drug Administration

b. Definitions

- i. Formulary – A continually updated list of medications and related information, developed using the clinical judgment of pharmacists, physicians, and other experts in the diagnosis and treatment of disease and promotion of health within hospitals, health plans, and health care systems
- ii. DUE – Process used to assess the appropriateness of drug therapy by evaluating data on drug use in a given health care environment compared with predetermined criteria and standards
- iii. Medication use evaluation (MUE) – Performance improvement method that focuses on evaluating and improving medication-use processes related to prescribing, medication preparation, dispensing, administering, and monitoring. Medication use evaluations are often also tied to cost savings.

c. Formulary management strategies

- i. Preferential use of generic drugs
- ii. Formulary exclusion: Process of limiting medications from the formulary (called non-formulary or non-preferred medications)
 - (a) Open formulary: Non-formulary or non-preferred medications may be covered at variable levels of cost within a health plan.
 - (b) Closed formulary: Non-formulary or non-preferred medications are not covered within a health plan unless under an exception where medically appropriate.
- iii. Formulary restrictions: Restricting prescriptive authority to a particular service or disease state (Box 8)

Box 8. Example Suboxone® (Buprenorphine/Naloxone) Sublingual Film Formulary Criteria for Use

Health systems may wish to restrict the use of agents that are deemed high risk, high cost, or as needing special monitoring (e.g., Suboxone®)

Criteria for use may include the following:

- ☐ Patient inclusion: Patients meeting diagnostic criteria for opioid dependence/use disorder needing opioid agonist therapy
- ☐ Provider inclusion: Authorized to prescribe Suboxone® by meeting all requirements for a waiver specified by the Drug Addiction Treatment Act (DATA) 2000 as codified at 21 U.S.C. 823(g), who has experience in addiction management. Assurance of the availability of necessary treatment resources must be completed by the physician before prescribing
- ☐ Considerations for use:
 - Alternative first-line therapies for opioid dependence include methadone, though this agent is not available for office-based opioid treatment
 - Consider the potential for QTc prolongation in unstable cardiac disease or low potassium concentrations
 - Consider the potential for drug interactions with CYP3A4 inhibitors or inducers and with central nervous system depressants
 - Patients will need monitoring for several hours after administration of induction doses
 - Patients should be seen weekly for the first 2 weeks of therapy and then at least monthly for the next 3 months
 - Patients should be discontinued from therapy if they are found to misuse, abuse, or divert the medication; to be noncompliant with therapy; or to be unresponsive to therapy
- ☐ System responsibilities:
 - Procedures to verify provider authorization and to restrict use to authorized prescribers must be in place
 - Quantity limits may be imposed such that enough medication is dispensed to last only until the next scheduled appointment

- iv. Therapeutic interchange: Authorized exchange of therapeutic alternatives in accordance with previously established and approved written guidelines, policies, or protocols within a formulary system
 - v. Guided-use requirements: Include use criteria, clinical practice guidelines, and operating procedures
 - vi. MUE: MUEs differ from DUEs in that MUEs emphasize improving patient outcomes using a process that identifies, resolves, and prevents medication-related problems (actual or potential). Steps in conducting MUEs include:
 - (a) Establishing and implementing criteria, guidelines, treatment protocols, and standards of care for medications and medication use policies
 - (b) Selecting medications for MUE on the basis of adverse medication events or risk of events, signs of treatment failures, expense of medication, patient population or disease state
 - (c) Identifying data points and collecting data
 - (d) Evaluating adherence to criteria, guidelines, treatment protocols, and standards of care for medications and medication use policies
 - (e) Interpreting and reporting MUE findings
 - (f) Identifying and implementing improvement strategies in the medication-use process
2. Medication Safety Monitoring and Reporting
- a. Differentiation between medication errors, adverse events, and adverse reactions is critical to the evaluation and risk minimization process. Table 3 outlines the differences between medication errors, adverse drug events, and adverse drug reactions, or non-preventable adverse drug events.

Table 3. Differences between Medication Errors, Adverse Drug Events, and Adverse Drug Reactions

Term	Definition	Example
Medication error	Any error occurring in the medication process (ordering, transcribing, dispensing, administering, and monitoring)	Order filled for the wrong patient
Adverse drug event	Injury resulting from medication use or misuse; may or may not result from a medication error	Hemorrhage from heparin
Preventable adverse drug event	Injury caused by medication error	Overdosage of a medication that resulted in a hospitalization
Potential adverse drug event	Medication error with the potential for injury	Overdosage of a medication that was intercepted before patient administration
Adverse drug reaction	Non-preventable injury caused by the drug at normal doses and with normal use; not a result of a medication error	Allergic reaction in a person with no known allergies

b. Medication errors

- i. In 1999, the IOM released a report titled “To Err Is Human,” which stated that medical errors claim as many as 98,000 lives a year. The 2004 IOM report titled “Patient Safety: Achieving a New Standard for Care” revealed the high incidence of adverse events occurring in hospitals.
- ii. The Patient Safety and Quality Improvement Act of 2005 (Patient Safety Act [PSA]) and the Patient Safety and Quality Improvement Final Rule (Patient Safety Rule) were a congressional response to these reports. It requires the AHRQ to administer a Network of Patient Safety Databases to assess national, de-identified patient safety events.
 - (a) Encourages health care providers and organizations to voluntarily report and share patient safety information without fear of legal action
 - (b) Authorized the creation of patient safety organizations (PSOs)
 - (1) PSOs can be private or public entities, profit or not-for-profit entities, provider entities such as a health system, or other entities.
 - (2) PSOs provide a secure mechanism for the collection, aggregation, and analysis of data to identify and reduce risks and hazards that may occur with patient care delivery.
 - (c) The AHRQ created the Patient Safety Organization Privacy Protection Center to support the implementation of the Patient Safety Act. The Privacy Protection Center provides technical assistance to PSOs to ensure that data on patient safety events submitted to the Network of Patient Safety Databases are non-identifiable. PSOs not listed with AHRQ are not recognized under the PSA.
 - (1) Data are submitted to PSOs through Common Formats, developed by AHRQ for acute care hospitals and skilled nursing facilities. Common Formats provide a systematic process for reporting adverse events, near misses, and unsafe conditions, and they allow a hospital to report harm from all causes.
 - (2) The NQF leads the public review and lends expert opinion regarding the Common Formats.
 - (3) In March 2013, CMS communicated that although the use of Common Formats is not required for CoP for Quality Assessment and Performance Improvement surveys, hospitals that use them will be in a better position to meet Quality Assessment and Performance Improvement requirements.
 - (4) CMS surveyors were also encouraged to become familiar with Common Formats.

- iii. The ACA charges PSOs to assist health systems with a high rate of risk-adjusted readmission rates to decrease readmission rates and improve transitions of care.
 - (a) The Institute for Safe Medication Practices began in 1975 to promote medication error prevention and initiated a voluntary practitioner error-reporting program. The institute is now a nonprofit PSO that publishes four medication safety alert newsletters for acute care settings, ambulatory care settings, nurses, and medications.
 - (b) Vizient, formerly known as the University HealthSystem Consortium (UHC), is an alliance of academic medical centers and affiliated hospitals that is listed as an AHRQ-listed PSO under the UHC Performance Improvement PSO. Offers the UHC Patient Safety Net, a web-based inpatient and outpatient safety event-reporting system that consolidates and aggregates data for specific event types and offers best practices and policies to address common systemic areas for improvement
- c. Adverse events
 - i. Grades of certainty criteria, including certainty/definite, probable/likely, possible, and unlikely/doubtful, determine whether an adverse event is caused by a medication and can be assessed by tools such as the Naranjo Adverse Drug Reaction (ADR) Scale or the World Health Organization (WHO)-Uppsala Monitoring Centre (UMC) Causality Assessment.
 - ii. Adverse drug events should be reported to the U.S. Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS), a database with more than 400 million adverse event and medication error reports.
 - (a) MedWatch Form FDA 3500 for voluntary reporting is for health care professionals to report a serious adverse event, product quality problem, or product use error with an FDA-regulated drug, biologic, medical device, or dietary supplement. The Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule specifically permits health care professionals to disclose PHI for public health purposes.
 - (b) MedWatch Form FDA 3500A is for regulated industry following investigational new drug (IND) and biologic regulations and user facilities such as hospitals and nursing homes.
 - (c) MedWatch Form FDA 3500B is available for consumer reporting.
 - (d) Submitted events are evaluated by CDER and monitored by CBER.
 - (e) Vaccine-related adverse effects, veterinary medicine product adverse events, and suspected unlawful Internet sales of medical products should not be reported to MedWatch.
 - iii. The Vaccine Adverse Event Reporting System is a national postmarketing vaccine safety surveillance program managed by the CDC and the FDA for vaccine-related adverse events to be reported, analyzed, and made available to the public. The National Childhood Vaccine Injury Act of 1986 requires health care professionals and vaccine manufacturers to report to the DHHS specific adverse events that occur after the administration of routinely recommended vaccines.
 - iv. The FDA's Sentinel Initiative was implemented as a result of the FDAAA of 2007 to proactively monitor the safety of FDA-regulated products, such as drugs, vaccines, and medical devices. It is being implemented in stages to complement existing reporting systems, and it will have functionality to query electronic medical records, administrative and insurance claims, and registries.
- d. Workplace safety – Occupational Safety and Health Administration
 - i. Ensures safe and healthful working conditions for employees
 - ii. Is part of the U.S. Department of Labor and was granted regulatory authority through the Occupational Safety and Health Act of 1970

- e. Safety of compounded products
 - i. The USP develops standards, enforceable by the FDA, on the identity, strength, quality, and purity of medications and dietary supplements, including compounded products.
 - ii. Pharmacies may be subject to inspection against these standards by boards of pharmacy, the FDA, the Joint Commission, and other entities.
 - iii. The USP General Chapters are as follows: Required (numbered below <1000>), Informational (numbered <1XXX>), or Specific for dietary supplements (numbered <2XXX>); the chapters pertaining to compounding include the following:
 - (a) USP 795: Pharmaceutical Compounding for Nonsterile Preparations
 - (b) USP 797 (being revised): Pharmaceutical Compounding for Sterile Preparations (CSPs)
 - (1) USP 797 standards historically assign risk levels (low, medium, and high) according to requirements for the types of admixtures and preparation procedures. The proposed revisions limit the risk categories to category 1 and category 2, depending on a product's beyond-use dating. Proposed revisions also introduce "in-use time," before which an ingredient used in a CSP must be used after it has been opened or punctured, or before which a CSP must be used after it has been opened or punctured.
 - (2) As a result of deaths associated with microorganism contamination, CSPs have been under scrutiny. In October 2015, CMS issued a revision to its Pharmaceutical Services CoP State Operations Manual aligning their standards of practice for drug compounding with USP requirements, particularly for CSPs.
 - (3) An area of interest for organizations is beyond-use dating and sterility for CSPs. According to USP 797, if sterility testing has been performed, pharmacies can assign a beyond-use date based on the maximum chemical stability as listed in valid references. If sterility testing has not been performed, pharmacies must use beyond-use dating according to the level of risk and storage.
 - (4) In-use dating: Once opened/punctured, must be used
 - (c) USP 800: Hazardous Drugs: Handling in Healthcare Settings
 - iv. Supporting Patient Access to Medications
 - i. Options exist for supporting and supplementing patient access to medications. Pharmacists are a conduit for linking patients to medication discount and prescription assistance programs.
 - ii. The 340B Drug Pricing Program, authorized through the Medicaid Drug Rebate Program in 1990 and expanded by the ACA in 2010, allows specific categories of safety-net providers to become established entities and procure outpatient prescription drugs at discounted prices. The 16 categories of covered entities use the discounts to expand or develop new services.
 - (a) Eligibility is defined at the level of the health care facility and not the individual; however, the HRSA's Office of Pharmacy Affairs states that only patients with an established relationship with the covered entity are eligible to receive 340B purchased drugs.
 - (b) Covered entities can procure drugs at 340B prices and distribute them in the following ways
 - (1) Procurement by the covered entity and distribution by covered entities with in-house pharmacies or to an outpatient clinic for direct administration to patients
 - (2) Procurement by the covered entity but distribution to the patient from a contracted pharmacy
 - (c) In August 2015, the HRSA released a draft "mega guidance" for comment that may have significant implications for 340B entities, including narrowing the definition of covered patients, prohibiting duplicate discounts for Medicaid Managed Care patients, increased pharmacy oversight. As of this writing, final guidance has not been released.

- (d) The OIG also released a report detailing alternative payment methods under which Medicare beneficiaries, the Medicare program itself, and 340B entities could share cost savings generated by 340B programs. The OIG recommended that CMS require states to use claims-level data to identify 340B drugs to reduce duplicate discounts and that HRSA clarify guidance to support this.
- iii. Patient and prescription assistance programs are operated by drug manufacturers to provide free medications to patients who cannot afford them.

VII. INSTITUTIONAL REVIEW BOARD IMPLICATIONS FOR CLINICAL PRACTICE AND RESEARCH

1. By federal regulation, every institution that conducts or supports biomedical or behavioral research involving human subjects must have an IRB that initially approves and periodically reviews research protocols to protect the rights of human participants.
 - a. A human subject is a living person about whom an investigator conducting research obtains data through intervention or interaction with the individual or through identifiable private information.
 - b. Governed by FDA Title 21 Part 56 and DHHS Office for Human Research Protections regulations at Title 45 CFR Part 46; requires the IRB or ethics committee to protect the rights, safety, and well-being of all study subjects. Specifically, subpart A constitutes the Federal Policy (Common Rule) for the Protection of Human Subjects. In 2015, the DHHS and 15 other federal agencies announced proposed changes to the Common Rule intended to better protect human subjects involved in research while facilitating valuable research and reducing burden, delay, and ambiguity for investigators. Comments on the proposed changes to the Common Rule closed in January 2016, and the final rule has not been made public.
 - i. Clinical investigations that support applications for research (e.g., new test articles or indications) or marketing permits for products regulated by the FDA, including food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products, are regulated by the FDA human subjects' protections.
 - ii. Research involving human subjects is regulated by DHHS regulations.
 - c. An IRB is a committee of physicians, statisticians, researchers, community advocates, and others that ensures that a clinical trial is ethical and that the rights of study participants are protected. It is composed of at least five members with varying backgrounds to promote the complete and adequate review of research activities while adhering to institutional commitments and regulations, applicable law, and standards of professional conduct and practice.
 - i. The committee must be sufficiently qualified through the experience, expertise, and diversity of its members, including race, gender, cultural background, and sensitivity to issues such as community attitudes, to promote respect for its advice and counsel.
 - ii. At least one member whose primary concerns are in scientific areas
 - iii. At least one member whose primary concerns are in nonscientific areas
 - iv. At least one member who is not affiliated with the institution and who is not an immediate family member of a person affiliated with the institution
 - v. IRBs assessing clinical investigations regulated by the FDA human subjects' protections must register, be subject to inspection by CDER, and follow FDA regulations.

