Society of
Critical Care Anesthesiologists
SOCCA

ICU Residents' Guide

2014 Edition

Introduction to Learning in the
Intensive Care Unit

Society of Critical Care Anesthesiologists

Residents' Guide
To Learning in the Intensive Care Unit
2014

Table of Contents

Preface

Welcome to critical care. Whether you are using this review guide for your first rotation in critical care or your tenth, we hope that you find it useful as a supplement to the other reading materials at your disposal.

The delivery of critical care continues to change rapidly. Therapies that were deemed beneficial in the past (drotrecogin alfa, tight glucose control, etc) are now considered harmful; it is difficult to keep up-to-date with textbooks alone. Our goal is to provide concise clinically relevant chapters that are useful for the trainee working in the ICU. Each chapter's relevance is illustrated with a sample case, and the concepts are then reviewed with self-test multiple choice questions. Further in depth learning can be obtained with the selected reference list at the end of each chapter.

For those who grew up with digital media, we have also tried to incorporate new technologies by adding videos, hyperlinks, and interactivity.

Finally, we would like to give our heartfelt gratitude to the many trainees and faculty mentors across the nation who have contributed to this edition and past editions. Without their help and expertise, we would have never succeeded. Thank you to the prior editors as well, for without their vision, we would not be here with the fifth edition.

Best wishes to the newcomers. May you enjoy the field as much as we have.

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May 2014

Preface to the Fourth Edition

Many things have changed since the last edition was released.

Perhaps the most obvious is the name of the society. The society has long had strong international connections, and after deliberating, we changed the name of the organization to the Society of Critical Care Anesthesiologists - SOCCA for short.

In the short time since the last edition was published, we have seen a variety of practices fall into and then out of favor, drugs be released and then withdrawn, monitoring technologies proliferate and the electronic health record become an overriding concern for all patient care. Even our options for publication are changing. This is likely to be the last edition that is created as a static electronic document.

About half of the authors are new for this edition. Where they have revised older chapters, the original authors are again acknowledged at the end of the chapter.

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Preface to the Third Edition

Intensivists have witnessed profound changes in the delivery of critical care medicine in the last decade. A large number of randomized, prospective clinical trials or "before and after" studies have impacted the way we practice critical care. Examples include the use of drotrecogin alfa activated for the treatment of severe sepsis and septic shock; low tidal volume ventilation in patients with acute lung injury and the acute respiratory distress syndrome; implementation of ventilator and catheter "bundles" to reduce nosocomial infections; and the use of alpha-2 agonists for sedation of the critically patient. It was clear that the "Anesthesiology Residents' Guide to Learning in the Intensive Care Unit" was in need of revision. We and the American Society of Critical Care Anesthesiologists (ASCCA) are pleased to provide this revised guide to supplement the critical care reading material used by anesthesia residents and fellow.

The third edition has been expanded to include several important topics including "Echocardiography", "Traumatic Brain Injury" and "Organ Donation and Procurement in the ICU". Similar to the second edition, we have retained the short case presentations and the self-study questions. The reading lists have been updated.

The majority of the authors who participated in the revision of this edition are new. We would like to thank the previous authors who were either the original authors or who helped revise the second edition. We have acknowledged their contributions at the end of each chapter. The ASCCA is dedicated to timely revisions of this guide and plans are already underway on the 4th edition.

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Preface to the Second Edition

Since the publication date of the first edition in 1995, the scope and practice of critical care medicine have continued to change. Examples of new issues encountered during this time include controversies over pulmonary artery catheter use and pressures over efficient management of critical care services as managed care demands are realized. Additionally, during this time period, academic departments have grappled with conflicting demands of resident education and efficient patient care in the new medical marketplace. A primary mission of the American Society of Critical Care Anesthesiologists is to assist anesthesiology residency programs to educate the future perioperative physicians, who are today's anesthesia residents and fellows. The hospitalized patients of today are older and sicker than ever before, and many will travel to locations in hospital where the primary medical caregiver will be an anesthesiologist. With proper skills and training, these anesthesiologists will be the most appropriate caregivers for these critically ill patients, helping maintain complex homeostasis by thorough evaluation and management preceding, during, and following surgical procedures.

The curriculum of the second edition was modified somewhat from the first edition by members of the Resident Education Task Force of the American Society of Critical Care Anesthesiologists in an attempt to bring "up-to-date" information to the hands of residents who are caring for critically ill and injured patients. To this purpose, several new sections have been added to the topical outline (e.g., ICU Management, Rational Use of PA Catheters, Lung Protective Strategies); the bulk of the topic outline remains as a presentation of the most important concepts of critical care. Short case presentations have been added to provoke interest and increase relevance. Self-study questions remain (with annotated answer keys) to allow the resident to evaluate his or her understanding. Reading lists have also been annotated to emphasize the relevance of most references.

Lucy A. Weston, Ph.D., M.D.

Preface to the First Edition

The field of critical care medicine continues to expand as new technologies are developed and old technologies are refined. Anesthesiologists have been pioneers in the development of critical care medicine. Changes in the health care environment have led the American Society of Critical Care Anesthesiologists to define the anesthesiologists as the perioperative physician. To achieve this role, anesthesia residents must be competent in critical care medicine. Assessing critically ill patients prior to operative procedures, management of intraoperative anesthetic care, treating postoperative pain, and management of organ function after a surgical procedure is best done by an anesthesiologist.

The members of the Resident Education Task Force of the American Society of Critical Care Anesthesiologists have developed this curriculum guide to help residents achieve competence in caring for the critically ill and injured patients. This guide is not meant to be an exhaustive curriculum for an intensivist but useful for all residents completing anesthesiology training. These were developed into outlines of the most important concepts with a reading list for each. Additionally, self-study questions are included with most sections to allow the resident to evaluate his or her current understanding.

This guide may also be used by residency program directors to evaluate or improve their own curriculums. It is not our intention that all aspects of critical care mentioned in the guide be part of the two month critical care rotation required by the American Board of Anesthesiology. Other experiences, including cardiac anesthesia, consult services, and postoperative recovery room would certainly contribute to mastery of these topics.

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Section 1: Introduction to the ICU

Chapters

• Structure, Staffing & Safety

• Analgesia & Sedation

• Neuromuscular Blockade

• Transport

• Cardiopulmonary Resuscitation

• Ethics

1. Structure, Staffing, and Safety

Gary R Stier MD MBA

Key Points

- The organization of the ICU can affect patient outcomes

- High-intensity ICUs have been shown to have better outcomes over low-intensity ICUs

- A multidisciplinary team approach is ideal for critically ill patients

- A robust quality improvement program is necessary to continually improve patient satisfaction and outcomes

A 67 year-old man is initially admitted to the hospital ward with a diagnosis of right lobar pneumonia. He has a history of COPD, diabetes mellitus, chronic kidney disease, and hypertension. Initial treatment consists of aggressive bronchodilators, fluids and antibiotics. During the first hospital night, he develops labored breathing, confusion, and hemodynamic instability (SBP 85 mm Hg; HR 128/minute), and requires transfer to the ICU. Initial ICU orders are written by the admitting primary care physician and include aggressive pulmonary care, increased fluids, and dopamine for blood pressure support. During the evening of the second hospital day, he demonstrates worsening respiratory distress, persistent hypotension despite dopamine at 15 mcg/kg/min, and minimal urine output. A blood transfusion is ordered for a hemoglobin of 9.8 mg/dL. At the strong urging of the nursing staff, an intensivist consultation is requested.

Introduction

In the United States, 55,000 adult critically ill patients are cared for each day[1], with approximately 200,000 patients dying in ICUs each year. The cost of this care is significant, reaching $81.7 billion nationwide in 2005.[2] A considerable amount of this expense is unnecessary, being related to a lack of care coordination and a failure to utilize evidence-based best practices. Such care results in prolonged hospital lengths of stay and excessive resource utilization. Within the ICU environment, the organization and structure of critical care services has significant impact upon ultimate performance, the achievement of optimal patient outcomes, and in the cost of care. The attainment of benchmarked outcomes will soon affect payments to both providers and hospitals. This chapter will review the basic components of ICU organization—structure, staffing, and quality improvement—that form the foundation for best outcomes.

Structure

An ICU is a well-defined area of a hospital where patients with acute life-threatening illnesses or injuries receive continuous specialized medical and nursing care. The ICU structure is important, impacting upon the quality of care delivered, and includes the physical aspects and architectural design of the ICU, available equipment (monitors, beds, ventilators, imaging devices), type of ICU practice model, leadership arrangement, and ICU-specific policies and order sets.

The architectural plan of the ICU varies among hospitals, incorporating semi-circular, circular, and rectangular designs. Modern designs focus on creating a healing environment with materials and furnishings that

reduce noise, glare, and stress, and have natural lighting.[3] Single patient rooms are superior to multi-patient rooms with regard to patient safety, with 4 to 6 feet of space provided around the bed perimeter to facilitate in-room procedures and services. The specific ICU design impacts upon staff communication, unit noise levels, and patient safety. Circular designs, which place patients near the nurses' station may enhance patient safety by earlier detection of adverse patient events, although noise levels tend to be excessive. Optimal designs enhance workflow efficiency and facilitate effectiveness of patient care.

The monitoring equipment in the ICU includes: continuous electrocardiogram (ECG), pulse oximetry, respiratory rate, temperature, capnography, blood pressure (invasive and noninvasive), central venous pressure, intracranial pressure, and the EEG. Support equipment include: emergency airway equipment (including laryngoscopes, endotracheal tubes, and fiberoptic bronchoscopy equipment), invasive and noninvasive mechanical ventilators, ICU beds (including specialty beds), equipment for hemodynamic support (infusion pumps, blood warmers, etc.), temporary pacemakers, supplies and adequate lighting for ICU procedures; positive and negative pressure isolation room(s); and computer stations for access to laboratory data, radiologic imaging studies, active medications, and medical information.

The ICU is organized into one of three practice models: an open unit (referred to as "low-intensity"); a semi-closed (hybrid) unit; and a closed unit. Both the semi-closed and closed unit models are referred to as "high-intensity" units. The *open unit* refers to the model where the admitting physician manages all aspects of the patient's care. The admitting physician may request an intensivist consultation to assist in guiding management decisions, but is not required to do so. A *semi-closed* (hybrid) unit refers to the model where the admitting physician continues to manage most aspects of the patient's care, but agrees to a mandatory intensivist consultation with co-management of the more complex medical issues. A *closed unit* refers to a care model in which an intensivist-directed ICU team manages all aspects of the care of the patient. Studies have demonstrated reduced cost, fewer medical errors, and better patient outcomes with high-intensity ICUs.[4]

ICU leadership is composed of an appointed physician medical director and a nurse manager. The medical director has many duties including: setting the overall vision and strategic direction, overseeing ICU policy and guideline development, educating staff, and reviewing unit performance and quality outcomes. The nurse manager is a hospital-appointed position, providing clear lines of authority, responsibility, and accountability within the assigned ICU and for ensuring quality of patient care. The nurse manager is responsible for setting nurse practice standards, education, and for assuring cooperation with physicians and other ancillary staff.

ICU-specific policies, utilization of *care bundles*, and use of diagnosis-specific order sets are necessary for best outcomes. The daily incorporation of care bundles into management plans has been shown to minimize medical errors and adverse events, reduce the incidence of nosocomial infections, decrease hospital and ICU length of stay, reduce the cost of care, and improve patient outcomes.[5] A care bundle refers to a limited set of evidence-based interventions (i.e. 3-5 interventions) that when delivered in aggregate, improves outcomes. Care bundles currently exist for a variety of situations, including sepsis management, central line placement, prevention of ventilator-associated pneumonia, indwelling urinary drainage catheters, and many other clinical situations. (Table

1.1)

Staffing

The ICU staff is comprised of physicians, physician extenders, nurses, and professional support staff. Each provider, working within the team concept, plays a vital role in attaining the best patient outcomes possible.

Physicians provide the daily care and management of the majority of critically ill patients. Intensivists are physicians with an additional 1 to 2 years of subspecialty training in critical care medicine. Intensivists' direct the medical care of patients in most ICUs operating as either closed or hybrid units. On-site ICU intensivist coverage utilizes ei-

Table 1.1: Common ICU Care Bundles	
Bundle	**Interventions**
Ventilator Bundle	- Elevation of the head of the bed 30-45 degrees - Daily "sedation vacations" and assessment of readiness to extubate - Peptic ulcer disease (PUD) prophylaxis - Deep venous thrombosis (DVT) prophylaxis - Daily oral care with chlorhexidine
Central Line Bundle	- Hand hygiene - Maximal barrier precautions - Chlorhexidine skin antisepsis - Optimal catheter site selection, with avoidance of using the femoral vein for central venous access in adult patients - Daily review of line necessity, with prompt removal of unnecessary lines
Severe Sepsis Resuscitation Bundle (to be completed within 3 hours)*	- Measure lactate level - Obtain blood cultures prior to administration of antibiotics - Administer broad spectrum antibiotics - Administer 30 mL/kg crystalloid for hypotension or lactate ≥4 mmol/L
Severe Sepsis Resuscitation Bundle (to be completed within 6 hours)*	- Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation to maintain a mean arterial pressure (MAP) ≥65 mm Hg) - In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥4 mmol/L (36 mg/dL): - Measure central venous pressure (CVP) - Measure central venous oxygen Saturation ($ScvO_2$) - Remeasure lactate if initial lactate was elevated

Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al; Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup: Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013; 41:580-637

ther a *dayshift* model (majority of ICUs), with availability during the nighttime hours by beeper or other communication device, or an *in-house 24/7* model (30% of university-affiliated ICUs). The benefit of one coverage model over the other has not been conclusively demonstrated.[6] Optimal daytime patient to intensivist ratios should be no more than 15:1, although higher ratios can be safely managed during off hours. Above this ratio, both the quality of care delivered and job satisfaction decline.

A physician extender refers to a nurse practitioner or a physician's assistant. A nurse practitioner (NP) is an RN who has completed advanced graduate level training. NPs have significant latitude to practice independently, typically under clinical agreements termed "standardized procedures" with a designated physician supervisor. Many states have granted NPs independent practice privileges. A physician assistant (PA) has obtained both a Bachelor's degree and a Master's degree in physician assistant studies from an accredited PA program. PAs are licensed to practice by the state medical board and always work under the direct supervision of a physician. As physician extenders, both NPs and PAs are granted extensive patient care duties including: medical management decisions, performing procedures, order writing, and coordination of care. Studies have shown that physician extenders can provide high quality and cost-effective care when working within a collaborative medical care team model.[7]

Registered nurses (RN) directly provide, or supervise, all bedside patient care. Critical care RNs have specialized training and or experience in taking care of critically ill patients. Typical ICU nurse-to-patient ratios vary from 1:1 to 1:2, based on patient disease acuity, and are defined by written hospital policies. Full-time nurses generally work 40-hours per week with nurse shift lengths ranging from 8 to 12 hours. Evidence from numerous studies has demonstrated an inverse relationship between the level of ICU nurse staffing and patient mortality, adverse outcomes, resource utilization, and staff turnover rates.[8]

The ICU Pharmacist has important responsibilities that include: attending ICU rounds, evaluating all drug orders, monitoring drug dosing, alerting the medical staff for potential adverse drug interactions, recommending cost effective drug substitutions, and helping develop policies and procedures focused on medication safety within the ICU workflow. The presence of a dedicated ICU pharmacist reduces medical errors and improves outcomes.