2. IRB Approval
 - a. IRB approval is required for interventional and observational studies, and applications must be reviewed annually.
 - b. Research exempt from FDA IRB requirements: Emergency use of a test article is permitted on a single-use basis but must be reported to the IRB review within 5 business days of use.
 - c. Research exempt from DHHS IRB requirements:
 - i. Research conducted in established or commonly accepted educational settings, involving normal educational practices such as:
 - (a) Research on regular or special education instructional strategies
 - (b) Research on the effectiveness of the comparison between instructional techniques, curricula, or classroom management methods
 - (c) Research involving the use of educational tests (cognitive, diagnostic, aptitude, or achievement), survey procedures, interview procedures, or observation of public behavior, unless:
 - (1) Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects
 - (2) Any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation
 - ii. Research involving the collection or study of existing data, documents, records, pathologic specimens, or diagnostic specimens; if these sources are publicly available or if the information is recorded by the investigator in a manner such that subjects cannot be identified, directly or through identifiers linked to the subjects
 - d. Research involving no more than minimal risk, and minor changes made to approved research protocols, may be considered for expedited review under both FDA and DHHS regulations.
3. The HIPAA Privacy Rule: Supplements and expands the Common Rule regulation of human subjects' research to protect the confidentiality of PHI used in clinical practice, research, and the operation of health care facilities
 - a. PHI includes information that:
 - i. Is created or received by a covered entity, which includes health care providers, hospitals, insurance companies, and business associates
 - ii. Pertains to the past, present, or future physical or mental health, or condition of the individual
 - iii. Pertains to payment for the individual's health care
 - iv. Pertains to the provision of health care in the past, present, or future
 - v. Identifies an individual or could be used to identify an individual
 - b. To use or disclose PHI for research purposes, one or more of the following must be obtained:
 - i. Written authorization specifically for the use and disclosure of PHI for research purposes involving human subjects
 - ii. Waiver of authorization approved by an IRB: Use of de-identified information or limited data sets (limited data set [45 CFR §164.514(e)] defined for research, public health, and health care operations)
 - iii. Preparatory to research certifications
 - iv. Database registration
 - c. A provision within HIPAA also mandated adoption of a standard unique identifier for health care providers. The National Plan & Provider Enumeration System of CMS collects information from providers and assigns each a unique National Provider Identifier.
4. Examples of typical documents submitted to the IRB for an initial review can be found at NIH's National Institute on Aging Clinical Study Investigator's Toolbox (Box 9).

Box 9. Documents That May Need to Be Submitted to an IRB for Initial Review

Cover sheet	Recruitment materials
Conflict of interest assessment	Surveys, questionnaires, other instruments
Application	Federal grant, if applicable
Formal protocol	Documentation of IRB approval from another institution
Informed consent forms	Data and safety monitoring plan
HIPAA authorization forms	Additional supportive documents as requested by IRB

HIPAA = Health Insurance Portability and Accountability Act; IRB = institutional review board.

5. Informed Consent

- a. Informed consent is the acknowledgment by the patient or study participant that they are aware of the risks and key facts about a clinical trial before deciding whether to participate. An informed consent document describes the rights of the study participants and includes details about the study.
- b. Informed consent documentation includes:
 - i. A description of the purpose of the research
 - ii. The expected duration of the subject's participation
 - iii. A description of the required procedures
 - iv. A description of any reasonably foreseeable risks or discomforts to the subject
 - v. A description of any benefits to the subject or to others that may reasonably be expected from the research
 - vi. A disclosure of appropriate alternative procedures or courses of treatment that might be advantageous to the subject
 - vii. A statement describing the extent to which confidentiality of records identifying the subject will be maintained
 - viii. For research involving more than minimal risk, an explanation of whether there is any compensation and an explanation of whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
 - ix. Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are no greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.
 - x. An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights and of whom to contact in the event of a research-related injury to the subject
 - xi. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled
- c. Waivers of informed consent will only be considered for DHHS regulated research if:
 - i. Research involves no more than minimal risk to subjects
 - ii. The waiver or alteration will not adversely affect the rights and welfare of subjects
 - iii. The research could not practicably be carried out without the waiver or alteration
- d. When appropriate, the subjects will be provided with additional pertinent information after participation.

VIII. INVESTIGATIONAL DRUG SERVICE

1. Investigational Drug Service (IDS)
 - a. The ASHP Policy on Institutional Review Boards and Investigational Use of Drugs (0711) strongly supports pharmacists' management of the control and distribution of drug products used in clinical research.
 - b. The purpose of an IDS is to procure, manage, prepare, dispense, and dispose of investigational drugs according to protocol and in compliance with the state and federal requirements that govern investigational drug activities.
 - c. Drugs, as defined by the FD&C Act, are "(A) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, and (B) articles (other than food) intended to affect the structure or any function of the body of man or other animals" (FD&C Act, sec. 201(g)(1)). An investigational drug is a chemical or biologic substance that has been tested in a laboratory and been approved by the FDA to be tested in human subjects. An investigational (also referred to as experimental) drug may be:
 - i. A new chemical or compound that has not been approved by the FDA for general use
 - ii. An approved drug undergoing further investigation for an approved or unapproved indication, dose, dosage form, or administration schedule or under an IND in a controlled, randomized, or blinded clinical trial
 - d. In addition to the regulations outlined by the Office for Human Research Protections (Common Rule) and the FDA to conduct research in accordance with the principles of good clinical practice and human subjects' protection, an IDS has federal and state requirements.
 - i. The Joint Commission standards require policies for the use of investigational drugs that specifically address their storage, dispensing, labeling, and distribution.
 - ii. The U.S. Environmental Protection Agency and the Occupational Safety and Health Administration regulate the disposal of investigational drugs.
 - iii. ASHP provides practice standards.
 - iv. The local IRB has its own requirements.
 - v. State-specific laws may vary.
 - e. Study-specific notebook: The notebook is maintained where study drugs are stored. It contains the files and contents listed in Table 4.

Table 4. Example of Documents Stored in Study-Specific Notebooks Maintained by an Investigational Drug Service

File Section	Contents
Protocol	Copy of the research protocol
Drug information	Investigator's brochure, drug data sheet, package inserts (if commercially available)
Pharmacy procedures	Study-specific pharmacy procedure information
Logs, forms, and labels	Study-specific materials
Procurement details	Receipt and disposition records
Correspondence	Correspondence
Computer matters	Copies of order entry codes
Billing	Financial agreements with investigator
IRB	IRB submission application, approval, and consent forms
Miscellaneous	Miscellaneous documentation
Master patient log	Record of patients enrolled
Drug accountability records	Data accountability record for each drug, dosage form, package size, and strength

IRB = institutional review board.

2. An investigational drug pharmacist's duties may include the following:
 - a. Participating on an IRB as a voting member
 - b. Maintaining a working relationship with the IRB, P&T committee, principal investigators, and the pharmacy department
 - c. Reviewing new and existing investigational drug study protocols
 - d. Meeting with investigators, study monitors, and other study personnel responsible for coordinating the logistics of a clinical trial
 - e. Receiving, organizing, and maintaining the contents of study notebooks
 - f. Providing randomization, blinding, or control functions of a clinical trial
 - g. Conducting the training of IDS staff and personnel regarding investigational protocols and study drug procedures

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ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS**1. Answer: D**

The FDA requires manufacturers, packers, and distributors of marketed prescription drug products to establish and maintain records and to make reports to the FDA of all serious, unexpected adverse drug experiences associated with the use of their drug products. Form FDA 3500 is for voluntary reporting by health care professionals, consumers, and patients, whereas 3500A is the mandatory form to be submitted by IND reporters, manufacturers, distributors, importers, and facility personnel, making Answer D correct and Answer A incorrect. Manufacturers, packers, and distributors should not include the names and addresses of individual patients. However, health care providers can continue to make adverse event reports under the HIPAA Privacy Rule. The HIPAA Privacy Rule is not intended to disrupt or discourage adverse event reporting in any way. In fact, the Privacy Rule specifically permits covered entities (e.g., pharmacists, physicians, hospitals) to report adverse events and other information related to the quality, effectiveness, and safety of FDA-regulated products, both to the manufacturers and directly to the FDA. As an explanation, the following statement has been provided: “The HIPAA Privacy Rule recognizes the legitimate need for public health authorities and others responsible for ensuring public health and safety to have access to PHI to carry out their public health mission. The rule also recognizes that public health reports made by covered entities are an important means of identifying threats to the health and safety of the public at large, as well as individuals. Accordingly, the rule permits covered entities to disclose PHI without authorization for specified public health purposes.” However, names of patients, individual reporters, health care professionals, hospitals, and geographic identifiers in adverse drug experience reports are not releasable to the public under the FDA’s public information regulations, making Answer C incorrect. Answer B is incorrect because consumers and patients should complete Form 3500B.

2. Answer: A

If a drug is subject to an ETASU REMS that requires the provision and review of a medication guide, it must be provided when a drug is dispensed in an outpatient setting and will be used without direct supervision by a health care professional, making Answer A correct. Moreover, it must be provided in all settings as specified

in the REMS program, including inpatient settings and outpatient settings, making Answers B and D incorrect. Requirements of a REMS to provide a medication guide can be revised and removed after approval at a later point, making Answer C incorrect.

3. Answer: B

An IND application is used for a new drug, a new indication, or off-label use that will be used in a clinical investigation’s preclinical development for that new drug to be distributed across state lines before undergoing full FDA review. An IND is drafted and submitted to the FDA after a preclinical study, before a phase I clinical trial, when the IND is first introduced into human subjects, making Answer B incorrect and Answers A, C, and D incorrect. The application must contain a general plan of investigation, drug information (i.e., chemistry, pharmacology, toxicology, pharmacokinetics, biologic disposition, laboratory and animal testing data, and existing human data), protocol, and manufacturing and control of the drug. An NDA is submitted after phase III studies, before market approval, making Answer D incorrect.

4. Answer: B

Answer B is correct. The Drug Price Competition and Patent Term Restoration Act of 1984, commonly called the Hatch-Waxman Act, named after the two lead sponsors, Representative Henry Waxman and Senator Orrin Hatch, is the legislative act that created an abbreviated FDA approval pathway for generic drugs. The Kefauver-Harris Amendments pertain to the requirement of a drug to show efficacy in addition to safety, making Answer A incorrect. The Durham-Humphrey Amendment differentiated prescription drugs from nonprescription drugs, making Answer C incorrect. The BPCI Act of 2009 was a provision passed in the 2010 ACA, and it created an abbreviated approval pathway for follow-on biologic products, or biosimilars, making Answer D incorrect.

5. Answer: B

The ORYX initiative assesses performance measures for hospitals using National Hospital Quality Measures, which include common standardized measures between the Joint Commission and CMS, making Answer A incorrect. The QRS uses quality measures such as HEDIS and PQA measures to determine a health plan’s

“star” quality rating, making Answer C incorrect. The Quality Compass is a comparison tool that allows users to view health plan rankings using the HEDIS measures, making Answer D incorrect. The CMS VBP Program was established by the ACA in 2010 and uses quality measures endorsed by NQF as well as HCAHPS to establish and apply criteria for reimbursement and incentive payments starting in 2013, making Answer B correct.

6. Answer: B

The Patient Safety and Quality Improvement Act of 2005 (Patient Safety Act [PSA]) and the Patient Safety and Quality Improvement Final Rule (Patient Safety Rule) required the AHRQ to administer a Network of Patient Safety Databases to assess national, de-identified patient safety events, making Answer A incorrect. The AHRQ established the Patient Safety Organization Privacy Protection Center to ensure that these data are not identifiable, making Answer B correct. The NQF coordinates the public review and expert opinion on the Common Formats developed by the AHRQ, making Answer C incorrect. The use of Common Formats is not required for CoP for Quality Assessment and Performance Improvement surveys, making Answer D incorrect. However, hospitals that use them will be in a better position to meet these requirements.

7. Answer: C

The Joint Commission is the organization whose standards require policies for the use of investigational drugs that specifically address their storage, dispensing, labeling, and distribution, making Answer A incorrect. The U.S. Environmental Protection Agency and the Occupational Safety and Health Administration regulate the disposal of investigational drugs, making Answer B incorrect. The purpose of an IDS is to procure, manage, prepare, dispense, and dispose of investigational drugs according to protocol and in compliance with the state and federal requirements that govern investigational drug activities, making Answer C correct. The IDS is charged with maintaining a study-specific notebook that includes IRB submission application, approval, and consent forms, drug accountability records, study-specific pharmacy procedure information, and financial agreements with the investigator, among other documents, making Answer D incorrect.

8. Answer: C

The Pregnancy and Lactation Labeling Rule requires a change from pregnancy letter categories to a new format to assist in the risk-benefit assessment for medication use related to pregnancy and lactation, making Answer A incorrect. The Disposal of Controlled Substances Final Rule does govern the secure disposal of controlled substances by DEA registrants and ultimate users, but it is promulgated by the DOJ, which does not fall under the DHHS, making Answer B incorrect. The Provider and Supplier Enrollment, Ordering and Referring, and Documentation Requirements; and Changes in Provider Agreements Final Rule expanded hospital, non-physician practitioners to include pharmacists, making Answer C correct. The Federal Policy for the Protection of Human Subjects (Common Rule) protects human subjects involved in research. Federally qualified health centers are regulated by rules outlined in Medicare CMS regulations in Title 42, making Answer D incorrect.

9. Answer: A

The Safe and Secure Drug Disposal Act of 2010 authorized the DEA, not the DHHS, to promulgate rules for patient disposal of unused controlled substances and controlled substance disposal by long-term care facilities, making Answer B incorrect. It authorizes manufacturers, distributors, reverse distributors, narcotic treatment programs, hospitals and clinics with on-site pharmacies, and retail pharmacies, including long-term care facilities and specialty pharmacies, to become collectors, but does not require it, making Answer D incorrect and Answer A correct. Although specified entities are permitted to reverse distribute in certain circumstances, they need not be registered as reverse distributors, making Answer C incorrect.

10. Answer: B

The FDA Safety and Innovation Act of 2012 requires that the manufacturer of a drug that is life supporting must notify the DHHS of a permanent discontinuation in manufacturing, together with the reasons for discontinuation, at least 6 months before the discontinuation, making Answer A incorrect. It also authorizes hospitals to repackage drugs without registering as an establishment if distributing within a health system, making Answer B correct. The DQSA of 2013 allows a compounding facility to voluntarily register as an outsourcing facility with the FDA and requires that outsourcing facilities report to the secretary every 6 months

and undergo inspection by the FDA, making Answer C incorrect, because it refers to the incorrect rule. The DQSA also institutes “track-and-trace” requirements for manufacturers, repackagers, and dispensers to provide transaction details when products change ownership, not the FDA Safety and Innovation Act, making Answer D incorrect.

11. Answer: C

Biosimilars require a Biosimilar Application submitted to CBER. Only a new biologic would require a biologics license application, making Answer A incorrect. Generic drugs receive 180 days of market exclusivity after approval of an Abbreviated New Drug Application (ANDA), not an IND application, making Answer B incorrect. The Biologics Price Competition and Innovation Act of 2009 created an abbreviated licensure pathway for biosimilars after 12 years of patent exclusivity for the parent biologic, making Answer C correct. The Prescription Drug User Fee Act of 1992 and the Biosimilar User Fee Act of 2012 require drug, biologic, biosimilar, and medical device manufacturers to pay fees for product applications, supplements, and other services, making Answer D incorrect.

12. Answer: D

Products with an “A” rating are both pharmaceutical equivalents and bioequivalents and can be interchanged, making Answer A incorrect. Products with a “B” rating are pharmaceutical equivalents only and cannot be interchanged, making Answer C incorrect. Interchangeable products must also be pharmaceutical equivalents and can therefore vary in their release mechanism or excipients, but not in their dosage form or route of administration, making Answer B incorrect and Answer D correct.

13. Answer: A

Answer B fits the definition of a preventable adverse event caused by a medication error, and Answer C is the definition of a medication error because it does not result in injury. Answer D depicts an adverse drug event that is not clearly the result of a medication error in the system, but perhaps the result of medication misuse by the patient. An adverse drug reaction is a non-preventable adverse drug event, such as an allergy or adverse effect, that is not the result of a medication error, making Answer A correct.