Professional support staff - respiratory therapists, physical and occupational therapists, dietitians, social workers, and case managers are a vital part of the ICU team in efforts to ensure quality care delivery, optimal outcomes, and patient satisfaction. Early involvement and coordination in patient care plans by the professional support staff members reduces the length of ICU stay while conserving economic resources. The specific duties of each professional support staff member are outlined in Table 1.2.

Quality
The Institute of Medicine (IOM) published a landmark paper in 1999 entitled "To Err is Human: Building a Safer Healthcare System". In this paper, it was disclosed that nearly 100,000 patients die each year as a result of medical errors. In response, healthcare policy has been focused on assuring the consistent delivery of evidence-based best practices (EBBP) and in measuring outcomes. A number of non-profit organizations, such as The Joint Commission (TJC), the Agency for Healthcare Research and Qual-

Table 1.2: ICU Professional Support Staff	
Staff Member	**Duties**
Respiratory Therapist	Evaluation of respiratory equipment needs and setup, management of the patient-ventilator system, airway care, delivery of bronchodilators, monitor blood gases, obtain ventilator weaning mechanics and supervise the delivery of protocol-driven respiratory care
Physical Therapist	Evaluation and treatment focused on increasing the patient's strength and functional training, including passive range of motion exercises, massage therapy, stretching techniques, hot and cold treatments, breathing exercises, and specialized exercises tailored to specific problem areas
Occupational Therapist	Work with patients who have suffered injuries that will adversely impact their ability to live or work normally; identify treatment goals, including exercises to improve motor skill development or use of new equipment.
Clinical Dietitian	Collaborate with the critical care team to identify the nutritional needs of each critically ill patient, creating nutritional programs tailored to the specific requirements of the patient. Nutritional assessment and plans (enteral vs. parenteral nutrition) are performed early during the ICU stay
Social Worker	Focus is mainly on the psychosocial elements of care, including facilitating discharge planning of socially complex patient situations, transitions of the patient from the acute care setting to lower levels of care, dealing with difficult family situations, hospice placements, nursing home placements, providing emotional support related to critical illness and crisis intervention, managing barriers to safe and timely discharge planning, arranging post-discharge follow-up.
Case Manager	An RN or social worker assigned to coordinate and facilitate clinical care, manage resource utilization and reimbursement for ICU services, verify insurance coverage and address financial barriers, transition the patient to the appropriate level of care when ready, coordinate discharge planning efforts, and participate in performance and outcomes management.

ity (AHRQ), National Quality Forum (NQF), the Institute for Healthcare Improvement (IHI), and the Leapfrog Group have strongly supported efforts to study and evaluate EBBP, to reduce medical errors, and to develop safety indicators. The Leapfrog Group, a quality-focused consortium of large corporations, companies, and health care purchasers, providing health benefits to more than 34 million Americans, obtains health care services from hospitals that demonstrate safety, affordability, and quality, including intensivist-directed ICUs.

Implementing a quality improvement (QI) and safety culture within the ICU is essential for reducing medical errors, controlling practice variation, and for improving outcomes.[9] The components of a successful QI program include: strong leadership and

vision, choosing attainable ICU-specific QI projects, utilizing standardized QI methods, staff motivation, teamwork, accurate data collection and reporting, careful evaluation of results, and adopting effective strategies to change physician and staff behavior. QI projects should focus on endeavors that are small, simple, and easy to complete, and should be designed to evaluate a broad variety of parameters that reflect unit-specific performance. QI projects begin with baseline data collection, performance of the study intervention with data collection, and review of the data at study completion. A typical QI project process should follow an accepted technique of study, such as the PDSA (plan-do-study-act) method. If the QI project is successful in improving unit performance, staff acceptance of future QI efforts is facilitated.

Effective communication among staff is necessary for optimal patient outcomes. Multidisciplinary team rounds—which includes providers, nurses, pharmacists, respiratory therapists, physical therapists, dietitians, social workers, and case managers—provide a forum for all members of the medical team to come together to discuss patient care plans, to problem solve, and to coordinate goals of treatment. Multidisciplinary rounds have been shown to improve efficiency, outcome, and cost of care.[10] Utilization of team-based communication-enhancement techniques, such as the SBAR (Situation, Background, Assessment, Recommendation) method, improves transitions of care (handoffs) between providers, while simulation training focuses on refining team communication skills in a dynamic learning environment.

Information technology (IT) is essential for evaluating the effectiveness of quality improvement efforts and for accurate monitoring of ICU performance. Automatic collection of a comprehensive ICU database assures completeness and reliability of data collection, which can be utilized to compare unit outcomes with published quality benchmarks. Other benefits of modern IT include support for computerized physician computer entry (CPOE), promoting the use of evidence-based best practices, ensuring better diagnosis capture, providing clinical reminders, inclusion of disease-specific order sets, better identification of incorrect medication orders, and clear medical record documentation.

The evaluation of ICU quality performance relies upon monitoring quality indicators of performance (Table 1.3) and comparing the results with published benchmarks. Individual ICU performance must be evaluated within the context of the ICU case mix (patient demographics, acuity of illness, presence of co-morbidities); this is done utilizing risk prediction models, such as the Acute Physiology and Chronic Health Evaluation (APACHE) score, Mortality and Probability Model (MPM), and the Simplified Acute Physiology Score (SAPS). These models utilize large databases of patient information that compare outcomes among similar groups of critically ill patients.

Summary

Patients with critical illness have high morbidity and mortality. An ICU with modern equipment, strong medical and nursing leadership, an intensivist-directed care team, sufficient ancillary staff support, good communication, and effective IT-driven process improvement efforts, will ensure the best outcomes for patients.

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Table 1.3: Common ICU Quality Indicators of Performance
ICU Mortality rate
Length of ICU stay (days)
Duration of mechanical ventilation
Incidence of unplanned extubations
Incidence of ICU readmissions
Infection rates 　Ventilator-associated pneumonias (VAP) 　Central line-associated blood stream infections (CLABSI) 　Catheter-associated urinary tract infections (CAUTI)
Rate of compliance with hand hygeine guideline
Rate of compliance with care bundles 　Sepsis bundle 　Central line bundle 　Ventilator bundle 　Urinary catheter bundle
Incidence of decubitus ulcers
Rate of appropriate peptic ulcer disease prophylaxis
Rate of appropriate DVT prophylaxis
Medical errors rates
Incidence of adverse drug reactions
Incidence of suboptimal management of pain
Patient/family satisfaction scores
Nurse turnover rate

Questions

1.1 Which of the following statements regarding a closed ICU model is FALSE?
    A. Patient care is shared between the admitting physician and the intensivist-led ICU team
    B. Patient care is exclusively directed by the intensivist-led ICU team
    C. Studies demonstrate better patient outcomes
    D. Studies show that cost of care is less compared with an open ICU model

1.2 Which of the following statements concerning care bundles is FALSE?
    A. A care bundle refers to the use of a limited set of evidence-based interventions consistently applied to a specific clinical situation
    B. Each care bundle consists of a set of 6-10 interventions
    C. Consistent use improves outcomes
    D. A care bundle exists for the placement and care of central venous lines

1.3 Which of the following statements regarding an ICU quality improvement program is FALSE?
    A. Requires strong leadership and vision
    B. Uses standardized quality improvement methods
    C. Should focus on larger projects with the greatest patient benefit
    D. Reduces practice variation while improving outcome

1.4 Individual ICU performance should always be evaluated in the context of the specific ICU's overall severity of illness (i.e. case mix). All of the following are risk prediction models used to more accurately estimate patient outcomes EXCEPT?
    A. APACHE
    B. SAPS
    C. MPM
    D. TISS

2. Analgesia and Sedation in the ICU

Stephanie Cha MD and Theresa Hartsell MD PhD

Key Points

• **Pain and agitation are commonly under-recognized and undertreated among ICU patients**

• **Inadequate treatment of pain or agitation can have detrimental physiologic as well as psychological effects.**

• **The routine use of reliable rating systems improves the recognition of pain and agitation and allows for goal-directed titration of medications.**

• **"Lighter" levels of sedation are associated with improved clinical outcomes.**

• **Opioids are the first-line therapy for analgesia, but the use of non-narcotic adjuncts can decrease the incidence of unwanted side effects.**

• **Non-benzodiazepene agents such as dexmedetomidine are emerging as the preferred sedative agents.**

Case: A 70-year old woman with a history of obesity, prior myocardial infarction, and chronic back pain status post cervical spine fusion is now admitted to the ICU following a multi-level lumbar posterior spinal fusion. She remains intubated due to concern for airway edema while in prone position during surgery. On exam she is hypertensive, tachycardic, and noted to have frequent ventilator dyssynchrony. What is the best approach to sedate this patient and manage her analgesic needs?

Analgesia

Pain is subjective and can be defined as an "unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"[1]. In ICU patients it can take multiple forms, and may be categorized as resting pain, acute post-surgical pain, chronic pain including neuropathic injury or cancer, pathologic pain, or procedural pain (e.g. manipulation of traumatic injuries, wound care and dressing changes, invasive procedures, or suctioning of airway secretions). Pain in the ICU is both prevalent and undertreated, and there are important hemodynamic and psychological consequences associated with unrelieved pain [2]. These include impaired wound healing, increased levels of circulating catecholamines, and the development of chronic pain, post-traumatic stress disorder, and a generally lower health-related quality of life [2].

Routine monitoring of patient pain levels is recommended. Pain may be self-reported by the visual analog scale (VAS), or inferred by the patient's behavior, assuming intact motor function and the absence of neurologic injury. For patients who are unable to self-report their pain, the Behavioral Pain Scale (BPS) and Critical Care Pain Observation Tool have been found to be the most valid and reliable assessment methods [2]. These scales score patient pain based on the presence of specific pain-related behaviors, which include facial expressions, body movements, muscle tension, vocalization and/or ventilator compliance. In addition, while a patient's vital sign trend may suggest the degree or presence of pain, it may be misleading and should not be used alone in the assessment of pain [2].

Principles of pain management in the ICU focus on pre-emptive analgesia, or the use of analgesics prior to potentially painful ICU procedures, as well as the use of combination therapy. IV opioids are considered to be the first-line treatment of non-neuropathic pain, and it is important to recognize that all opioids are equally effective when titrated to comparable clinical endpoints (Table 2.1) [3]. Opioids can be administered by continuous, as-needed, or even patient-controlled dosing. Dosing strategy is influenced by many factors, such as the patient's neurologic status (need for frequent neurologic monitoring may favor bolus dosing), hemodynamic lability (continuous infusions are least likely to exacerbate hypotension), and the presence of renal or hepatic dysfunction. It is also important to recognize that opioids exhibit many adverse side effects, which may be particularly difficult to manage in critically ill patients. These include respiratory depression, CNS depression, nausea and vomiting, constipation, withdrawal with acute discontinuation, miosis, and pruritus [3].

Table 2.1: Opioids

Opioid	Pharmacology	Use
Remifentanil	Onset: 1-3 min Elimination: t1/2: 3-10 min Tissue esterase metabolism	0.5-15mcg/kg/h 1-1.5mcg/kg IV load
Fentanyl	Onset: 1-2 min Elimination: t1/2: 2-4h Hepatic metabolism	0.7-10mcg/kg/h 0.35-0.50mcg/kg IV push q30-60 minutes
Morphine	Onset: 5-10 min Elimination t1/2: 3-4h Hepatic metabolism; active metabolites renally cleared	2-30 mg/h 2-4mg IV push q1-2h
Hydromorphone	Onset: 5-15 min Elimination t1/2: 2-3h Hepatic metabolism	0.5-3mg/h 0.2-0.6 mg IV push q1-2h

Pharmacologic adjuncts may limit these unwanted side effects by reducing a patient's opioid requirements. Adjunct classes include non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen, which antagonize prostaglandins receptors. NSAIDs are renally cleared, and must be used cautiously in patients with GI ulcers and increased bleeding risk due to their nonselective COX inhibition of prostaglandin and platelet synthesis. Similarly, acetaminophen dosing must be modified in patients with liver insufficiency. Other adjuncts include ketamine, anti-epileptics (gabapentin and carbamazepine) for the treatment of neuropathic pain, as well as alpha-2 adrenergic agonists (clonidine and dexmedetomidine), tramadol, antidepressants, and topical lidocaine3. In addition, epidural analgesia is recommended for postoperative pain following abdominal aortic aneurysm surgery, and should be considered in the management of patients who have undergone thoraco-abdominal surgeries or who have traumatic rib fractures [2]. The major disadvantage of epidural analgesia is hypotension due to a sympatholytic-mediated decrease in systemic vascular resistance.

Agitation and Sedation

ICU patients frequently require sedating agents to provide comfort and ensure the safety of life-sustaining interventions (e.g. central venous catheters or endotracheal tubes). Indications for sedation include anxiolysis, agitation or delirium, discomfort during mechanical ventilation or ventilator dyssynchrony, and management of intracranial hypertension. Common sedatives act primarily through centrally mediated inhibition of neuronal signaling, and include barbiturates, benzodiazepines, NMDA antagonists, and alpha-2 agonists, as listed in Table 2.2. Adverse effects are similar across sedative classes and may include delirium, sleep disturbance, withdrawal, and increased risk for infection [2].

Table 2.2: Sedatives

Sedative	Pharmacology	Usage	Adverse Effects
Propofol (GABA-A agonist)	Onset: 1-2 min Elimination t1/2: 3-12h (short term use) Hepatic metabolism, no active metabolites	5 mcg/kg/min load over 5 min followed by 5-150mcg/kg/min infusion (usually < 50 mcg/kg/min)	injection site pain, **hypotension**, myocardial depression, **respiratory depression/apnea**, hyperlipidemia, **Propofol Infusion Syndrome (PRIS)**
Benzodiazepines (GABA-A agonists)	**Midazolam** Onset 2-5 min Elimination t1/2: 3-11h (longer if elderly/cirrhotic) Hepatic metabolism Active metabolites renally cleared **Lorazepam** Onset: 15-20 min Elimination t1/2: 8-15h (longer if elderly/cirrhotic) Hepatic metabolism, no active metabolites	**Midazolam** 0.01-0.05mg/kg load followed by 0.02-0.1mg/kg/h infusion **Lorazepam** 0.02-0.04 mg/kg load followed by 0.01-0.1 mg/kg/h (<10 mg/h) infusion 0.02-0.06 mg/kg q2-6h push	hypotension, **respiratory depression,** withdrawal following abrupt discontinuation, **propylene glycol toxicity** *Propylene glycol toxicity may be seen with lorazepam use, and is characterized by metabolic acidosis with elevated osmolar gap and renal dysfunction
Ketamine (NMDA Antagonist)	Onset: 1 min Duration: 10-15 min Hepatic metabolism Active metabolites renally cleared	0.1-0.5 mg/kg IV followed by 0.05-0.4 mg/kg/h infusion	**Dissociative hallucinations** ("out of body experience"), emergence delirium, increased secretions (lacrimation, salivation), increased myocardial oxygen demand, possible increase in ICP
Dexmedetomidine (alpha-2 agonist)	Onset: 5-10 min Elimination t1/2: 1.8-3.1h Hepatic metabolism	1 mcg/kg load over 10 minutes followed by 0.2-0.7 mcg/kg/h infusion, for <24 h 0.5-1mg/kg IV push	xerostomia, bradycardia, **hypotension**, transient hypertension following bolus

The most reliable and valid assessment tools for monitoring the depth and quality of sedation in adult ICU patients include the Richmond Agitation-Sedation Scale (RASS) and the Sedation-Agitation Scale (SAS), as shown in Table 2.3 [2]. Monitoring brain function (e.g. Bispectral Index, Auditory Evoked Potentials) has also been proposed, but is not well-substantiated [2]. EEG monitoring in ICU patients with elevated intracranial pressure, however, may be useful for goal directed titration of sedatives in order to minimize cerebral metabolic demand [2].