COMMUNICATION STRATEGIES IN PHARMACY

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Learning Objectives

1. Use strategies that develop patient rapport, foster trust, and effectively and efficiently obtain accurate, comprehensive histories, despite potential barriers in communication.
 2. Use assessments of patients' knowledge, health literacy, self-management skills, health beliefs, and attitudes toward medications to tailor educational interventions that will improve adherence and self-efficacy.
 3. Communicate patient care activities and medication-related information effectively to other health care professionals verbally and in writing through the medical record.
 4. Discuss factors and methods used to assess and select appropriate written educational materials intended for the general public.
 5. Describe how to serve as a patient advocate on medication-related issues within and outside the health care system.
- A. The Adherence Estimator questionnaire
 - B. The Morisky questionnaire
 - C. The Background, Affect, Troubling, Handling, Empathy (BATHE) technique
 - D. Motivational Interviewing
3. An older adult male patient correctly completed the calculation in the Newest Vital Sign (NVS) questionnaire. In the package insert dispensed with his prescriptions, he was able to find relevant facts about adverse effects associated with medications he was taking. He is selecting a Medicare D program and is struggling to compare brochures from several companies to identify the best program for him on the basis of his medications. Which National Assessment of Adult Literacy (NAAL) classification is this patient most likely in?
 - A. Below basic
 - B. Basic
 - C. Intermediate
 - D. Proficient

Self-Assessment Questions

Answers and explanations to these questions can be found at the end of the chapter.

1. A Spanish-speaking woman is scheduled for an initial appointment for asthma education today. Two hours before her appointment, the patient's interpreter calls, saying he will not be in until tomorrow because he has a family emergency. The clinic's receptionist, who speaks fluent Spanish, offers to help fill in for the interpreter. Which would be the most appropriate request for the pharmacist to make of the receptionist?
 - A. Step in for the interpreter during the encounter.
 - B. Call the patient to reschedule the appointment.
 - C. Ask the patient to bring a family member or friend.
 - D. Explain to the patient on arrival why the interpreter will not be there.
2. A pharmacist is performing a patient medication history and would like to assess the likely risk of a patient's nonadherence to his or her multidrug diabetes regimen. Which method would be best to use for this purpose?
 - A. The Adherence Estimator questionnaire
 - B. The Morisky questionnaire
 - C. The Background, Affect, Troubling, Handling, Empathy (BATHE) technique
 - D. Motivational Interviewing
4. A pharmacist is considering whether a commercially developed multimedia presentation would be appropriate to include as part of his institution's comprehensive asthma education program for adults. Which would be the most appropriate method to evaluate the usability of this presentation?
 - A. Ask a multidisciplinary group of colleagues to review the presentation's content.
 - B. Evaluate the presentation by using the Suitability Assessment of Materials (SAM) tool.
 - C. Assess the presentation by using the Patient Education Materials Assessment (PEMAT) tool.
 - D. Use the video in a random class and perform a survey on patient opinions of the video after class.
5. A pharmacist is asked to give a presentation to a group of physical therapists regarding new methods of pain management. Of the topic areas indicated in the following, which would likely be of most interest to this audience?
 - A. Mechanism of action and adverse events
 - B. Cost and formulary status

- C. Pharmacology and pharmacokinetics
 - D. Dosage and administration
6. In performing medication reconciliation for a patient, the pharmacist detected a discrepancy in the dosage of insulin glargine between the prescriber's medication orders and the patient's list. After clarifying the dosage with the prescriber, which would be the most appropriate way to document the correct dose and frequency of insulin in the patient's medical record?
- A. "Inject 15 units daily at bedtime."
 - B. "Inject 15 U QD at HS."
 - C. "Inject 15 units QD at HS."
 - D. "Inject 15 U daily at bedtime."
7. A pharmacist reads an editorial in the newspaper recommending the rejection of the school board's latest policy for required vaccinations of new students. The pharmacist strongly agrees with the school board's plan and carefully writes a 600-word rebuttal to this editorial. Which would be the most effective way to use this rebuttal to advocate for the new policy?
- A. Send the rebuttal as a letter to the school board to voice support.
 - B. Submit the rebuttal as a letter to the newspaper's editor.
 - C. Read the rebuttal at the next open school board meeting.
 - D. Offer the rebuttal to the newspaper as an "op-ed" piece.

I. COMMUNICATING VERBALLY WITH PATIENTS AND CAREGIVERS**A. General Communication Tips (*Domain 2*)**

1. Listen patiently and allow the patient to tell his or her story. If necessary, gently redirect or explain by whom and when the patient's other concerns might be addressed.
2. Use paraphrased summaries to indicate your understanding or for a transition to the next topic; allow the patient to make additions or corrections.
3. Use questions appropriately.
 - a. Open ended: Useful to begin a topic. Permits patients to provide their perspectives on what is important. Helps assess patient knowledge and understanding of the situation, medical problem, and medication.
 - b. Use of prompts: After the initial response, prompts help patients continue or complete their train of thought (e.g., "You mentioned [...]; what else do you remember?").
 - c. Probing questions: Ask for more focused or clarifying information. "Tell me more about..." "How did you feel when...?"
 - d. Closed ended: After patients seem to have completed their story, focused or closed-ended questions can screen for other pertinent positives/negatives. "Did you have any diarrhea or cramping?"
 - e. Avoid leading or compound questions.
 - f. Sequence questions in a logical, organized manner to avoid duplication.
 - g. Phrase questions tactfully and respectfully.
4. Consider your body language. Examples: Make regular eye contact; interviewer is positioned ideally at eye level with body turned toward, and at an appropriate spatial distance from, the patient. Avoid nervous and annoying habits (e.g., playing with a pencil or tapping foot).
5. Actively listen. Examples: React to ideas (not the person), read the patient's body language, listen to the patient's tone of voice as well as to the patient's words, ask for clarifications as needed, jot notes of follow-up questions to use after the patient finishes talking (do not interrupt), allow the patient to pause before jumping to next question, and permit silence for the patient to gather his or her thoughts.
6. Enunciate clearly. Modulate tone, volume, and rate of speech.

B. Developing Relationships and Maintaining Rapport During Patient Interviews (*Domain 2*)

1. Introduction
 - a. Set aside an appropriate time and place for speaking with the patient so that you may devote your full attention to the patient.
 - b. Warmly greet patients by using their preferred mode of address (usually Mr., Ms., or Mrs.). Use their first name only if invited to do so.
 - c. Introduce yourself by name, give your role, and describe the purpose for the interaction.
 - d. Acknowledge what you know about the purpose for their visit. "The receptionist said you had a question about your asthma medication?"
 - e. Establish a mutual agenda for the visit. "So you believe your pain medication is not working well and you need refills on your other medicines. Blood work is due for your diabetes. Anything else?"
 - f. On closing, summarize joint decisions and verify next steps. Provide contact information and offer assistance with future questions or problems.
2. Incorporate patients' perspectives and concerns
 - a. Provide opportunities for them to voice concerns throughout the encounter (e.g., during the initial introductions, ask the patient what they hope to accomplish; pause to allow patient to voice concerns throughout the encounter).
 - b. Repeat the patient's concerns or perspective with nonjudgmental language. Allow the patient an opportunity to clarify and make additions or corrections.

- c. Describe how you will address their concern. If you cannot address their concern, explain why it cannot be addressed, to whom their concern will be referred, or when their concern might better be addressed.
 - d. Encourage and respond to patient questions. Provide the patient with additional sources of reliable information to support answers to their questions when possible.
 - e. Be transparent when incorporating their perspective. "Because you said taking medication several times a day is difficult to incorporate into your schedule..."
 - f. Ask the patient about requests or goals. "What bothers you most about...?"
 - g. Include patients in decision-making, depending on their degree of interest.
 - i. Offer and explain available options and provide resources for them if they wish to research further.
 - ii. Identify any of their desired support partners. Respect their desire to include (or not include) others in the decision-making process.
3. Handle emotions and be empathetic and respectful. Ignoring emotions can appear uncaring (e.g., sadness, tears, pain) or can escalate if patients think their concerns are not being heard (e.g., anger, frustration, aggressiveness).
- a. Respond to emotions by acknowledging the patient's verbal and nonverbal cues. "You seem very distracted today. Are you concerned about something?"
 - b. Address the emotion by reflecting back. "You are angry that..."
 - c. Encourage the patient to expand as appropriate. "What frustrates you most about having to..."
 - d. Redirect the conversation tactfully back to the goal of the encounter when needed. "I will see that the receptionist deals with this billing issue after we finish. Let's get back to..."
 - e. Offer appropriate apologies. "I am sorry we dropped the ball on your request for... I will make sure that is done today." In addition, make sure you address all their concerns around a missed item. "Is there anything else that I need to make sure I address that you are concerned about?"
 - f. Maintain composure.
 - g. Offer comfort, compassion, reassurance, or support. "You are worried about how you will do with all of this. I will help you by..."
 - h. Nonverbal cues and empathetic listening can be more genuine and sincere than routine offers of sympathy such as "I am sorry about your loss."
4. Assessment of pharmacist communication during patient encounters
- a. Several frameworks and instruments have been developed to teach and assess physician communication skills during patient encounter. Among these frameworks, there are differences between the specific criteria and content. Common areas include organization of the interview, development of patient rapport, and general verbal and nonverbal communication skills (Fam Med 2005;37:184-92).
 - b. The Four Habits Model is one of the best-known assessment frameworks of this type (Permanente J 1999;3:79-88).
 - c. A limitation of applying these frameworks to pharmacists is that the terminology, criteria, and examples may not pertain to or be inclusive of pharmacist-patient encounters. In 2012, a pharmacist-specific communication assessment framework, Patient Centered Communication Tools (PaCT), was developed and validated (<https://www.stlcp.edu/health-literacy/pact.html>).

C. History Taking (*Domains 1, 2*)

1. Current problem and chief concern for visit
 - a. Opening question: Usually is open ended (“Tell me about your stomach problem”).
 - b. The **PQRST** (Provocative/Palliative, Quality/Quantity, Region/Radiation, Severity, Timing/Temporal relationship) method after the patient’s opening story encourages a comprehensive description of the problem. Commonly used for pain but also suitable for a variety of problems.
 - i. Provocative or palliative: “What makes the problem better (or worse)?
 - ii. Quality or quantity: “How many times...?” “Describe the sensation.”
 - iii. Region or radiation: “Point to where you feel...”
 - iv. Severity: “On a scale of 1–10, with 10 the worst, how bad is this?” “How does this compare to usual (state of health)?” “How bothered are you by this problem?”
 - v. Timing/Temporal relationship: “What time did this start?” “How long after you started exercising did...?”
 - c. A variant used for hospice palliative health is the **OPQRSTUV** method. The additional portions may be useful in other situations as well.
 - i. Onset of the problem
 - ii. Provoking/palliating
 - iii. Quality
 - iv. Region/radiation
 - v. Severity
 - vi. Treatment: “What have you tried so far?” “What has been the effect?” “Has this treatment caused any problems?” “What have you used in the past?”
 - vii. Understanding impact on you: “How is this affecting your daily activities?” “What has been the impact on your family?” “What do you believe is causing this problem?”
 - viii. Value: “What is your goal for this problem?” “What would be an acceptable level for this problem?”
 - ix. (www.fraserhealth.ca/media/SymptomAssessmentRevised_Sept09.pdf)
 - d. Follow-up or other visits without a chief concern, start with open-ended questions to begin dialogue about what patient hopes to accomplish at this visit.
 - e. The Background, Affect, Troubling, Handling, Empathy (**BATHE**) method can be useful to gather data and the patient’s perspective on problems that have an emotional component or that affect quality of life. For example, identify how a patient is coping with a new diagnosis (Prim Care Companion J Clin Psychiatry 1999;1:35-8).
 - i. Background: Use an open-ended question similar to the standard question to elicit the chief concern.
 - ii. Affecting: Solicit feelings or effect on quality of life. “How do you feel about this?” or “How is this problem affecting your life?”
 - iii. Troubling: Identify the relative importance or specific areas of concern. “What troubles you the most about...?”
 - iv. Handling: “How are you dealing/coping with this problem?”
 - v. Empathy: Reflect back the concern and/or emotion. “You seem frustrated by the lack of...”
 - vi. The BATHE method should be used in severe situations (e.g., when the patient is in extreme pain, when the patient is psychotic or suicidal).
 - (a) The BATHE technique is a psychotherapeutic procedure, meaning it seeks to empower patients to trust themselves and others, confirm their positive feelings about themselves, and enhance their ability to control the circumstances of their lives.
 - (b) This method will also serve as a rough screening test for anxiety, depression, and situational stress disorders.

Patient Cases

Questions 1 and 2 pertain to the following case.

The pharmacist is meeting today with a 78-year-old man who presents to the pharmacy today with a chief concern of new-onset back pain.

1. Which would be the most appropriate way to begin a discussion about his chief concern?
 - A. When did this back pain start, and what have you done for it so far?
 - B. How has your back pain been affecting your daily activities?
 - C. Tell me in your own words about the back pain you are experiencing.
 - D. Describe your back pain, including other symptoms.
2. This man has returned twice in 6 months with the same concern. His physician has changed his pain medication each time. He currently describes his pain intensity at 3 or 4 (on a 10-point scale, with 10 as the worst). He is able to work, but he limits some of his desired daily activities because of pain. Today, he asks about having back surgery. Instead, his physician prescribes a third pain medication and gives him a referral for physical therapy. After the physician leaves, the man turns to the pharmacist and bursts out: "When my brother had back surgery, it helped the pain right away! If I had better insurance, she would do the surgery." Which would be the best initial response to the patient?
 - A. "Surgery is serious, so it is done only if medication and physical therapy don't work."
 - B. "The physician was trying to explain that your back pain is not severe enough for surgery just yet."
 - C. "It is common to try two or three medications to find the right one at the right dose."
 - D. "You suspect that she is treating your problem differently because she will not get paid as much."

2. Components of an initial medication history: History should be correct (drug, dose, frequency, route), clear (not missing any information), complete (all drugs including over-the-counter [OTC], supplements, vitamins, natural products, herbs, physician samples), and current (include all recent changes).
 - a. Prescription medications include the following:
 - i. Oral and other routes such as topical, injectable, and inhalation.
 - ii. Both routine and as-needed medications: Note the dose, route, frequency, approximate starting date, and indication for each medication.
 - iii. Home oxygen: Note if continuous or intermittent (e.g., for exercise or during sleep) and the rate (in liters per minute).
 - iv. Past medications, especially those used to treat current problems: Inquire about when the medication was started or stopped (approximately) and for what reason (e.g., lack of effect, problem now resolved, adverse event).
 - v. Vaccinations: Check for specific vaccinations depending on the patient's age (pediatric, adolescent, adult, or elderly) or current problems (e.g., diabetes). For each, ask for the date of the initial vaccination and any boosters. If patient has not received vaccination, ask the reason why. Obtain a copy of a vaccination card if the patient has one or check your state vaccine registry.
 - vi. Drugs from other sources: Ask about samples, medications from patient assistance programs or clinical research studies, or use of another's prescription medications. Drugs from these sources are often not documented in the common places (e.g., medical records, community pharmacy profiles, electronic databases from pharmacy benefit managers).
 - b. OTC medications: Include vitamins, topical products, and herbal and nutritional supplements. Inquire about the frequency of use: Routine, seasonal, or as needed (often patients do not consider these as medications and therefore may omit them when gathering a medication history).