There has recently been a paradigm shift in sedation management. First, lighter levels of sedation or daily sedation interruption are recommended over deep, uninterrupted sedation. Exceptions include severe lung injury, severe traumatic brain injury, and hemodynamic instability associated with myocardial ischemia. Findings of clinical trials suggest shorter duration of ICU length of stay, shorter duration of mechanical ventilation, and a reduction in radiologic tests ordered for altered mental status [4]. Furthermore, a trend toward better psychosocial outcomes has been associated with lighter levels of sedation [5]. While lighter levels may increase a patient's metabolic demand through an increased stress response, there is no data to suggest an associated increase in the incidence of myocardial ischemia[2]. In addition, an analgesic-based regimen is recommended as sedation may mask pain that is present from reasons listed above. Finally, non-benzodiazepine agents are associated with an improved clinical profile, and are preferred in mechanically ventilated patients. Dexmedetomidine in particular, has emerged as a useful new therapy, as it has been shown to be associated with a shorter duration of mechanical ventilation, decreased incidence of delirium, improved cognitive function, and

Table 2.3: Richmond Agitation-Sedation Scale (RASS) vs Sedation Agitation Scale (SAS)		
	RASS	SAS
Agitated	+4 Combative +3 Very Agitated +2 Agitated +1 Restless	7 Dangerously Agitated 6 Very Agitated 5 Agitated
Calm	0 Alert and Calm	4 Calm and Cooperative
Sedated	-1 Drowsy -2 Light Sedation -3 Moderate Sedation -4 Deep Sedation -5 Unarousable	3 Sedated 2 Very Sedated 1 Unarounsable

decreased inflammation as compared to midazolam [5]. Compared to midazolam, propofol was also associated with earlier extubation, but carried a greater incidence of hypotension requiring pressor support, as well as the risk for Propofol Infusion Syndrome (as listed in Table 2.2) [5].

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Questions:

2.1 Which of the following conditions may be improved by the use of ketamine for sedation?
    E.   Recent traumatic brain injury
    F.   Extensive psychiatric history
    G.   Asthma exacerbation
    H.   Atrial fibrillation with poor heart rate control

2.2 Which of the following agents has no analgesic property?
    A.   Ketamine
    B.   Midazolam
    C.   Remifentanil
    D.   Ketorolac

2.3 An 80-year old woman has been sedated with propofol at 50 mcg/kg/min for the past 48 hours while requiring mechanical ventilation. Which of the following is most consistent with the development of propofol infusion syndrome?
    A.   Metabolic alkalosis
    B.   Hypokalemia
    C.   Immune suppression
    D.   Renal dysfunction

2.4 Which of the following is a true statement about dexmedetomidine?
    A.   It is an NMDA receptor antagonist
    B.   Its administration can precipitate both hypertension and hypotension
    C.   It is predominantly metabolized by the kidneys
    D.   It has no effect on the sleep-wake cycle

3. Neuromuscular Blockade

Monirath Saly MD and Matthias Merkel MD PhD

Key Points

- There is still much debate and controversy surrounding the use of NMBAs in the ICU.

- The choice in the use of a neuromuscular blocking agent in the ICU must be guided by an understanding of the drug's properties and a risk-benefit analysis.

- Medications given in the ICU and the physiology of the critically ill patient can affect the pharmacodynamics and pharmacokinetics of NMBAs.

- There are many complications of NMBAs including DVTs, ICU-acquired weakness, awareness, and anaphylaxis.

- Hourly monitoring to minimize the dosing and daily reassessment of the indications for NMBAs should be performed.

A 36 year-old woman with a history of a difficult airway suffered a ruptured left middle cerebral artery (MCA) aneurysm and was admitted to the neurocritical care unit with a Fisher 3 subarachnoid hemorrhage and a Hunt and Hess score of 5. She emergently went to the operating room for clipping of her aneurysm. Over the ensuing week, she slowly started to regain neurologic function. She was extubated on POD#7. Unfortunately, 48 hours later after extubation, her neurologic function declined and she had a witnessed aspiration event resulting in severe hypoxia. A decision was made to intubate her urgently. She was induced with IV propofol and succinylcholine was used as the NMBA given her history of a difficult airway and need for a rapid sequence induction. Approximately 15 seconds after induction, while performing the endotracheal intubation, the providers noticed peaked T waves on the monitor that immediately progressed into pulseless ventricular tachycardia (VT).

The use of neuromuscular blocking agents (NMBAs) in the ICU is still much debated and its use is controversial. The decision to treat a patient in the ICU with NMBAs (for reasons other than the placement of an endotracheal tube or a surgical procedure) is a difficult one that is guided more commonly by individual practitioner preference than by standards based on evidence-based medicine. According to the 2002 guideline published by the Society of Critical Care Medicine (SCCM), "NMBAs should be used for an adult patient in an ICU to manage ventilation, manage increased ICP, treat muscle spasms, and decrease oxygen consumption only when all other means have been tried without success."[1]

NMBAs are usually categorized according to their mechanism of action (depolarizing versus nondepolarizing) and by their duration of action (short, intermediate, and long-acting). The non-depolarizing agents can be further subdivided by their structural composition (aminosteroids versus benzylisoquinolinium). (Table 3.1) Depolarizing agents function by binding to postsynaptic acetylcholine receptors in the neuromuscular junction (NMJ) and cause a persistent depolarization leading to flaccid paralysis. Nondepolarizing agents act as competitive antagonists of postsynaptic nicotinic receptors in the NMJ and block the actions of acetylcholine. The choice of an NMBA for sustained paralysis in the intensive care unit must be guided by an understanding of the drug's properties and by a risk-benefit analysis.[2] The practitioner needs to be familiar with the relevant pharmacologic features for each NMBA including but not limited to structure, ED95 (the dose necessary to depress a mechanically evoked twitch response by 95% in controls), usual bolus dose, infusion dose range, onset time, duration and recovery times, major route of elimination, residual activity of major metabolites, autonomic interactions, and other major side effects.[3]

Table 3.1: Neuromuscular blocking agents by mechanism of action and duration

	Short (5-10 min)	Intermediate (20-60 min)	Long (60-100 min)
Depolarizing	Succinylcholine	-	-
Non-depolarizing	Mivacurium*	Atracurium cis-Atracurium Rocuronium Vecuronium	d-Tubocurarine Doxacurium Metocurine Pancuronium Pipecuronium

*no longer available
adapted from: Greenberg SB & Vender J [5], and Miller RD [3]

Many drugs interact with the actions of NMBAs. Some drugs such as aminoglycoside antibiotics and magnesium potentiate their actions and could be involved in the patho-physiology of muscle weakness following NMBA use. Others such as phenytoin may antagonize the paralytic effect. (Table 3.2)

In terms of drug selection, no specific recommendation can be given due to a lack of data. However, cis-atracurium was used in a randomized controlled trial in patients with severe acute respiratory distress syndrome (ARDS).[4] In this randomized trial, the patients receiving a cis-atracurium infusion for the first 48 hours had an increased adjusted 90-day survival and a significant improvement in the PaO2:FiO2 ratio even after the infusion was stopped. Furthermore, patients in the treatment group had higher number of ventilator-free days, organ failure-free days, and reduced barotrauma.[4] Although cis-atracurium was used in this study, the primary goal was to assess the use of an NMBA versus no NMBA. The 2002 SCCM guideline for sustained neuromuscular blockade in the adult critically ill patient recommends vecuronium, though these recommendations are currently being revised.[1] Common dosing regimens for available NMBAs can be reviewed in Table 3.3.

The need for an NMBA should be reassessed daily and administration should be stopped as early as possible. Despite the lack of evidence that monitoring prevents adverse effects, in addition to the lack of a standardized method of monitoring, assessment of the depth of neuromuscular blockade in ICU patients is recommended. (1) Monitoring the depth of neuromuscular blockade may allow usage of the lowest NMBA dose and may minimize adverse events.[1] By using Train-of-Four (TOF) monitoring, the rate of infusion can be adjusted to achieve one or two twitches. The TOF (four 2 Hz electrical stimulus delivered every 0.5 seconds applied to the ulnar, facial, or posterior tibial nerve) is based on the concept that acetylcholine is depleted by successive stimulations; with increasing neuromuscular blockade, there will be fade and less twitches.[3,5] However, the TOF might be difficult to assess in an edematous and/or diaphoretic patient.[5] A second option is to stop the paralytic on a daily basis ("drug holiday") to reassess the need for continuing the drug and assure rapid recovery from the drug effects.[1]

The complications of neuromuscular blockade in the ICU can be categorized as short-term (anaphylaxis, ventilator disconnect, accidental extubation, acute hyperkalemia with succinylcholine use), mid-term (corneal abrasions/ulcerations, edema, hypostasis, pressure ulcers, venous thrombosis) and long-term (muscle weakness). Additionally, the

possibility of awareness and its deleterious consequences is also present.[5,6]

Hypersensitivity reactions associated with NMBAs are usually IgE related. The ammonium ion in NMBAs is usually the culprit and may hold cross-reactivity with other inciting agents. Hence, it may be possible to have an anaphylactic reaction after the first exposure to NMBAs.[5] Surveys from a large French study suggested that the most frequent perioperative agent responsible for allergic reactions was NMBAs (more so than latex, colloids, and antibiotics).[7]

Succinylcholine should be avoided in patients 24 to 72 hours after major burns, trauma, devastating strokes, and extensive denervation of their skeletal muscle for fear of life threatening hyperkalemia and cardiac arrest.[3] Extra-junctional acetylcholine receptors proliferate in the absence of neural activity. Extrajunctional acetylcholine receptors differ from postjunctional receptors in composition by a subunit (epsilon subunit replaced by a gamma subunit) that allows the ion channel to remain open for a longer period of time when activated leading to an increase in extracellular potassium concentration. This, in turn, leads to life threatening concentrations of potassium that can lead to cardiac arrest, especially in patients with an acidosis (hydrogen-potassium shift).[3]

Table 3.2: Drugs that interact with neuromuscular blocking agents

Drug	Effect
Antibiotics (aminoglycosides, vancomycin, clindamycin, tetracycline, bacitracin)	Potentiation
Anticonvulsants (phenytoin, carbamazepine)	Resistance
Antidysrhythmics (lidocaine, calcium channel blockers, quinidine, procainamide)	Potentiation
Antihypertensives (trimethaphan, nitroglycerine)	Potentiation
Dantrolene	Potentiation
Inhaled anesthetics	Potentiation
Furosemide	Potentiation
Local anesthetics	Potentiation
Magnesium Sulfate	Potentiation
Ranitidine	Resistance
Steroids	Potentiation
Theophylline	Resistance

 adapted from: Greenberg SB & Vender J [5], and Murray MJ et al [1]

NMBAs are not sedatives; therefore, before initiating neuromuscular blockade, patients should receive appropriate sedative and analgesic drugs to avoid awareness and post-

traumatic stress disorder (PTSD). The use of depth of anesthesia monitors to assure a proper level of sedation while patients are paralyzed seems logical although there is not enough evidence to support their routine use.[5,6] There has been no universally accepted bedside monitor to detect awareness in the ICU; processed electroencephalogram devices, such as the bispectral index (BIS), have been used successfully and unsuccessfully to detect awareness in the ICU.[5,6]

Although thought to be multifactorial, prolonged skeletal muscle weakness in ICU patients is closely related to the use of NMBAs.[8,9] A confusing list of names and syndromes, including acute quadriplegic myopathy syndrome (AQMS), floppy man syndrome, critical illness polyneuropathy (CIP), critical illness myopathy (CIM), critical illness polyneuromyopathy (CIPNM), acute myopathy of intensive care, rapidly evolving myopathy, acute myopathy with selective lysis of myosin filaments, acute steroid myopathy, and prolonged neurogenic weakness have been reported in the literature. [1,5,10] However, the term ICU-acquired weakness has become the more frequently used "catchall" phrase for this disease process.[5,11] Although the exact mechanisms of this problem are unknown, the common factor seems to be damage to the neuromuscular membrane.[11] The use of steroid-based NMBAs (pancuronium, vecuronium) and/or the concomitant use of steroids have been associated in the development of prolonged muscle weakness.[1,12,13,14] However, benzylisoquinolinium-based NMBAs (cis-atracurium, atracurium) have also been reported to produce this phenomenon.[1,14] In addition, muscle weakness has been associated with the persistent presence of the drug or its metabolites in plasma. Alterations in clearance mechanisms such as hepatic and/or renal failure can contribute to this problem.[15] Unintentional overdose, drug interactions (Table 3.2), electrolyte imbalances (hypermagnesemia, hypophosphatemia), acidosis, hypothermia and underlying muscle disorders (polyneuropathy of critical illness, myasthenia gravis) are also involved.[10,15]

In summary, NMBAs should be used judiciously in the critically ill patient. The effects of these agents on the neuromuscular membrane can lead to severe adverse events. If deemed necessary to use, monitoring the depth of the blockade to minimize dosing and constant reassessment of the indications are vital. If prolonged use is needed, "drug holidays" should probably be performed.

This chapter is a revision of the original chapter authored by Naga Pullakhandam, Devanand Mangar, and Enrico M Camporesi, MD

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Table 3.3: Pharmacology of neuromuscular blocking agents

	ED95 (mg/kg)	Onset to Maximum Twitch (min)	Intubating Dose (mg/kg)	Continuous Infusion (mcg/kg/min)	Elimination
Succinylcholine	0.3-0.5	< 1	1	not recommended	plasma cholinesterase
Atracurium	02-0.25	3-5	0.4-0.5	4-20	5-10% renal, Hoffman elimination
cis-Atracurium	0.05	2-3	0.1-0.2	1-3	5-10% renal, Hoffman elimination
Rocuronium	0.3	1-2	0.6-1.2	8-12	10-30% renal, < 75% hepatic
Vecuronium	0.05	3-5	0.08-0.1	0.8-1.7	10-50% renal, 35-50% hepatic
Pancuronium	0.05-0.08	3-5	0.05-0.1	0.8-2	45-70% renal, 10-15% hepatic

adapted from: Greenberg SB & Vender J [5], Miller RD[3] and Murray MJ et al [1]

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Questions:

3.1 All of the following drugs potentiate the effects of NMBAs EXCEPT:
    A. Aminoglycosides
    B. Magnesium
    C. Phenytoin
    D. Quinidine

3.2 Which of the following NMBAs are NOT appropriately paired based on their duration of action?
    A. Cis-atracurium: short
    B. Mivacurium: short
    C. Rocuronium: intermediate
    D. Vecuronium: intermediate

3.3 Complications of using non-depolarizing NMBAs in the ICU may include all of the following EXCEPT:
    A. Awareness
    B. Critical Illness Myopathy
    C. Hyperkalemia
    D. Venous Thrombosis

3.4 Potential causes of prolonged weakness in the ICU patient after NMBA administration include all the following EXCEPT:
    A. Concomitant use of steroids
    B. Drug or drug metabolites accumulation
    C. Electrolyte disturbances
    D. Propofol interaction with the neuromuscular junction

4. Transport of the Critically Ill

Ronald Pauldine MD

Key Points

• The goal during transport is to maintain the same monitoring and supportive care that the patient receives in the intensive care unit.