- c. Other pharmaceuticals: If a patient is coming from another institution, inquire about recent use of diagnostic, contrast, and radioactive agents; blood derivatives; and intravenous solutions, including any additives.
 - d. Adverse reactions and allergies
 - i. Differentiate between adverse effects and true allergic reactions.
 - ii. Document any known details, such as the date it occurred, the specific reaction, and its severity.
 - e. Medication-related social history
 - i. Street drugs: Consider the potential connotations of other terms such as *illicit*, *illegal*, or *recreational drugs*. Inquire about oral, inhaled, and injectable forms.
 - ii. Tobacco products: Phrasing the question as “Do you smoke?” or “Do you use cigarettes?” may narrow the response to exclude non-cigarette forms of tobacco (e.g., pipes, cigars), routes of tobacco (e.g., snuff, chewing tobacco), or nicotine products (e.g., vaporized, patch, lozenges). Ask age at initiation, discontinuation, and average frequency of use per day, week, or month. Calculate pack-year history of cigarettes. Ask the patient if he or she would like to quit smoking/ determine his or her readiness to quit.
 - iii. Alcohol: Ask about the amount (ounces), type of alcohol (e.g., beer, wine), and number of drinks per day, week, or month. Note the pattern of use (e.g., seven beers per week could be either one drink daily or seven beers on Saturday night).
 - iv. Medical or other sources of marijuana: Amount, frequency, age at initiation, purpose for use, and source
 - f. Adherence. Inquire about the following:
 - i. The number of specific doses missed per week in a nonjudgmental fashion. “How often in a typical week do you miss one of your medicines?” Adherence patterns may vary according to the medication, a specific disease, or the time of day. “When is the last time you missed taking this medicine?”
 - ii. Whether the patient has a specific method or system to assist in taking daily medications (e.g., pillbox, timer, calendar) or tracking the doses and frequency of as-needed medications (e.g., journal or logbook). If the patient misses more than a few doses, ask the patient or caregiver what they have tried in the past and what seems to work the best for them to remember doses.
 - iii. The most recent dose of medication taken: This may be important to correctly schedule the next dose when patients are being transferred, admitted, or discharged.
3. Using the medication history as part of medication reconciliation
- a. A standardized process should be used for reviewing a patient’s specific medication regimen at transition points in care. Discrepancies should be identified and resolved. The correct regimen should be clearly documented and communicated to all who are involved in care.
 - b. A pictorial tool, Medication Reconciliation Review of Systems Subject (MR ROSS), has been used to increase the number of medications identified by the patient during medication reconciliation (J Am Pharm Assoc 2013;53:652-8).
 - c. The Joint Commission includes medication reconciliation in its National Patient Safety Goals (http://www.jointcommission.org/assets/1/6/2015_npsg_hap.pdf).
 - d. The Joint Commission does not specify procedures or recommend best practices. A suggested procedure is included in Table 1.

Table 1. Process for Medication Reconciliation

Collect information from available sources	Patient/caregiver verbal history Any written medication lists from the patient Medical records from the provider, discharge lists, or admission lists
Identify discrepancies	Check for the following: Completeness: All prescription, over-the-counter, and as-needed medications and supplements Clear instructions: For example, dose, route, frequency, therapy duration Currency: Up to date with all new orders and dosage changes; all discontinued medications are deleted Duplicate therapy: Same drug or in same drug class (e.g., brand names or combination products) Compare/verify information from additional sources Family members or caregivers, if appropriate Community pharmacies medication profile(s) Prescriber records Electronic sources with data from pharmacy benefit managers (e.g., Capture Rx, Surescripts, RxHub)
Resolve discrepancies	Identify the cause/reason for the discrepancy. For example: A more recent order for a dosage change, for a new drug, or for discontinuing a drug Formulary substitutions (hospital drug formulary, insurance coverage, etc.) Patient misunderstanding or confusion Changes in patient status (e.g., renal function, worsening disease, laboratory values, patient improvement, weight loss) Make recommendations according to the cause of the discrepancy Obtain prescriber approval
Communicate changes	Have a methodical process for following up with pending discrepancies until ultimately resolved Document order changes in the medical record Update the medication list Transmit the updated list to other providers as needed Educate ambulatory patients on the reconciled regimen, emphasizing any changes Provide the reconciled list to ambulatory patients; a chart organizing the medications by administration times may be preferred Encourage the patient to maintain a complete and up-to-date list and to bring it to each provider visit

D. Assessing Patient-Specific Needs When Tailoring Educational Sessions (*Domain 2*)

1. Health literacy: Defined as the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions (Institute of Medicine 2004).
 - a. The National Assessment of Adult Literacy (NAAL) categorizes health literacy into four performance levels (Kutner 2006).
 - i. **Below basic (level 1):** Around 14% of the population or about 40 million Americans. These adults may be able to interpret short, simple text to perform routine tasks. However, those at level 1 have trouble matching information or identifying numbers touse in mathematical problems.

- ii. **Basic (level 2):** An additional 22% (about 50 million American adults) can solve routine mathematical problems or make simple inferences. However, people with level 1 or level 2 skills would find it difficult to interpret a dose chart on an OTC cold medication to calculate the correct dose for a child (Institute of Medicine 2004).
- iii. **Intermediate (level 3):** About 53% of the population can summarize text, find and apply facts from denser text, and identify and apply information to solve arithmetic calculations.
- iv. **Proficient (level 4):** Only 12% of the population can analyze and integrate several pieces of information or solve more abstract or multistep mathematical problems.
- b. Four major health literacy domains have been identified (Health Promot Int 2005;20:195-203).
 - i. Fundamental domain includes reading, writing, speaking, and basic numeracy. This is what most would think of as general literacy.
 - ii. Scientific domain includes the ability to understand basic scientific concepts. Examples include knowledge of the basic purpose and function of various organs, understanding of biologic concepts behind medical tests, and application of higher mathematical concepts such as trends, risk, and statistics.
 - iii. Cultural domain incorporates beliefs, customs, and social identity into personal decision-making.
 - iv. Civic domain requires applying health information to make decisions regarding general public policy. Examples include school board members making policy decisions regarding a nutritious diet for school lunch programs or voters deciding whether tobacco use should be banned in public.
- c. Risk factors for low or inadequate health literacy
 - i. Include age older than 65 years, less than a high-school education, low income, those for whom English is a second language, and immigrants. However, the largest group numerically consists of white individuals (Institute of Medicine 2004).
 - ii. The presence of risk factors alone does not reliably identify low or inadequate health literacy.
 - iii. Assessment tools have been developed for research or clinical settings. Information regarding common screening tools for low health literacy is summarized in Table 2.

Table 2. Summary of Common Health Literacy Assessment Screening Tools

Tool	Description	Comments
REALM	A brief (3–6 minutes) tool; adults pronounce a list of 66 common words related to anatomy or illnesses	Commonly used in research studies Does not directly measure comprehension of health information but has been highly correlated with reading comprehension (i.e., reading-grade level) Primarily assesses reading skills but not numeracy or mathematical ability Identifies those with inadequate health literacy REALM-R is a shorter version (eleven words) but is not as widely validated
TOFHLA	Consists of 50 reading and 17 numeracy items involving common medical situations; takes up to 22 minutes to administer	Commonly used in research studies A shorter version (s-TOFHLA) uses 36 of the reading questions and takes only 7 minutes Results are categorized into inadequate, marginal, or adequate levels of health literacy Spanish versions available for both the full and shorter versions of the TOFHLA; these are not as widely studied as the English version; scores between men and women varied on the shorter version

Table 2. Summary of Common Health Literacy Assessment Screening Tools (*continued*)

Tool	Description	Comments
NVS	Contains six questions regarding interpretation of a standard nutritional label; takes 3 minutes to administer	Assesses both literacy and numeracy (includes arithmetic calculations) Validated in English and Spanish Both versions correlate with the TOFHLA Has been tested in primary care settings
SILS	Is only one item: “How often do you need to have someone help you when you read instructions, pamphlets, or other written material from your doctor or pharmacy?”	Response scale is from 1 (never) to 5 (all of the time); response of more than 2 (sometimes, often, always) has a 54% sensitivity and 83% specificity for identifying inadequate health literacy Very brief; easy to integrate into clinical practice Other (individual) questions have also been tested Developed initially and validated in Veterans Affairs clinics but has also been tested in primary care population More reliably identifies those at risk of low/inadequate health literacy compared with confirming those with adequate health literacy; stronger correlation with s-TOFHLA and REALM in detecting inadequate compared with marginal health literacy Does not assess numeracy
SAHLSA-50	Involves reading 50 words; choice between two distractors is used to indicate understanding	Based on the REALM (but is not a Spanish translation of REALM)

NVS = Newest Vital Sign; REALM = Rapid Estimate of Adult Literacy in Medicine; SAHLSA-50 = Short Assessment of Health Literacy for Spanish Adults; SILS = Single Item Literacy Screener; TOFHLA = Test of Functional Health Literacy in Adults.

Institute of Medicine (IOM). Health Literacy: A Prescription to End Confusion. Washington, DC: National Academies Press, 2004:66-8.

North Carolina Program on Health Literacy. Literacy Assessment Instruments. Available at www.nchealthliteracy.org/instruments.html. Accessed September 26, 2014.

Weiss BD, Mays MZ, Martz W, et al. Quick assessment of literacy in primary care: the Newest Vital Sign. *Ann Fam Med* 2005;3:514-22.

Morris NS, MacLean CD, Chew LD, et al. The Single Item Literacy Screener: evaluation of a brief instrument to identify limited reading ability. *BMC Fam Pract* 2006;7:21.

Consumer Health Informatics Research Resource. Health Literacy. Available at <http://chirr.nlm.nih.gov/health-literacy.php>. Accessed September 29, 2014.

2. Topic-specific educational needs: With complex diseases (e.g., diabetes, asthma, hypertension), even patients with good health literacy may lack the necessary knowledge, understanding, or skills to optimally care for their condition at home. Educational needs can be assessed by asking the patient open-ended questions such as “Tell me what you know so far about...” or “What do you still need/want to know about...?” Patients may have questions regarding the following:
 - a. Disease or disease process and what they can expect (e.g., prognosis for a cure or developing complications, need for ongoing testing and monitoring).
 - b. Specific medications: For example: How to take them, why they are needed, how they work together, how long they might be necessary, and what options are available.
 - c. Nondrug therapy and lifestyle changes, including healthy eating habits and physical activity levels; role of surgery or physical therapy; and pulmonary, cardiovascular, or poststroke rehabilitation programs.
3. Health beliefs: Pharmacists should be alert for aspects of patients’ belief systems that may affect participation in care and adherence to medications and other treatments. Examples include the following:
 - a. General health-related attitudes such as trust in or skepticism about organized or Western medicine, openness to complementary and alternative medications, relative safety or efficacy of prescription versus OTC medications, importance of self-care and healthy lifestyles, or causes of disease.

- b. The Health Belief Model uses four constructs to predict whether a patient will participate in disease prevention or treatment. Identifying an individual's disease-specific beliefs may help identify barriers to adherence and assist in tailoring effective educational messages (Champion 2008). See Table 3.

Table 3. Using the Health Belief Model to Identify Issues and Tailor Educational Messages

Construct	Description	Patient Case Example	Tailored Educational Message
Perceived susceptibility	Individuals' beliefs about their likelihood of contracting the disease or condition	A 35-year-old woman is not interested in learning about how she can prevent type 2 diabetes mellitus; she says, "I will worry about it if it ever happens."	Explaining her many risk factors, such as obesity, history of gestational diabetes, and significant family history may help her understand the high likelihood of her developing diabetes
Perceived severity	Concern regarding the seriousness of the condition	She says, "Diabetes is not that big of a deal; all my family has it and they are just fine."	A tailored message might include the many complications of diabetes and connecting information from her family history (mother's heart attack at 55 years of age) to a complication from diabetes
Perceived benefits	Belief that making a suggested change can have an important impact	"There is nothing I can do about my genes; I am going to get diabetes regardless; I'll just take the pills like my mother."	Explaining how losing weight, eating a healthy diet, and becoming more active can delay or even prevent the onset of diabetes might increase her motivation to change her lifestyle
Perceived barriers	Beliefs about the negative aspects of change	"Cooking healthy food with my crazy work schedule would be too hard; I don't like vegetables and salad."	Help her brainstorm about possible foods that she likes, that are healthier, and that can be successfully integrated into her schedule
Cues to action	Factors that trigger action	"I've only gained a little bit of weight; it's not that big of a deal."	Point out the connection between her continued weight gain and the rise in her blood glucose into the prediabetic range; reassure her that even small changes in her diet or activity level can help decrease her risk of developing diabetes
Self-efficacy	Confidence that one can perform the behavior to reach the desired outcome	"There is no way I am going to lose 50 pounds, and I can't afford a gym."	Explain that coaching and assistance will be available to help her identify affordable resources, develop a specific plan, and successfully implement it (see more on self-efficacy in Table 7)

4. Religious or moral beliefs and value systems affecting medication use include medications from human cell lines (e.g., vaccinations), use of contraceptives, abortion-inducing and psychotropic medicines, decisions related to advanced directives, and practices affecting diet, such as religious fasting and vegetarianism.

5. Adherence

a. Terminology (Horne 2005)

- i. Compliance: The degree to which a patient's behavior is consistent with the prescriber's recommendations
- ii. Adherence: The degree to which a patient's behavior meets the agreed plan from the prescriber. This is the generally accepted term in the literature in the United States.
 - (a) Persistence: Whether the patient continues a medication beyond the first refill. In general, taking 80% or more of prescribed doses is considered "acceptable" adherence but may vary depending on the prescription medication (e.g., insulin).
 - (b) Primary nonadherence: Patient never fills, or fills but does not initiate the medication or behavior change.
 - (c) Secondary nonadherence (or nonpersistence): Patient begins but subsequently discontinues a medication or behavior change.
 - (d) Improper use: Patient continues to take the medication but in a manner inconsistent with the prescriber instructions (e.g., different dose or frequency, takes intermittently).
- iii. Concordance: Prescriber and patient in consultation agree on decisions incorporating their respective views. This process begins at prescribing but continues with patient support for taking the medication.
 - (a) This term (i.e., *concordance*) is more recent and is primarily promoted in the United Kingdom; it describes a higher-level therapeutic partnership between patient and prescriber.
 - (b) It should not be confused with patient coercion (e.g., providing the patient with information in such a way as to influence the outcome).

b. Measurement

- i. Indirect methods include calculating the proportion of days covered (PDC) or the medication possession ratio from prescription refill history. Of these, generally the PDC is the preferred method, because it provides a more conservative estimate of adherence (<http://ep.yimg.com/ty/cdn/epill/pdcmp.pdf>).
- ii. More direct methods, such as pill counts, are generally too labor intensive for routine assessment of adherence. Like the indirect methods, pill counts only infer the degree of adherence. Even if the appropriate number of doses are missing, one cannot assume that the patient is adherent to prescription instructions; for example, the patient could be taking at different intervals or different amounts.

c. Assessing risk of future nonadherence: The medication history or review of the pharmacy patient profile can retrospectively identify nonadherence. It would be helpful to prospectively identify the risk of nonadherence and its potential causes when tailoring educational messages.

- i. The Adherence Estimator can be used to prospectively assess the likelihood that a patient will adhere to a newly prescribed medicine (Curr Med Res Opin 2009;25:215-38).
 - (a) Scoring: Three questions are answered by the patient by using a 6-point scale from agree completely to disagree completely. Scores range from zero (low risk of nonadherence) to 36 (high risk of nonadherence). See Table 4.
 - (b) Usefulness: This tool is easy to use and quick to administer and to calculate the score. Assesses risk of nonadherence to an individual drug (not to a particular disease regimen or an entire regimen).
 - (c) Targeted messages can be provided to the patient's specific issue(s). Note that the tool measures patients' perceptions of the drug rather than its actual toxicity, efficacy, or cost.

Table 4. The Adherence Estimator

Question	Issue	Score
Worry the prescription will do more harm than good?	Is concerned that the risk of harm exceeds the medication's potential benefit	0 (strongly disagree), 4, or 14 (strongly agree) points
Convinced of the prescription's importance?	Committed to take the medication because it is necessary	0 (strongly agree), 7, or 20 (strongly disagree) points
Perception of financial burden?	The cost is perceived to be affordable	0 or 2 (strongly disagree) points
Scoring		0 points = low risk of nonadherence 2–7 points = medium risk of nonadherence 8–36 points = high risk of nonadherence

McHorney CA. The Adherence Estimator: a brief proximal screener for patient propensity to adhere to prescription medications for chronic disease. *Curr Med Res Opin* 2009;25:215-38.

- ii. The Morisky questionnaire is a predictive adherence measurement tool available in four- and eight-question formats. It can be used to screen for patient knowledge gaps and motivational issues that may affect adherence. Questions ask about missing doses, stopping medication, or cutting back on medication because of adverse effects or disease control. An advantage is that a single questionnaire can be used to screen a disease-specific regimen involving several drugs (e.g., hypertension). It is also available in languages other than English, including French and Chinese.

Patient Cases

Questions 3–5 pertain to the following case.

A pharmacist is initially counseling a 75-year-old, lower-middle-class man of Middle Eastern descent on sliding-scale insulin. He is a native-born American who, after completing high school, worked 40 years as a security officer. He says his wife most often reads the medical information for him that he brings home. The prescriber's instructions are to take 2 units of insulin for every 100 mg/dL that his blood glucose concentration is higher than 100 mg/dL. To check his understanding, the pharmacist asks him how much insulin he would take if his blood glucose were 300 mg/dL. The man takes several minutes but correctly calculates the dose.

3. Using NAAL levels and interpreting the patient's response to the Single Item Literacy Screener (SILS), what is the best assessment of this patient's health literacy?
 - A. At risk of inadequate health literacy according to SILS; likely NAAL level 2.
 - B. Adequate health literacy according to SILS; likely NAAL level 3.
 - C. At risk of inadequate health literacy according to SILS; likely NAAL level 3.
 - D. Adequate health literacy according to SILS; likely NAAL level 2.
4. Which is most likely a risk factor for low health literacy in this man?
 - A. His educational level
 - B. His race/ethnicity
 - C. His income level
 - D. His age

Patient Cases (continued)

5. When the patient returns 3 months later, the pharmacist wants to assess the likelihood of his continued adherence moving forward to the insulin sliding-scale regimen to identify further educational needs. Which would be the best method to make this assessment?
 - A. Check his profile for aspart refill dates to calculate his medication possession ratio.
 - B. Scan his blood glucose log to see how many times he has used insulin aspart correctly.
 - C. Ask him to complete the Adherence Estimator questionnaire regarding insulin aspart.
 - D. Use the Health Belief Model to assess his perception of the importance of insulin aspart.

E. Providing Educational Messages (Domain 2)

1. When starting with a new patient or beginning a new topic, a “universal precautions” approach is recommended (i.e., all patients should be considered at risk of low health literacy until a patient-specific assessment can be made of the individual’s knowledge and skills) (AHRQ 2010).
 - a. Health literacy screening tools (e.g., SILS or REALM) are better at identifying those at risk and are less reliable for assessing the adequacy of an individual’s actual health literacy. Example: In response to the SILS question, a patient responds that he always reads medical information himself. This response normally implies good health literacy. However, someone with low health literacy may make the same response if he has no one to help him.
 - b. Even those with generally good (general) health literacy may have topic-specific misconceptions or gaps in knowledge or skills.
2. Start with an open-ended question to assess the patient’s baseline knowledge.
 - a. Indian Health Service Prime (medication) questions (www.ihs.gov/healthcommunications/documents/toolkit/Tool9.pdf)
 - i. What did your prescriber tell you the medication was for?
 - ii. How did your prescriber tell you to take the medication?
 - iii. What did your prescriber tell you to expect?
 - b. To assess baseline knowledge of a disease state, another open-ended question appropriate for the situation may be used. “What has the diabetes educator reviewed with you so far?” “What do you want to learn most about...?”
 - c. From the patient’s responses, the provider can reinforce correct knowledge and make an initial assessment of the patient’s needs to clarify misunderstandings, address misperceptions, fill in information gaps, or demonstrate needed skills.
3. Communicating clearly. See techniques in Table 5.

Table 5. Techniques to Communicate Clearly

Technique	Comments
Use plain, nonmedical language	Listen and reflect back terms used by the patient for medical and nonmedical terms (e.g., menopause vs. change of life, dinner vs. supper) Use plain language and avoid medical jargon. Consult the <i>Plain Language Thesaurus</i> for suggested medical and nonmedical terms to avoid and for better alternatives to these words Avoid abbreviations (e.g., “Use your ICS medication...”) Be specific: “Take this medication at least 2 hours after eating” vs. “Take on an empty stomach” Give examples: “Dairy includes milk, cheese, ice cream, and yogurt” Use the consistent terms recommended by disease guidelines (e.g., <i>quick relief</i> and <i>long-term controller</i> inhalers for asthma medications)

Table 5. Techniques to Communicate Clearly (*continued*)

Technique	Comments
Limit content	Prioritize key points Limit verbal information to three to five key points; if more, provide written instructions Provide information that can be digested in the time available; this may mean scheduling additional educational sessions
Use visual aids	Draw or show pictures Use dimensional models or placebo devices Explain and demonstrate skills (e.g., respiratory device technique, use of home blood pressure monitor)
Tailor the message	Adapt to the patient's motivational or interest levels (e.g., provide sources for additional information if interested, shorten the topic to essential information if less interested) Explain the relevance of the information to the patient's own situation Provide information in the patient's preferred style, if possible: "There is a pamphlet I can give you, but there is a great website, or I could show you a video. Which would you prefer?"
Increase patient participation	Use familiar analogies to explain concepts Encourage questions "What questions do you have?" "What parts would you like me to go over again?" "That would be a great question to ask your doctor at your visit today" More formal methods can be used to encourage patient questions such as the following: Ask Me 3 (www.ihs.gov/healthcommunications/documents/AskMe_8-pg_NatAmer.pdf) What is my main problem? What do I need to do? Why is it important? The "Questions Are the Answer" tool on the Agency for Healthcare Research and Quality website helps patients articulate their own questions regarding medications or other therapies (www.ahrq.gov/patients-consumers/patient-involvement/ask-your-doctor/index.html?utm_source=buffer&utm_campaign=Buffer&utm_content=buffer31ff3&utm_medium=twitter) Ask the patient to personalize the information: "It is important to take this at the same time each day. What is something you do at the same time every day?"
Assess knowledge and skills	Use the teach-back method to assess understanding In the initial teach-back question, the provider accepts responsibility for communicating clearly and correctly: "To be sure I included everything, tell me how you will..." or "I want to be sure I was clear; when will you...?" Acknowledge correct information If necessary, clarify, supplement, or correct information, and then repeat the teach-back process Many teach-back "loops" may be necessary until the patient understands Use the "show-me" technique as appropriate: "Show me which column you would record this blood glucose number in" or "Show me how many pills you would take tomorrow morning." Have patient demonstrate each skill (e.g., coding the glucometer, checking the memory, obtaining a blood sample) Provide situation-based "what if" examples: "What would you do if your blood glucose were 70?"

Table 5. Techniques to Communicate Clearly (*continued*)

Technique	Comments
Chunk and check	Break down complex topics into manageable sections Assess knowledge at the end of each section
Emphasize key points	Summarize at the end of the session Write down complex information or provide health literacy–friendly handouts Point out the instruction booklet and any “quick-start guides” for devices Provide patients with disease-specific care plans (e.g., written asthma action plan with instructions based on red-yellow-green zones) Provide a call back number, e-mail, or other form of contact if questions arise after the patient leaves.

Centers for Disease Control and Prevention. Plain Language Thesaurus. Atlanta, GA: CDC, U.S. Department of Health and Human Services, 2007. Available at http://depts.washington.edu/respcare/public/info/Plain_Language_Thesaurus_for_Health_Communications.pdf. Accessed September 26, 2014.

F. Specific Topics (*Domains 2, 4*)

1. Medication labels are often misinterpreted (Am J Health Syst Pharm 2006;63:1048-55). Common issues include the following:
 - a. Several instructions included in one sentence are complex and easily misread. For example: “Take 1 tablet by mouth twice daily for seven days or as directed.”
 - b. Instructions can be vague or misunderstood: For example, “take two tablets daily” could mean two tablets in the morning, one tablet every 12 hours, or one tablet in the morning and evening.
 - c. Words within instructions are commonly misread. For example, teaspoon versus tablespoon or 1 versus 2 versus ½ tablet.
 - d. For patients with low literacy, the ability to correctly read the label may not mean full comprehension of instructions.
 - e. Misinterpretation of warning labels is a potential issue. Many patients ignore all warning labels. Labels with many instructions may be written at the 12th-grade reading level. (Goal is fifth-grade reading level.) Pictograms may be misunderstood.
 - f. Labeling does not eliminate the need for verbally reviewing instructions with the patient and assessing patient understanding. Use either the teach-back or the show-me method, as appropriate, to verify comprehension.
 - g. In 2010, the United States Pharmacopeia initially released recommendations for standardizing and improving prescription labeling. See Table 6.
 - h. In the area of labeling, pharmacists can be advocates for patient safety by doing the following:
 - i. Working with the appropriate corporate or institutional committees to implement the United States Pharmacopeia labeling recommendations and developing clear medication instructions as the default settings on computerized physician order entry programs.
 - ii. Verbally clarifying instructions during patient education. Pharmacists should be aware of their state board of pharmacy’s regulations regarding pharmacists’ ability to actually change written labeling. Verbally clarifying the medication label instructions from “take twice daily” to “take every 12 hours” may be done during education. Changing the label instructions may require a verbal order from the prescriber.
 - iii. When prescribing or taking verbal orders, write prescriptions consistent with the United States Pharmacopeia labeling recommendations.

Table 6. Recommendations of the United States Pharmacopeia on Prescription Labels

Recommendation	Comments
Organization of the label	Include only the patient information critical for understanding and safe use
Simplify the language	Wording should be concise Information should be clear, using common terms Do not use Latin terms or medical jargon
Use explicit terms for instructions regarding dosage and interval	Use specific frequency intervals (e.g., morning and evening, every 12 hours) Use numbers rather than words (e.g., “take 2 tablets” is preferred to “take TWO tablets”)
Include the purpose for use	When possible, the prescriber should include the indication for the medication in lay language (e.g., high blood pressure)
Provide labeling in the patient’s preferred language	Translations should be available, especially for those with low English proficiency Use high-quality process for translation
Improve readability	Lettering should be in a minimum of 12-point and sans serif font, such as Arial Sentence punctuation should be used; do not use all capital letters
Include supplemental information	Auxiliary labels should be limited to evidence-based information that is necessary and important Information should be supplied in a standardized manner
Standardize directions	Use consistent language in e-prescribing programs

United States Pharmacopeia. USP Advisory Panel Recommends Standardizing Prescription Container Labeling to Improve Patient Understanding of Medication Instructions. Available at <http://us.vocuspr.com/ViewAttachment.aspx?EID=2WSh2u7neSflu2bXW1HJ5VQ48HGFAOGH1NdNBeuPwJE%3d>. Accessed September 26, 2014.

2. Building skills and self-efficacy: Self-efficacy is a patient’s confidence in or perception of his or her ability to correctly perform a behavior, and it is one of the concepts in the Health Belief Model (Health Educ Q 1986;13:73-91).
 - a. Self-efficacy varies by a particular behavior, but it is also situationally dependent. For example, a patient may be confident in managing a hypoglycemic reaction normally but may be worried about managing reactions when at work or away from home.
 - b. Low self-efficacy may have the following effects:
 - i. Discourage a patient from learning new skills or changing behaviors
 - ii. Decrease the amount of time or effort a patient would spend attempting to learn a new skill
 - iii. Be a source of anxiety or depression or cause avoidance in dealing with a medical problem
 - c. Methods to improve self-efficacy: See Table 7.

Table 7. Methods to Improve Self-Efficacy

- Break complex skills into manageable tasks
- Arrange tasks in a series of logical, progressively difficult steps
- Implement changes slowly over time as patient is successful
- Use frequent follow-up to address questions or problems
- Show that progress is being made (e.g., small weight loss, slight improvement in blood pressure)
- Acknowledge and encourage even small initial steps in implementing the plan
- Attribute successes to an improvement in the patient's abilities
- Assist in setting patient-specific and achievable short- and long-term goals
- Brainstorm with the patient to identify personalized methods to implement the plan
- Analyze lapses or problem situations for lessons learned; identify potential solutions for avoiding or dealing with that situation in the future
- Identify peer coaches, mentors, or role models for ongoing support

3. Self-management of medications requires the patient to have the ability to optimally integrate the series of steps to independently implement a drug regimen at home (Image J Nurs School 1991;23:231-5).
 - a. *Medication management* is a term that encompasses a series of steps, starting with obtaining the medications (initially and then refills), remembering to take the medications, correctly interpreting labels and instructions, integrating several label instructions to develop a personal medication schedule, correctly measuring and preparing dosages, following supplemental administration instructions, and monitoring for efficacy and toxicity.
 - b. Problems with medication management are more common in patients with low executive functioning or low health literacy, those receiving complex medical regimens, or those who are elderly. Poor medication management skills may result in unintentional nonadherence.
 - c. Methods have been developed to assess individuals' capacity to manage their own medications. Tools such as the Drugs Regimen Unassisted Grading Scale (DRUGS) may be useful in identifying patients who need more assistance in handling their medication regimen at home (Ann Pharmacother 2008;42:1026-36).
 - d. Pill boxes, medication organizers and reminder aids, automatic refills, and prescription delivery may address only some types of medication management issues.
 - e. Patients with low medication management skills may need extra assistance with the following.
 - i. Correctly interpreting label instructions
 - ii. Developing a simple regimen with the minimal number of administration times
 - iii. Integrating any medication changes into their current regimen (e.g., adding new medicines, making dosage changes, and discontinuing medications)
 - iv. Updating and maintaining a current medication list
4. Addressing adherence behaviors: Often, health care professionals narrowly view nonadherence as unintentional (i.e., the patient did not understand the instructions, has trouble remembering to take medications, or cannot afford the regimen). However, much nonadherence is actually intended and is often logical from the patient perspective. Some of these adherence factors and behaviors are outlined in Table 8.

Table 8. Adherence Factors and Behaviors

Adherence Factors	Adherence Behaviors	Patient Case Examples
Physical factors	Medications are judged “effective” or “ineffective” by whether or not the patient’s desired physical response, such as control of symptoms (e.g., pain relief) or activity level, is reached Medications are discontinued or adjusted according to the patient’s desired goal Regimens are modified to avoid adverse reactions, which are not reported to their provider	A middle-aged man with diabetes is nonadherent to both diet and oral medications; he takes the medication when his blood glucose concentration is high enough to cause polyuria and discontinues it when urination becomes less frequent; he understands and appears unconcerned that a hemoglobin A1C of 13.5% puts him at high risk of a future heart attack or kidney failure; he begins to take his medication regularly when he understands that his erectile dysfunction and painful neuropathy will more likely worsen when his diabetes is poorly controlled.
Economic aspects	Medications are continued, discontinued, or adjusted according to the patient’s perception of cost to the perceived benefit The actual cost of the medication may not be as important as the perceived financial distress Generic medications may be perceived as less effective Less value may be placed on medications when there is little or no cost to patients; adherence may be better when there is a co-pay	A middle-aged woman is nonadherent to two generic medications for asymptomatic hypertension (\$5 co-pay each). She is willing to pay \$60 each month for a third-tier pain medication that improves her back pain. She becomes somewhat more adherent to the blood pressure medications when shown her systolic blood pressure was 20 mm Hg lower when taking her medication. She was encouraged to do home blood pressure monitoring monthly to see the benefit from the medication.
Psychological aspects and self-regulation	Testing: Patients test for the continued need for therapy by stopping or adjusting medications	A woman’s cholesterol concentration was well controlled with a low-dose statin; she stopped taking it because she thought her cholesterol was cured; she was willing to restart it after her cholesterol increased 40 points after stopping the medication.
	Control: Medications are adjusted because of the patient’s perception of control or dependence	A woman resisted taking insulin twice daily because the regimen was perceived as too rigid for her lifestyle; she was actually more adherent to a more complex regimen requiring several injections and carbohydrate counting because she could adjust it to her variable mealtimes and food intake.