• It is never "just another road trip." Movement of patients is associated with a number of adverse events and requires careful consideration of the reasons for transport.

• It is useful to ask, "How likely are the results of this patient transport to change the present course of treatment?"

• Transport personnel should be familiar with transport procedures and equipment. Checklists are a useful tool to facilitate safe transport and improve communication.

A 45 year old man is involved in a high speed motor vehicle collision. He is transported by ambulance to a nearby rural hospital. He becomes unstable during initial assessment in the emergency department requiring intravascular volume resuscitation and endotracheal intubation. Identified injuries include blunt chest trauma, pelvic fractures and extremity fractures. He is stabilized and arrangements are made for aeromedical transport by helicopter to a regional trauma center for further management. On arrival to the trauma center he requires a series of transports within the hospital. These include movement between the emergency department and intensive care unit with transport to specialized areas for diagnostic imaging, angiographic embolization of pelvic hemorrhage and operative repair of orthopedic injuries.

Introduction

Movement of critically ill or injured patients is a common event in the delivery of modern healthcare. Patient movement can occur in a number of settings including the prehospital environment, transfer between facilities and movement within the hospital. Prehospital transport is classified as primary transport and later movement within or between facilities is designated as secondary transport. Reasons for movement include gaining access to healthcare via emergency medical services, evacuation from disaster areas or hostile or austere environments, transfers between facilities for increasing complexity of care and movement within a facility for diagnostic or therapeutic procedures. Modes of transport vary greatly and include the use of mobile beds, transport litters, ground vehicles, and rotary wing or fixed wing aircraft. While the indications, modes, and sites of transport are variable, the general concepts governing safe and effective movement of critically ill and injured patients share many of the same principles.

General Considerations for Patient Transport

Transport of any critically ill patient begins with careful consideration of the necessity of transport, assessment of the patient's condition, defining command and control for the process, ensuring appropriate communication between care teams, choosing a mode of transport, preparing the patient, pre-movement checks of all equipment and verification of necessary supplies. The transport is performed with attention to transfer of care at the conclusion along with proper documentation. Critical events should be reported in addition to any process or quality improvement information. Specialized equipment is employed for patient transport and often has significantly different operational characteristics from the equipment used at the bedside in the intensive

care unit (ICU). It is imperative that transport personnel understand the operation, potential limitations and how to troubleshoot the transport equipment they utilize. Ideally, transport equipment will be interoperable with all equipment across a given system. This includes issues such as compatible cables, device interfaces and infusion tubing sets and cartridges. The process of patient transport is well suited for the use of checklists to standardize care and avoid errors of omission. A number of checklists have been published for use in the transport environment. A sample transport checklist is provided in Table 4.1.

A significant body of literature demonstrates that physiologic derangements occur during all phases of transport and transport increases the risk for adverse outcomes. Adverse events may reflect deterioration in one or more physiologic variables or critical situations, which require urgent therapeutic intervention. Several studies have reported complications related to gas exchange with manually assisted ventilation. Transport ventilators are increasingly employed to mitigate this risk that has been particularly associated with adverse outcome in brain injury. Adverse events reported across all transport domains are reviewed in Table 4.2. A wide range of factors have been implicated in contributing to adverse events. These include human factors relating to knowledge, judgment and technical performance, process problems such as inadequate communication, insufficient protocols and lack of training, as well as multiple problems with transport equipment. Prehospital and interhospital transport are associated with an increased risk of occupational injury and death for providers related to the inherent risks associated with the mode of transportation, design limitations of the vehicles and vulnerability associated with delivering care in the transport environment.

Prehospital Transport

Prehospital care is provided by emergency medical personnel in the setting of out of hospital illness or injury. The scope of care, standardized practices and equipment are specialized for the clinical environment and may differ from those employed during secondary transport. Prehospital transport typically occurs in the setting of an integrated emergency medical system. Triage decisions regarding the transport destination of a particular patient are important. Available evidence demonstrates improved outcomes for patients triaged to dedicated centers for conditions including trauma, acute coronary syndromes and stroke. Under-triage, the referral of patients who may benefit from specialized care erroneously to lower acuity centers, may adversely affect outcome. Likewise, over-triage, transferring patients not needing specialized care to dedicated centers, may result in overcrowding and misuse of resources. The role of pre-hospital transport using helicopter emergency medical systems (HEMS) over ground transport for patients with major trauma has been a widely debated subject with recent data suggesting an advantage for HEMS. Controversies remain in several areas of prehospital transport including the benefit of stabilization of patients at the scene via advanced life support ("stay and play") versus rapid transport to an appropriate facility ("scoop and run"). Other controversies include the role of advanced airway management, the composition and training of team members and the precise elements of HEMS that confers benefit. These elements include speed of transport, team composition, team expertise, and appropriate, specific therapeutic interventions.

Inter-hospital Transport

Interfacility transport is most commonly considered to allow critically ill patients to access a higher level of care or to receive treatment for conditions requiring specific specialty expertise or procedures not available at the referring facility. Federal regula-

Table 4.1 Sample Transport Checklist	
DECISION TO TRANSPORT	
☐	Does the expected benefit of transport outweigh the risk?
☐	Staff/Equipment/Vehicles available?
☐	Receiving location prepared?
TEAM	
☐	Adequately trained and experienced
☐	Detailed handoff to transport team
EQUIPMENT	
☐	All equipment operational
☐	Portable power supply/Batteries charged
☐	Alarm limits checked and set
☐	Lines and tubes simplified, secured and labeled
☐	Oxygen supply with back-up
☐	Transport pack with emergency drugs and supplies
PATIENT	
☐	Stabilized on transport stretcher
☐	Monitors in place and operational/Equipment secured
☐	Ventilation adequate/Assessment of gas exchange if using transport ventilator
☐	Appropriate sedation/neuromuscular blockade (if indicated)
☐	Measures to prevent heat loss
COMMUNICATION	
☐	Transfer documents prepared
☐	Full physician and nursing report to receiving location
DOCUMENTATION	
☐	Vital signs/Notations of events during transport
☐	Adverse Events/Process Improvement

tions in the United States stipulate that hospitals receiving funding from Medicare have a duty to evaluate and provide treatment to stabilize patients with an "emergency medical condition" regardless of citizenship, legal status or ability to pay as initially describe in the Consolidated Omnibus Budget Reconciliation Act (COBRA) and later refined in the Emergency Medical Treatment and Active Labor Act (EMTALA). Considerations for choosing a mode of transport include the urgency of transport, time to mobilize the transport team and vehicles, geographical factors, weather, traffic conditions and cost. In general, ground transport is suitable for many patients and has the advantage of lower cost and is less likely to be affected by inclement weather. Rotary wing transport can be considered for transport distances of 50 to 200 miles and in situations where terrain fac-

Table 4.2 Adverse Events Associated with Transport	
Cardiovascular Events	Hypotension Hypertension Dysrhythmia Loss of Vascular Access Hemorrhage Cardiac Arrest Death
Respiratory Events	Hypoxia Hypercarbia Bronchospasm Pneumothorax Respiratory Arrest Inadvertent Extubation Increased Risk of VAP
Neurological Events	Agitation Altered Mental Status Intracranial Hypertension
Equipment & Medical Supply Events	Equipment Failure Improper Use of Equipment Battery Failure Inadequate Medical Supplies Oxygen Failure Critical Medications/ Supplies/ Equipment Unavailable
Staff & Administration Related Events	Inadequate Staff Communication and Liaison Problems
Miscellaneous Events	Hypothermia

tors limit ground access. Fixed wing transport may be considered for distances greater than 200 miles. Important aspects of inter-hospital transport are summarized in Table 3. The optimal team composition, team training, skills verification, practice specific algorithms, implementation of crew resource management principles and effect of process improvement initiatives on patient outcome are not well defined.