Table 8. Adherence Factors and Behaviors (*continued*)

Adherence Factors	Adherence Behaviors	Patient Case Examples
Psychological aspects and self-regulation	Stigmatization: The patient may perceive having the disease or taking medication as a stigma; taking medication may be an acknowledgment to patients or others that they have an illness	An adolescent with a seizure disorder is resistant to taking his medications; he becomes more adherent when he realizes he can take his driver's license test like his friends when he has been seizure-free for 2 years.
	Being practical: Medications are adjusted to diminish the perceived disruption in the patient's lifestyle	An elderly woman with heart failure wanted to discontinue her diuretic while on a vacation because she did not want to worry about finding a bathroom while on the side tours; it was explained that if she stopped it, her heart failure would worsen and she would not have the energy to go sightseeing.
	Gambling: The perception that short-term "costs" exceed the long-term "gains" of therapy	A man in his 40s smoking 2 packs of cigarettes per day is unconcerned regarding the long-term health risks: "Not everyone who smokes dies from it," he cut back to 1 pack/day when he realized that his early morning cough was an early indication of COPD.
	Medication as a resource: Adherence may improve when therapy is perceived as a resource or when it allows patients to accomplish desired goals	An elderly woman with severe COPD refused to use oxygen when outside of her home; she began to use it when she realized that it could give her enough energy to visit and play with her grandchildren.

COPD = chronic obstructive pulmonary disease.

Morris L, Schulz RM. Medication compliance: the patient's perspective. Clin Ther 1993;15:593-606.

5. Techniques to improve motivation

- a. Motivation theory: Many patients lack motivation to make lifestyle changes or adhere to medication on the basis of proposed health benefits alone. Motivational theory proposes that everyone has one or more primary need. Expressing messages in terms of those primary needs may open individuals to hearing messages and implementing behavior changes. One framework of motivational theory is the Open Management Concept (Kafka 1990). Table 9 describes the five "needs" in this framework. Examples are given of tailored messages in the context of a patient's specific motivating need.

Table 9. Use of the Open Management Concept

The pharmacist asks patients to describe what they dislike most about using tobacco; listening carefully, pharmacists tailor their response to the patient according to their assessment of the individual's likely motivator	
Motivator	Patient Case Examples
Need for economic or financial security	Patient: "Cigarettes are now more than \$3.50 a pack, and most of that is taxes! Years ago, they were only a buck." Pharmacist: "So you spend more than \$2500 per year; I bet you could find a better use for that money! What would you do with an extra \$50 a week?"

Table 9. Use of the Open Management Concept (*continued*)

Motivator	Patient Case Examples
Need for control	Patient: “Sometimes I wonder who is in charge, me or the cigarettes. I can’t even sit through a movie without going out for a cigarette. After break at work, I start watching the clock to my next cigarette at lunch.” Pharmacist: “Wouldn’t it be nice to sit with your girlfriend through the movie or just go through the day without wondering when you can smoke the next cigarette?” Note: If the patient believes that tobacco helps him deal with stress, his need for control could be a barrier to quitting
Need for recognition	Patient: “I used to think that smoking was cool in high school; now I am conscious that my clothes smell and I use tooth whiteners.” Pharmacist: “You are right! It used to be really acceptable to smoke, but you don’t see as many people smoking in public anymore; smoking not only yellows your teeth but also causes early tooth loss.”
Need to belong	Patient: “At Thanksgiving or Christmas dinner, my sister makes me go outside by myself because she says it stinks.” Pharmacist: “So you are the only one in the family left who smokes?” Patient: “Yes, they all stopped; even my brother...” Note: If key family, friends, or colleagues use tobacco, the desire to belong can be a barrier to quitting
Need for personal self-worth	Patient: “I have three children who hate my smoking.” Pharmacist: “How old are they?” Patient: “The oldest boy is 13; my daughter is 10; the youngest boy is 6.” Pharmacist: “In general, young children dislike cigarettes. In the preteen years, peer pressure begins; young girls often start smoking because they’ve heard the myth that smoking keeps one thin. What a great example you would be to your children if you chose to stop.”

Kafka VW, Schaefer JH. Working Relationships: Everyone’s Guide to Working with People. Moraga, CA: Effective Learning Systems Press, 1990.

- b. Motivational interviewing: When providers try to convince patients to change, it may cause patients to justify why change for them is not possible (i.e., the “righting reflex”). Motivational interviewing uses a series of strategies to encourage the patient (instead of the provider) to articulate/explore reasons for changing behavior (Berger 2013; Rollnick 2008). Some key motivational interviewing concepts are briefly outlined in Table 10.

Table 10. Motivational Interviewing

Concept	Patient Case Example	Explanation
Roll with resistance	“You are reluctant to give little Billy an asthma controller medicine every day because you don’t think his asthma is bad enough to need a medicine every day. Tell me a little more about that...”	Accept the patient’s reluctance by paraphrasing the concern; encourage the patient to discuss his or her concerns further; a better understanding of the situation may help the provider answer questions, address concerns, or clarify misperceptions

Table 10. Motivational Interviewing (*continued*)

Concept	Patient Case Example	Explanation
Express empathy	“So you are concerned about the cost and the long-term effects of a daily medicine on a 6-year old; is that right?”	Reflect back the patient’s concern in a nonjudgmental manner; empathy does not necessarily mean expressing agreement
Avoid arguing	“There are no generic controller inhalers, so the controller seems expensive every month” (restate patient concern); May I tell you of my concerns about Billy’s asthma? (ask permission); You said he awakens often at night; when he has an asthma episode, he misses school, and we give him large doses of prednisone for several days to control his asthma; I think asthma is affecting Billy’s schoolwork (voice medical perspective in context of patient concern); What do you think?” (listen to response)	Arguing may just reinforce patients’ reluctance to change; ask permission before challenging their opinions, perceptions, or concerns; then, inform them of your concerns from a medical perspective; listen to their response
Develop discrepancy	“You want him to do well at school and give him the least amount of medicine; every episode requires lots of albuterol and prednisone, and the emergency visit is expensive; he is also not keeping up at school; giving a controller medicine in a tiny dose every day might actually expose him to less medication and help him do better at school...Is that worth a try?”	Explore their ambivalence about change; help them see inconsistencies between their goals and their behavior
Support self-efficacy	“I can show you how to track his albuterol use and nighttime asthma episodes, so we can see if his asthma improves during the next several weeks. Do you think that you would be willing to track this information to see if there is any improvement?”	Table 7 lists items to build and support self-efficacy

- c. Transtheoretical model
 - i. This is another method for tailoring the patient intervention according to patients’ readiness to change their behavior.
 - (a) The pharmacist assesses the patient’s stage of change and provides an appropriate intervention to encourage or maintain change.
 - (b) Potential interventions include the following:
 - (1) Providing timely information
 - (2) Identifying and emphasizing personal motivators
 - (3) Recognizing progress and encouraging further change
 - (4) Building self-efficacy (see Table 7)
 - (5) Troubleshooting lapses and encouraging continued efforts
 - ii. Definitions of the stages (or constructs) and examples are listed in Table 11.

Table 11. Transtheoretical Model

Stage of Change	Definition	Patient Case Example	Explanation of Pharmacist Response
Pre-contemplation	No plan to implement change in the next 6 months	A middle-aged, overweight, sedentary woman develops prediabetes; her pharmacist reviews her latest laboratory results and the health benefits of weight loss	The pharmacist seeks the patient's permission and, with this, explores her potential motivators and attitudes toward healthy eating habits and exercise; he offers to help her whenever she is ready; afterward, she begins to think about her daughter's wedding next fall
Contemplation	Thinking of changing in the next 6 months, but usually does not have a specific plan	At her next visit, she tells the pharmacist that she is looking at mother-of-the-bride dresses with her daughter but that losing weight seems too hard; she has spotted ads for community-based weight-loss support groups	The pharmacist helps her explore and evaluate her resources; he explains how small changes in diet and gradual increases in activity can make a significant difference over time; he offers to help her develop a realistic, successful plan
Preparation	Plans to make a change in the next 30 days and has usually taken some steps toward change	At the next visit, she tells the pharmacist she plans to join the support group at work that is forming next month; she liked the trial session at her friend's gym, but the monthly fee seems too expensive	The pharmacist brainstorms with her some affordable alternatives for increasing activity
Action	Has overtly changed behavior for less than 6 months	Six weeks later, she has switched a daily afternoon soda to plain iced tea; her daughter offered to pay for the gym membership, she did not like the one aerobics class she tried; the pharmacist congratulates her on making the diet change and notes the 1-kg weight loss	The pharmacist recommends trying out a variety of activities at the gym and to inquire if a personal trainer is available; because she is doing so well with the beverage change, he asks what small diet change she would like to try next; any roadblocks or setbacks are addressed
Maintenance	Has changed behavior for more than 6 months	She has lost 5 kg during 6 months; she has kept up with several small diet changes and exercises routinely twice weekly; she is a little discouraged that she regained 1 kg at Thanksgiving	The pharmacist is upbeat regarding her overall progress; he notes that her repeated blood glucose reading is just under the goal of 100 mg/dL; they briefly discuss why she regained weight (holiday baking) and how she might avoid that at Christmas
Termination	No temptations or lapses and is confident that change can be maintained	Her weight loss has leveled off at 8 kg during 8 months; she is happy maintaining her current diet and exercise plan at this time	The pharmacist monitors her weight at each visit and reviews her blood glucose results with her periodically

Prochaska O, Redding CA, Evers KE. Transtheoretical model and stages of change. In: Glanz K, Rimer BK, Viswanath K, eds.

Health Behavior and Health Education: Theory, Research, and Practice, 4th ed. San Francisco: John Wiley & Sons, 2008:97-119.

- iii. Patients may exit and re-enter the model at any stage before successfully reaching the maintenance/termination stage.

G. Special Populations (*Domain 2*)

- 1. Older adult patients
 - a. May have different medical educational needs (Centers for Disease Control and Prevention 2009)
 - i. Have complex medical problems that call for higher health literacy and better medication management skills
 - ii. Are less likely to use the Internet and other sources to obtain health information; so are more dependent on family, friends, and providers for health information
 - iii. In general, process information more slowly and have more trouble recalling information later
 - iv. Are less confident and more easily confused
 - v. Are more likely to have impairments to learning information such as less dexterity or visual or hearing problems
 - b. Cognitive decline may impair the executive functioning necessary for management of their medications.
 - c. General tips for counseling older adults are listed in Table 12.

Table 12. Tips for Educating Older Adult Patients

Clear communication strategies are especially important, such as the following:

- Using plain language
- Demonstrating and allowing patients to practice skills
- Documenting patient understanding by using the teach-back and show-me techniques to verify understanding

Use briefer educational sessions

Keep information focused and organized

Pause often, and allow the patient more time to process information

Information may need to be repeated more often, both during a session and over time

Use more face-to-face communication to permit more interaction

Use more personal examples for relevancy

Follow up more often and at shorter intervals when implementing new plans

Develop and use personalized decision-making tools (e.g., disease-related care plans)

Ideally, use educational materials designed specifically for older adults (e.g., written material should be large print; high contrast between the print color and paper; essential points should be bulleted or in list formats)

Be alert for physical (vision, hearing, and dexterity) and cognitive impairments that might diminish medication management skills; assess medication management capacity as needed

Assist in maintaining an accurate medication list

Provide medication charts to organize administration times

Inquire about support systems and difficulties with activities of daily living

Assess for low self-efficacy, and implement strategies as needed

Centers for Disease Control and Prevention. Improving Health Literacy for Older Adults: Expert Panel Report 2009. Atlanta: U.S. Department of Health and Human Services, 2009. Available at www.cdc.gov/healthliteracy/pdf/olderadults.pdf. Accessed November 23, 2016.

- 2. Low literacy: For these patients:
 - a. Introduce new concepts more slowly.
 - b. Use teach-back more often throughout the session.
 - c. Use more visual aids.
 - d. Inquire if they have a preferred family member or friend to assist them.

3. Use of interpreters (<https://www.aamc.org/students/download/70338/data/interpreter-guidelines.pdf>)
 - a. The qualifications for a medical interpreter involve more than being bilingual. Interpreters are trained in the expectations of both cultures so that they can anticipate the potential for misunderstandings, be knowledgeable about medical terminology and jargon, and agree to abide by a code of ethics.
 - b. The National Culturally and Linguistically Appropriate Services (CLAS) Standards in Health and Health Care require that timely language assistance be provided to those with limited English proficiency without charge (<https://www.thinkculturalhealth.hhs.gov/content/clas.asp>).
 - c. Even patients who initially appear bilingual may not comprehend the complexities of a medical interview or educational session. The services of an interpreter should be used if there is any concern that the patient may not fully understand. The Team Strategies and Tools to Enhance Performance and Patient Safety (TeamSTEPPS) program has training materials for enhancing safety for patients with limited English proficiency (<http://teamstepps.ahrq.gov/>).
 - d. Tips for speaking to patients through interpreters. A similar process is used whether the interpreter is used for a different language or for hearing impairment. See Table 13.

Table 13. Tips for Speaking to Patients with Interpreters

Brief the interpreter about the purpose and goals for the encounter
 Verify that the interpreter will function in a conduit manner (i.e., interpret in the first person without revising, adding, or deleting any of the message)
 Face the patient, make eye contact with the patient, and talk by using the first person
 Use a normal speaking tone and volume
 Expect that the interpreter will do the following:

- Greet the patient and introduce himself or herself at the beginning of the encounter
- Transmit any exhibited emotion (by you or the patient)
- “Step out” of the interpreter role to ask his or her own questions of you or the patient if the interpreter does not understand what is being said
- Stand off to the side so that the facial expressions of both parties can be seen

Use normal good communicate strategies; for example:
 Use lay language; the interpreter will not simplify your words
 Check patient understanding by using the teach-back or show me techniques
 Be aware of the policies in your institution for using bilingual colleagues as interpreters; asking colleagues to function outside their normal training and responsibilities can be problematic (e.g., asking a receptionist to translate a diabetes education session)
 Avoid using family members or friends of the patient to interpret

- They may have conflicts of interest or trouble being objective
- They may have difficulty understanding the information to be translated
- Document the patient’s requests to use the interpreter of his or her choice
- If a family member or friend functions as an interpreter, first assess his or her English proficiency with informal conversation; then, assess his or her health literacy with a basic question related to the encounter
- Be specific with expectations for accurate, complete translation of words from both the patient and the provider
- Use minors only in emergencies

Document in the medical record that an interpreter was used, together with his or her name and that of his or her company

II. SELECTING WRITTEN PATIENT EDUCATIONAL MATERIALS

- A. Written Patient Health Educational Materials: Only effective when used as part of your overall patient education strategy (e.g., use in combination with spoken instructions) (*Domain 2*)
- B. Understandability: Suitability Assessment of Materials (SAM) (Doak 1996) (*Domain 3*)
 1. Useful tool to qualitatively evaluate materials under consideration for health literacy and understandability
 2. Can be used to quantitatively compare different materials by ranking each factor on a 3-point scale: 0 (not suitable) to 2 (superior). The maximum score is 2 points times the number of factors considered.
 3. Areas to be evaluated (each area may include one or more factors)
 - a. The purpose is clear, the scope is limited to the purpose, and a summary is provided.
 - b. Literacy demand
 - i. Reading level (<https://www.cms.gov/Outreach-and-Education/OutreachWrittenMaterialsToolkit/>)
 - (a) The desired level for the average population is about the fifth-grade reading level.
 - (b) Various methods, including Flesch-Kincaid, Fry Readability Formula, and Simple Measure of Gobbledygook (SMOG), are available to calculate reading level. One should be aware of the advantages and limitations of the various methods. The calculated reading-grade level can vary depending on the method used (e.g., the Flesch-Kincaid method often results in a lower calculated reading level than other methods). In addition, “reading level” is not a precise concept.
 - (c) Follow the instructions for using the specific tool (e.g., the minimum number of words in the sample to be analyzed).
 - (d) Be cautious when interpreting the results (e.g., the calculation is based on the length of the words and sentences; the assumption that longer words are harder to read and understand is not always true; in addition, the reading level can vary across the document).
 - ii. Writing style: An active voice, using a conversational style and short, simple sentences, is preferred.
 - iii. Vocabulary: Common words are ideally used. Technical words should be limited to keywords that patients should learn. Jargon should be avoided. Examples or definitions should be given for any technical words used.
 - iv. Sentence structure should provide the context for the new information before providing the new information. For example, “To see if your heart function is normal (*context*), your doctor may perform a test to check (*new information*)...”
 - v. Content should be organized under headers.
 - c. Graphics
 - i. Type: Illustrations should be real and use familiar images but not distract from the message. Pictures should also be age appropriate.
 - ii. Relevance: Illustrations should present key messages. Borders, backgrounds, and colors should support, rather than distract from, the message.
 - iii. Tables, graphs, charts should have the following:
 - (a) Step-by-step instructions, with examples
 - (b) Captions to identify and explain the figure
 - d. Layout should be inviting and easy to read. For example:
 - i. The flow and sequence of the material should be logical.
 - ii. There should be adequate white space. Two (shorter) column texts are preferred to a single (lengthy) column of more than 50 characters in width.
 - iii. Visual cues are used to highlight key points (e.g., arrows, insert boxes).
 - iv. Use low (or no) gloss paper with high contrast to the text.
 - v. Chunk information with bullets and headers, but use no more than five bullets per subheading.

- e. Typography
 - i. Use sentence case (capitalize only the first word of a sentence). Do not use all capital letters.
 - ii. Font should be readily legible and consistent (e.g., 12-point sans serif font, such as Arial).
 - (a) Boldface or larger font can be used for emphasis.
 - (b) Colored fonts can also be used if they are in sufficient contrast to the paper and not distracting.
 - f. Cultural appropriateness: Images are positive and realistic. Logic, language, and ideas are familiar to the target audience.
- C. Other Factors to Consider That Are Not Included in SAM Tool (*Domain 3*)
1. Content: Aspects of content other than health literacy including the following:
 - a. Source is credible.
 - i. The author has suitable expertise or training (e.g., credentials, experience).
 - ii. The sponsoring organization is easily identifiable (e.g., pharmaceutical company, health foundation, or government agency/grant).
 - iii. Facts are easily verified from tertiary sources such as disease guidelines.
 - iv. Ideally, cites the sources and references for the content
 - b. Potential biases are limited and identifiable.
 - i. Any opinions are separate from the evidence and clearly labeled as such.
 - ii. Source of funding, if different from the sponsor, is included (e.g., a foundation grant).
 - iii. Promotes all products in drug class fairly and in similar frequency
 - (a) Appearance in pictures/visuals
 - (b) Inclusion in discussion and examples
 - (c) Discussion in studies and evidence
 - (d) Identifies drugs by generic name with reference to brand name(s) with ®
 - c. Information is current.
 - i. Ideally, lists the date the information was most recently reviewed or updated
 - ii. Dates of the references are within the past 5 years.
 - iii. Content is consistent with current disease guidelines or standards of care.
 - iv. Materials should be reviewed initially and periodically for continued currency.
 2. Selecting materials for a comprehensive disease program
 - a. Materials are age appropriate for the target audience.
 - b. Have available a variety of materials for different literacy levels (e.g., low literacy, basic, and high literacy) and across a variety of learning styles (e.g., visual, auditory).
 - c. Select materials across a range of topics. Match content of materials to the desired teaching objectives.
 - d. Consider a focus group from the target audience to provide feedback on the usability of the information.
- D. Other Assessment Tools for Content and Literacy (*Domain 2*)
1. Other variations of, and scoring sheets for, the SAM tool are available on the Internet. For example:
 - a. Materials Assessment Tool (MAT): https://extension.umd.edu/sites/default/files/_images/programs/insure/Materials%20Assessment%20Tool%204-29-13.pdf

- b. The Patient Education Materials Assessment Tool (PEMAT). This recently published tool contains many criteria similar to those of SAM, such as understandability, layout, and design (www.ahrq.gov/professionals/prevention-chronic-care/improve/self-mgmt/pemat/pemat-av.html).
 - i. Has an additional domain called “actionability,” which addresses whether the materials encourage, describe, or provide tools for the patient to implement health-related skills and activities
 - ii. Can be used to compare written materials and audiovisual educational materials, such as multimedia presentations
2. The Medical Library Association has published a user’s guide for evaluating medically related websites for the lay public (www.mlanet.org/resources/userguide.html).

III. ALTERNATIVE METHODS OF COMMUNICATING WITH PATIENTS

A. Telephone Tips (*Domain 2*)

1. Ask for the patient’s preferred phone number and contact him or her at that number.
2. Before discussing specific patient information, do the following:
 - a. Verify the identity of the caller.
 - b. Ask if this is a convenient time (e.g., if patient is alone and able to talk).
 - c. Protect patient privacy.
 - i. Leave very limited messages. “This is _____, the pharmacist at XYZ pharmacy, with a message for (patient name). Please call me back at (number).”
 - ii. Be aware of whether the telephone number is for a general home phone, personal cell phone, or work phone.
3. Use the teach-back method to verify the correct understanding of messages.
4. For efficiency and consistency, consider developing documentation templates for common encounters in the electronic medical record (e.g., requests for refills, anticoagulation test results).
5. Document the content and results of the interaction in the patient’s medical record.

B. E-mail Etiquette (*Domain 2*)

1. For extra privacy and security, communicating to an individual’s personal account on a Web-based corporate system is preferred to using a patient’s personal e-mail account (i.e., patients send and access messages to and from their health team by a stand-alone personal account on the health system’s website by using a password).
2. Follow the general communication tips in Table 5 (e.g., use plain language, limit amount of content, tailor the message).
3. Apply appropriate criteria from the SAM tool (in section II). For example:
 - a. Literacy demand: Reading level, sentence structure, active voice, and so forth
 - b. Layout: If several points, chunk information with headers and bullets instead of using a paragraph
4. Ask patient to verify by responding to the message. Avoid using request delivery or read receipts. Use teach-back if appropriate.
5. General e-mail etiquette is outlined in Table 14.

Table 14. General E-mail Etiquette

Balance conciseness with clarity Answer patient questions and anticipate additional questions Be professional • Use correct spelling, punctuation, and grammar • Respond in a timely manner (usually within 24-48 hours) • Do not use medical or texting abbreviations • Restrict to essential information; avoid confidential details • Use complete signature with credentials, organization, position, and contact information • Watch tone to avoid the appearance of being curt or abrupt or the impression that the patient is bothersome • Provide a closure that encourages a follow-up for questions Reread e-mail before sending it Use a clear, meaningful subject in the subject line Do not use e-mail when personal contact is more appropriate Ensure e-mail is compliant with privacy standards before sending any type of information related to a person's health (e.g., secure send out of information)

Silberman L. 25 Tips for Perfecting Your Email Etiquette. Available at www.inc.com/guides/2010/06/email-etiquette.html. Accessed September 26, 2014.

Email Etiquette. Available at www.emailreplies.com/. Accessed September 26, 2014.

IV. COMMUNICATING WITH OTHER HEALTH CARE PROFESSIONALS

A. Making Interventions to Implement Medication-Related Recommendations for Patients (*Domain 2*)

1. Do your homework before making the recommendation.
 - a. Hypothesize the reasons that this situation occurred. Is this likely an oversight or an intended choice by the prescriber? Identifying the possible reasons will help you to anticipate and respond to questions or requests for additional information.
 - b. Is additional information needed to assess the situation, such as blood work or information from the patient history?
 - c. Identify and weigh therapeutic alternatives to identify the best recommendation to resolve the situation. What is the strength of the evidence to support each recommendation? How might the recommendation change depending on the additional patient information requested?
 - d. Consider to whom you will be communicating the recommendation. Knowing your audience will be helpful in framing your recommendation. What will they know or want to know?
 - i. Discipline: Physicians, nurse practitioners, and physician assistants will generally have a different level of knowledge of therapeutics and evidence-based medicine.
 - ii. Generalist versus specialist: Is this therapeutic recommendation within or outside their area of specialty?
 - iii. Academic versus nonacademic provider: Academicians may have a greater interest in detailed rationales and the results of clinical research, and they may be open to new evidence. However, they may also be more skeptical of suggestions from those outside their discipline or specialty.
 - iv. Personality of the provider (e.g., confidence in their ability, openness to new ideas)
 - v. Differences in communication styles: According to cultural or ethnic background, age, sex, or generational differences
 - e. Choose an appropriate time: What is the level of urgency? When is a good time to talk? (e.g., "Is this a busy time for you?")

- f. What is the optimal method of delivery (e.g., written, verbal, or electronic)? Ideally, verbal recommendations should still be documented as a note in the patient's medical record.
2. Delivering the message: Be clear, complete, concise, timely, professional, and organized.
 - a. Introduction
 - i. Greet the provider by the preferred method of address. Always use a formal greeting (e.g., Doctor) if a third party is present.
 - ii. Identify yourself and your role, if necessary.
 - iii. The opening should catch the provider's attention and signal the level of urgency. What do you want the provider to do?
 - b. Define the problem or issue. Support the assessment with patient-specific data.
 - c. Clarify the problem or request additional information. Be prepared to modify your recommendation according to this new information.
 - d. Suggest a solution (with any acceptable alternatives) to the problem. If there are several suitable alternatives, present them objectively.
 - e. Use an appropriate verb according to the strength of your recommendation (e.g., recommend, suggest, consider).
 - f. Provide the rationale and offer evidence to support the recommendation. Clearly separate opinion from published evidence or guidelines.
 - g. Develop rapport while delivering the interventional message. Watch the terminology, tone, and body language.
 - i. If the message is delivered verbally, choose a time that is as convenient as possible (e.g., if nonurgent, wait for the provider to finish current task or ask to speak with the provider after rounds are completed).
 - ii. The message should be patient focused rather than about organizational policy (e.g., explain why your recommendation [based on this policy] would improve the care of this patient).
 - iii. Be calm, respectful, and assertive, but not aggressive. Include patient data to support recommendation.
 - iv. Be tactful. Phrase the recommendation positively. How would this change benefit the patient?
 - v. Be persuasive, but do not overstate the case for change.
 - vi. Use of correct medical terminology, pronunciation, and confident body language will add to credibility. Avoid nervous mannerisms.
 - vii. Revise delivery according to the cues and body language of the provider (e.g., shorten the conversation if the provider appears stressed or hurried).
 - h. Be prepared to modify your recommendation in response to new information or challenges from the provider.
 - i. Answer questions and offer further explanation. Elaborate on justification.
 - ii. Collaborate to identify the best alternative. Sometimes, the best solutions are completely different from the initial recommendations and arise from the synergy between the pharmacist and the provider.
 - iii. If the recommendation is partly accepted or rejected, advise whether further or more frequent monitoring might be necessary to avoid future problems.
3. Closure
 - a. Use the check-back technique: Repeat the change in plan or new orders (TeamSTEPPS program) (www.ahrq.gov/professionals/education/curriculum-tools/teamstepps/instructor/essentials/pocketguide.pdf).
 - b. Offer to provide additional information (e.g., copy of clinical study, institutional policy, clinical protocol) or to do a further information search.
 - c. Thank provider for his or her time.

4. Acronym for organized message delivery: **SBAR** (situation, background, assessment, recommendation) (<http://www.saferhealthcare.com/sbar/what-is-sbar/>)
 - a. **S:** Situation – Briefly describe the situation or the patient problem.
 - b. **B:** Background – Add necessary information to understand the problem.
 - c. **A:** Assessment – Provide an assessment of the problem, such as cause and severity.
 - d. **R:** Recommendation – Make recommendations to address or resolve the problem.

Table 15. Use of SBAR to Organize a Patient-Specific Recommendation

	Patient Case Example
Situation	“Dr. Jones, regarding Mrs. Smith: I am concerned about her potential for hyperkalemia.”
Background	“Her furosemide dose was cut back by one-half to 20 mg daily today because her edema is better; her current potassium concentration is normal; however, she is still receiving lisinopril 40 mg daily with potassium 20 mEq twice daily, and her estimated creatinine clearance is estimated to be 30 mL/minute/1.73m ² .”
Assessment	“At her age and with her renal function, her potassium concentration could rise pretty quickly during the next several days; there are no current orders to monitor potassium values.”
Recommendation	“I recommend decreasing her potassium dose to 20 mEq once daily and checking her concentration in 3 days and then again early next week.”

SBAR = situation, background, assessment, recommendation.

Agency for Healthcare Research and Quality (AHRQ) [homepage on the Internet]. TeamSTEPPS® Program. Rockville, MD: AHRQ. Available at <http://teamstepps.ahrq.gov/>. Accessed September 26, 2014.

5. Special situations
 - a. Dealing with anger, irritation, or frustration
 - i. Stay calm and assertive.
 - ii. Reflect back the emotion (e.g., “So you are feeling frustrated because...”).
 - iii. Keep the focus of conversation on what is best for the patient (vs. personalities).
 - iv. Accept alternative viewpoints. Respect decision-making authority.
 - v. Offer to pass on concerns regarding policies or procedures to those in authority.
 - b. When recommendations are rejected or partly accepted
 - i. Document the initial recommendation made, the provider’s decision, and a brief rationale for the decision.
 - ii. If concerned about the plan, propose compromises to limit the potential for adverse outcomes (e.g., “Because current therapy is to be continued, strongly suggest rechecking potassium in 3 days to be sure it is not still rising”).
 - c. Assertively communicate concerns about safety: TeamSTEPPS program recommends using the CUS technique to structure messages to other team members about potential safety issues. CUS is an acronym for concern, uncomfortable, safety. For example: “I am concerned about... I am uncomfortable that this could... This is a safety issue.” (<http://teamstepps.ahrq.gov/>)

B. Providing Health and Educational Programming for Other Health Care Professionals (*Domain 3*)

1. Tailoring the presentation to the audience
 - a. Content: Specific objectives to be addressed
 - b. Disciplines and level of training of the attendees
2. Logistics: Includes location, room size, available audiovisual equipment, whether the presentation will be recorded, the exact time allotted, deadlines for any slides or handouts, arrival time, reimbursement for travel or expenses, number of attendees

3. Format for the presentation. Examples: Lecture, round table, panel discussion, interactive cases, and question and answer
4. Special circumstances include the following:
 - a. Additional requirements if attendees are to receive continuing education credit
 - b. Whether the presentation is part of a larger conference. Know the topics and credentials of the other presenters. How does this presentation fit in with the other presentations?
 - c. Any particular reasons this topic is of interest to the audience, such as the development of new programs or policies and procedures or the result of a patient care problem

V. DOCUMENTING IN THE MEDICAL RECORD

- A. References That Outline Effective Medical Documentation (*Domain 2*)
 1. Medical Insurance Exchange of California. Medical Record Documentation for Patient Safety and Physician Defensibility (www.miec.com/Portals/0/pubs/MedicalRec.pdf)
 2. Psychiatry (Edgmont) 2004;1:26-8 (www.ncbi.nlm.nih.gov/pmc/articles/PMC3010959/pdf/PE_1_3_26.pdf)
- B. Notes Documented in the Medical Record Should Have the Following Features. (*Domain 2*)
 1. Be clear and concise yet complete. Note should not require further verbal explanation (e.g., “Renewed lisinopril 10 mg daily for 3 months” is better than “Refilled lisinopril x 3”).
 2. Be appropriate for all likely target audiences (e.g., prescribers, nurses, physical therapists, dietitians).
 3. Include the necessary information to be interpreted within the short- and long-term time context in which they were written. For example, “Pending the return of cultures, the empiric antibiotics started are...”; “Awaiting information from the family to clarify drug dose”; “Current first-generation cephalosporin on formulary is...”; “According to the Third Expert Panel Report on Asthma guidelines, suggest...”
 4. Include the time and date of the note (unless already electronically time stamped).
 5. Write tactfully and persuasively. Document the patient’s concerns, health beliefs, and reasons for declining therapy in a nonjudgmental manner. Objectively document the results of interactions with other health professionals; do not be critical.
 6. Use professional terminology and format.
 - a. Avoid abbreviations, especially of drug names. Do not use any abbreviations on The Joint Commission’s “Do Not Use List” (http://www.jointcommission.org/facts_about_do_not_use_list/) and avoid the use of abbreviations on Institute for Safe Medication Practices (ISMP)’s error-prone abbreviation list when possible (available at www.ismp.org/Tools/errorproneabbreviations.pdf).
 - b. Follow the institutional or corporate norms and conventions. Many institutions use a subjective-objective-assessment-plan (i.e., SOAP) format. However, this format has many variations. For example, all disease/problem assessments may be written together, followed by the disease plans for all problems, or alternatively, the assessment and plan for each problem may be grouped together.
 7. Document in a timely manner.
 - a. Ideally, charting should be completed at the end of each patient visit or as soon as the encounter has ended. Notes become increasingly less credible the longer the time between the encounter and the writing of the note. It is easy to forget or confuse details regarding the encounter.
 - b. Payment claims may be rejected if submitted 24 hours or more after the encounter.
 - c. In paper charts, notes should immediately follow the most recent note. Do not leave room for others to write their notes.

8. Be transparent when making addendums, corrections, or changes.
 - a. Reasons for addendums, updates, or changes to the chart should be explained (e.g., “Dose of atorvastatin was clarified with community pharmacy as 20 mg daily [not 10 mg daily]).”
 - b. Errors or modifications
 - i. In paper charts
 - (a) For small errors: Draw a single line through the error and continue writing. Do not use correction fluid, heavily cross out, write over, or erase.
 - (b) For larger modifications: If a note has already been completed, an addendum (or a revised note) may need to be generated. The original note is left in the chart, perhaps with a comment showing the date of the revised note. Provide an explanation, if needed (e.g., started note in wrong patient chart).
 - (c) Initial and date the correction. Even if the error was made at the time of the entry, the correction should be initialed and dated.
 - ii. In electronic charts, a separate addendum is generally required.
 - c. Late notes in paper charts: Start the note after the most recent note currently written in the chart, even if that patient encounter occurred after yours. Include not only the date and time of the actual encounter but also the time the note was actually written. Do not insert pages into the chart.
9. Record formal names and the disciplines of the colleagues involved (e.g., “Referred to S. Jones, RD, for diabetes diet instruction”).
10. Include documentation of even brief interactions, such as telephone calls.
11. Write legibly in paper charts. Be especially careful with writing numbers and inserting decimal points. Rather than squeezing in information, start a new page.
12. Tips for electronic charting
 - a. Developing and using practitioner-specific templates for common types of patient encounters can assist in the efficiency and completeness of documentation.
 - b. Be cautious when routinely cutting and pasting information and assessments from previous notes. For example, do not recopy physical findings unless the physical examination was actually repeated or the actual date of the finding is documented.
 - c. Reread notes carefully before submitting to avoid addendums. Do not rely on automatic spell-check.
 - d. Institutions may encourage practitioners to begin or complete patient notes during the patient encounter to improve the efficiency and timeliness of documentation. However, using the computer during the encounter should not impede patient-practitioner communication (e.g., decrease eye contact, increase physical distance between practitioner and patient).

Patient Case

6. A pharmacist is documenting a patient order change for morphine sulfate in her medical record. Which method of writing the order would be most consistent with the Joint Commission’s recommendations?
 - A. “Morphine sulfate 10.0 mg IV q 6 hours for pain.”
 - B. “MSO4 10 mg IV every 6 hours for pain.”
 - C. “Morphine sulfate 10 mg intravenously every 6 hours for pain.”
 - D. “MSO4 10.0 mg intravenously q 6 hours for pain.”

C. Documenting Educational Assessments and Interventions (*Domain 2*)

1. Subjective data obtained from patient interviews, medication histories, and results of medication reconciliation should be documented in the medical record as discussed previously (e.g., adherence behaviors, results of SILS or other health literacy assessments, misperceptions, personal goals and health beliefs about medications, preferred learning styles).
2. List the educational content, skills taught, and verification of the patient's understanding at the highest level appropriate for that content.
 - a. "Patient verbalized/indicated understanding of..." is generally an inadequate verification of understanding. "Indicated" could merely mean the patient nodded, said "I understand," or just did not have any questions.
 - b. The minimum level of understanding that should be documented is comprehension (e.g., results from teach-back method). For example, "The patient repeated the new warfarin dose and that she is to return for blood work next week."
 - c. Ideally, any required skills should be demonstrated by the patient (e.g., using the show-me technique). For example: "Patient correctly showed 8-mg dose from combination of 5-mg and 1-mg warfarin tablets." "Patient obtained an adequate blood sample and correctly recorded the blood glucose reading."
 - d. If the instructions are situation-dependent, the documentation should state the patient's ability to apply the information (e.g., "Given peak flow and symptoms, patient was able to identify the correct zone and corresponding activities on the asthma action plan").
3. Document both the educational message and the implications for adherence/nonadherence if applicable. For example, "Patient voiced reluctance to return for blood monitoring. Explained the importance of frequent blood work and medication adjustments to minimize the risk of significant bleeding."
4. Further educational needs and plans for follow-up. Note the patient's level of difficulty or ease in learning new skills and any particular steps with which the patient struggled. For example: "Patient demonstrated correct inhaler technique on first attempt" or "Patient struggled with timing of the inhalation to the release of medication."
5. Any specific educational materials or resources such as written pamphlets given (e.g., title and source of material, referrals to websites or support groups). For example: "Patient given American Heart Association pamphlet 'What Is Hypertension?'" If several versions exist, the version or revision date should be noted.

Patient Case

7. A pharmacist is counseling a patient on a new sliding-scale insulin regimen. Which would be the best way to document the patient's full understanding of how to use the sliding-scale insulin in the medical record after the session? The patient:
 - A. Correctly repeated insulin dose and demonstrated injection technique.
 - B. Verbalized understanding of dose, route, frequency, and injection technique.
 - C. Described sliding-scale insulin dosage and the correct injection technique.
 - D. Showed injection technique and calculated dose for hypothetical blood glucose.

- D. Documenting Therapeutic Assessments and Making Persuasive Recommendations (*Domain 2*)
1. Provide sufficient patient data to support the assessment and plan.
 2. Assessments should be clear and consistent with patient's data. Use appropriate terminology for the disease (e.g., "Patient has stage II hypertension, uncontrolled to goal pressure of..." "Carvedilol is an appropriate β -blocker for heart failure, but current dose is below target of...").
 - a. Use of ICD-10 terminology
 - b. Complete assessments will support higher billing codes based on patient acuity
 3. Making written recommendations
 - a. Use the active voice whenever possible. The note should reflect the writer's professional opinion, not that of others. For example, "I recommend..." versus "It was decided..."
 - b. Choose a verb that corresponds to the strength of the recommendation (e.g., recommend, suggest, advise, consider).
 - c. Be specific (e.g., the complete drug regimen, the person who will follow up, what blood work was ordered, time frame for monitoring).
 - d. Clearly document the results of the recommendations; for example:
 - i. Whether recommendations were accepted and whether there were any order changes
 - ii. When recommendations are partly accepted or rejected
 - (a) Document respectfully and objectively. As stated previously, the active voice is usually preferred. However, the passive voice can be useful in situations when one wants to document one's recommendation and acknowledge provider's decision without reflecting one's agreement with it. For example, "Suggested that the ramipril dose be decreased to 5 mg because of rising serum potassium (now at 5 mEq/L). Checked with Dr. Jones. *Ramipril to be continued at same dose (10 mg) at this time. Serum potassium to be checked again tomorrow.*" (*passive voice*)
 - (b) Document actions taken to limit the potential for adverse effects. "Verbal order from Dr. Jones to recheck potassium in 3 days and decrease the ramipril to 10 mg daily if still greater than 5 mEq/L."

VI. OPPORTUNITIES FOR PATIENT ADVOCACY OUTSIDE THE HEALTH CARE SYSTEM

Many people without medical training will be in a position to make decisions about or influence health-related policies (e.g., legislators, school board members, news reporters) but will lack adequate health literacy (i.e., civic domain of health literacy). Pharmacists should seek opportunities to positively influence public policy for safe and efficacious medication use.

- A. Collaborate with Professional Organizations (e.g., American College of Clinical Pharmacy, American Pharmacists Association, American Society of Health-System Pharmacists, state associations) and Disease Advocacy Groups (e.g., American Lung Association, American Heart Association, American Cancer Society) for legislative days in your state. These groups may also offer training sessions beforehand on how to effectively speak to legislators. (*Domain 4*)
- B. Offer to Speak in Public Forums such as town hall or school board meetings on timely topics of interest to the organization as a private citizen, or provide a presentation as a medical expert. (*Domain 4*)

- C. Letters to the Editor: These are usually short (100–250 words) and in response to a recent news story. Tips for writing letters are available online (<http://ctb.ku.edu/en/table-of-contents/advocacy/direct-action/letters-to-editor/main>). (*Domain 4*)
1. Follow the organization's guidelines for length and submission.
 2. If the letter is in response to a recent article, include the date and title of the article.
 3. Keep a copy of the letter to see whether it was edited when it appeared.
 4. Include full contact information. Papers will print the author's name and city, but most will not print anonymous letters.
 5. Choose topics important to you. Most papers will not print letters from the same person more than every few months.
- D. Opposite the Editorial Pieces (also known as “op-ed” pieces) (*Domain 4*)
1. Can be influential and highly visible in local newspapers. Often written in response to the paper's editorial or can be unsolicited on a timely topic.
 2. A limitation is that only a few are published compared with letters to the editor.
 - a. Timing is critical. Today's top story is old news tomorrow. Submit quickly if you wish to respond to an editorial or hot news item. If a topic is likely to be brought up in the near future, you might draft a piece in anticipation and then tailor it to the actual event.
 - b. Be concise and to the point. Keep the length to a maximum of 600–750 words.
 - c. Make one carefully crafted main point. Be clear and accurate with facts and evidence.
 - d. Help the readers care about the issue. A personal story about yourself or a patient situation provides human interest. (Be careful to protect patient privacy in examples.) Use an example that readers can understand and that is memorable.
 - e. Write it for a lay audience: Follow the suggestions in the Health Literacy section on written materials (e.g., use short sentences and common words, avoid jargon and abbreviations, use an active voice).
 - f. Follow the rules and guidelines from the newspaper or media source (e.g., length, to whom it is sent, whether or not to use an attachment, preferred method of submission).
 - g. Write a cover letter with key points, state why this topic is timely, and provide your credentials.
 - h. Make a favorable first impression and a memorable last impression. A catchy opening grabs attention, and a good closing is what the reader may remember.
- E. Letters to Legislators and Senators (*Domain 4*)
1. Follow guidelines similar to those for letters to the editor with respect to length, style, and preference for electronic submission.
 2. Be aware that politicians usually accept only letters from their constituents.
 3. Use the appropriate form of address. For example: The Honorable...
 4. Note clearly in your letter if your communication is in response to a particular piece of legislation (e.g., House Bill No. —).
 5. Include a clear recommendation to support or oppose the legislation.
 6. In closing, provide your credentials and contact information with an offer to provide more information if necessary.
- F. A Speaker's Bureau for Your Organization: Hospitals and corporations may have public relations/media departments that keep a list of employees who are able to comment on various health-related topics. As issues arise, reporters may contact these organizations when looking for experts to comment. Training by the organization may be provided to learn how to effectively speak to the media. (*Domain 4*)

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ANSWERS AND EXPLANATIONS TO PATIENT CASES**1. Answer: C**

An open-ended question is best used to open a discussion about the patient's chief concern. Compound questions (Answer A) should be avoided. Answer B and Answer D are more focused questions, which are better saved for later in the conversation.

2. Answer: D

When dealing with emotions such as anger, it is usually best to first reflect back the emotion and acknowledge the patient's concerns or complaints. Once this patient believes his concern is understood, he may be willing to listen to one of the other responses as a reason for what appears to him to be a delay in resolving his problem.

3. Answer: A

Patients who respond to the SILS question by stating that they sometimes, often, or always ask others to help them read medical information are considered at risk of inadequate health literacy (either Answer A or Answer C). This patient was able (with some difficulty) to correctly calculate the correct dose when given the specific numbers to use, and only very simple arithmetic was necessary. So he is likely at NAAL level 2 (basic level) (Answer A). Those at level 3 would be able to identify which numbers to use and perform basic calculations (e.g., calculate a pediatric dosage from a chart).

4. Answer: D

Adults older than 65 years are at higher risk of inadequate health literacy. Other risk factors are less than a high school education and low income. This patient completed high school, and he is part of the middle class. One should not assume English is the patient's second language on the basis of his or her ethnicity. It should not be automatically assumed that all in minority groups have low health literacy.

5. Answer: C

The Adherence Estimator is a useful tool to assess a patient's perception of concern, commitment, and cost of an individual medication. Adverse perceptions of a medication likely discourage continued adherence and could therefore be areas for tailored educational messages (Answer C correct). Answer A and Answer B would be ways to assess his past adherence, but would

not assess the likelihood of continued adherence moving forward. The Health Belief Model may be useful to assess reasons for nonadherence, but it does not predict continued adherence (Answer D).

6. Answer: C

According to The Joint Commission recommendations, abbreviations, especially those for drug names (MSO4), should be avoided. Trailing zeros (10.0) should not be used with drug doses. Other abbreviations should be avoided (IV, q).

7. Answer: D

In this case, documentation should include both the ability to perform the necessary skill (i.e., injection) and to apply the sliding scale to calculate a situation-specific dose. Answers A, B, and C are limited to comprehension of the dosing scale and/or technique.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS**1. Answer: B**

Because this routine maintenance medication therapy management is not an emergency, it would be best to use a professional interpreter according to the guidelines for using medical interpreters by the Association of American Medical Colleges. Therefore, only Answer B is the best option of those given.

2. Answer: B

The Morisky and the Adherence Estimator questionnaires are both methods to assess the likelihood of adherence. However, only the Morisky questionnaire is intended to evaluate adherence to one or more drugs in a regimen for a particular disease. The Adherence Estimator is used only with individual drugs. The BATHE technique or Motivational Interviewing may help identify reasons for nonadherence, but neither assesses the likelihood of adherence.

3. Answer: C

This patient is able to identify facts from dense text (the package insert) and perform simple calculations, so he is at least at the intermediate literacy level. Because he is having trouble integrating and applying information from several sources, he is unlikely to be considered proficient.

4. Answer: C

The PEMAT tool would be most appropriate because it was specifically designed for assessing the usability of audiovisual materials. The SAM tool has similar criteria, but it was designed originally for written materials. Obtaining feedback from either knowledgeable colleagues or typical patients would be useful, but this may not provide a comprehensive assessment of usability.

5. Answer: A

Whereas health care professionals typically learn at least some of the aspects of medication therapy, audiences are usually most interested in information related to their job responsibilities. Physical therapists would want to know the neuromuscular effects of a medication and their potential impact on patient movement. For example, the adverse effects of dizziness, hypotension, or sedation might impair a patient's ability to participate in physical therapy sessions. Because these professionals

are typically not responsible for prescribing or administering pain-related medications, they would usually be less interested in cost, dosing, formulary status, or pharmacokinetics. Thus the most correct option would be Answer A.

6. Answer: A

U is listed on the ISMP error-prone abbreviations list and should not be used if possible. *Units* is the preferred way to note the insulin dose. The term *QD* (daily) is also listed on the ISMP list and is often mistaken as *QID* (four times a day) and should not be used; *daily* is preferred. The Joint Commission does not state a preference with respect to *HS* versus *bedtime*; however, ISMP lists this on the error-prone list because it is often confused with *half-strength* and, in general, these abbreviations should be avoided.

7. Answer: D

Responses to editorials of between 300 and 750 words are suitable for placement opposite the editorial (or op-ed piece). Letters to the editor can be used to respond to editorials, but they receive less visibility and generally should be fewer than 250 words. The school board would appreciate the support. Ideally, however, the pharmacist's comments should reach the same readership as the newspaper's original editorial. Sending them to the school board would not achieve this.