Intrahospital Transport

Movement of patients from the intensive care unit to other locations within the hospital is most often performed to obtain diagnostic radiographic studies or for operative procedures. The relative risk of transport should be weighed against the potential benefit derived from the anticipated diagnostic or therapeutic intervention. The goal as with any other transport is to maintain the same level of monitoring and supportive care that the patient receives in the ICU. As discussed previously, a variety of adverse events have been reported during intrahospital transport and this represents an area for potential improvement in patient safety. There is evidence that dedicated transport teams may reduce the incidence of adverse events during transport while having beneficial effects on ICU staffing, job satisfaction and time spent in transport related activities. However,

dedicated transport teams may incur increased direct costs to healthcare organizations. An increasing number of procedures frequently required by ICU patients including tracheostomy and percutaneous endoscopic gastrostomy can be performed safely at the bedside avoiding the need for patient transport and the associated allocation of resources.

Table 4.3 Considerations for Interhospital Transport	
Administrative	- informed consent obtained from patient or legally authorized representative - if consent cannot be obtained, the reason should be documented along with the indication for transport - a written order for transfer is recommended
Coordination & Communication	- referring physician communicates with accepting physician to confirm acceptance of the patient, availability of required resources and to give detailed report of patient condition - designate a physician to assume responsibility for treatment during transport if no physician is on the transport - determine the mode of transport - nursing report is performed by a nurse at the referring facility or a member of the transport team - send/deliver a copy of the medical record along with pertinent studies to the receiving facility
Team Composition	- team composition is variable and often based on patient acuity
Monitoring & Equipment	- Minimum monitoring includes continuous pulse oximetry, electrocardiogram, and regular measurement of blood pressure and respiratory rate. - advanced monitoring including capnography, invasive hemodynamic monitoring and intracranial pressure monitoring can be considered as needed. - Basic equipment includes airway adjuncts, physiologic monitors, suction, infusion devices and agents for resuscitation and maintenance of vital functions. - transport ventilators should be utilized for intubated patients - all equipment and supplies are checked before transport including available IV fluids, drips and blood products

Patient Factors and Preparation ("Packaging the Patient")	- Resuscitation and Stabilization via CAB approach
	  - hemorrhage controlled
	  - blood pressure stabilized
	  - C-spine immobilized (trauma)
	  - fractures splinted
	- Is there a need to control the airway?
	  - consider transport time and potential alterations in airway integrity and gas exchange with transport
	- is there a need for increased IV access or invasive monitoring?
	- is there a need for nasogastric decompression, urinary catheter placement or tube thoracostomy?

Conclusions

Available data suggest that critically ill and injured patients can be transported safely in a variety of transport environments with proper understanding and mitigation of risk. However, the transport environment remains associated with an increased risk for adverse events. A number of factors likely influence the safety, efficacy and efficiency of the transport process, but these are not yet fully defined.

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Questions

4.1 Interhospital transport is MOST LIKELY to be performed in which of the following scenarios?

A.   Transfer of an unstable patient with urosepsis who is unable to pay for treatment in the emergency department at the referring facility
B.   Transfer of an inpatient with acute kidney injury and hyperkalemia from a hospital without a hemodialysis service to a hospital with availability of renal replacement therapy
C.   Transfer of a patient with an acute coronary syndrome from a regional cardiac center to a nearby community hospital
D.   Transfer of a trauma patient who has tachycardia and orthostatic hypotension upon arrival to the emergency department of a community hospital

4.2 Which of the following is the MOST LIKELY reason transport ventilators are recommended for use in patient transport?

A.   Transport ventilators are capable of maintaining the same ventilator parameters as critical care ventilators
B.   Transport ventilators use special batteries that do not require frequent recharging
C.   All transport ventilators use less oxygen than simple hand bag ventilation
D.   Transport ventilators may prevent harmful hypoventilation or hyperventilation of patients with increased intracranial pressure

4.3 Which of the following statements regarding intrahospital transport is MOST LIKELY true?

A.   It is impossible to maintain the same monitoring and supportive care received in the ICU due limited capabilities of transport equipment
B.   Additional medical supplies do not need to be carried if the transport location is on the same hospital floor as the ICU
C.   Patient movement is associated with an increased risk of ventilator associated pneumonia
D.   Adverse events are rare during intrahospital patient transport

5. Cardiopulmonary Resuscitation

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Key Points

• Anesthesiologists need to recognize the signs and symptoms of a dysrhythmia as well as understand the pathophysiology, therapeutic management, and direction of care following return of spontaneous circulation.

• Adequate chest compressions is now considered the priority of any resuscitative initiative, followed by establishment of airway and providing breaths

• Post-cardiac arrest care requires as much vigilance as the resuscitative measures during the arrest.

68yo WM with PMHx of HTN, Hyperlipidemia, IDDM noted to collapse and become unresponsive while playing golf. Patient's friends' state that he was complaining of chest tightness prior to the event, and after finding no pulse, they initiated CPR. Emergency personnel arrived within 3 minutes and performed defibrillation with 200J when rhythm analysis revealed ventricular fibrillation. A palpable pulse is noted after defibrillation, although the patient remains unresponsive. He is then intubated and transported to the nearest hospital for further management.

Introduction

The skills acquired while training to become a critical care physician affords one to be of great resource during times of uncertainty; this holds true regardless of location both in and out of the hospital. The time when this is most evident is when someone experiences a cardiac arrest or other life threatening arrhythmia. It is therefore of great importance for us to not only recognize the signs and symptoms of dysrhythmia but also understand the pathophysiology, therapeutic management aimed at correcting the disease state, and direction of care following return of circulation.

The most daunting of tasks can be determination of the primary insult but in an unstable situation this should not delay initiation of cardiopulmonary resuscitation. Calling a code, establishing a secured airway, performing chest compressions (30:2) with minimal interruptions, placing external defibrillator pads for EKG analysis and possible electric conversion should occur almost simultaneously. This typically requires multiple personnel to be involved. In addition to the aforementioned steps, one must establish intravenous access and obtain labs to help determine potential causes of the dysrhythmia. It is therefore paramount for a code leader to be identified and serve as a director to coordinate these events to happen as seamlessly as possible.

Return of circulation and stabilization of the patient is only half of the battle. Post-cardiac arrest care requires as much vigilance as the resuscitative measures prior. Optimize ventilation and oxygenation (SpO_2>94%, $PEtCO_2$ 35-40mmHg). Treat hypotension with fluids and vasoactive agents, and work-up potential contributing factors with review of EKG, CXR, and labs (ABG, BMP, CBC, glucose, coagulation panel, etc.). Con-

sider induced hypothermia if patient remains unresponsive despite return of circulation, and coronary reperfusion interventions if there is a high likelihood of STEMI or MI. Unfortunately, despite these measures, morbidity and mortality remain high following cardiac arrest with most related to neurologic and cardiac injury. It has been shown, however, that 20-50% of comatose patients who presented to the hospital following cardiac arrest may have good one-year neurological outcome. Therefore admitting the resuscitated patient to an ICU with advanced neurologic monitoring may help to improve long term prognosis.

Resuscitative Algorithm

Studies have revealed that providing circulation to a patient in cardiac arrest is the primary determinant of improved outcome. Therefore initiation of adequate chest compressions is now considered the priority of any resuscitative initiative, followed by establishment of airway and providing breaths. To stress the importance of this order the American Heart Association promotes the use of the acronym "CAB".

I. Circulation
  A. Initial assessment should include determination of pulsatile flow, underlying rhythm, and heart rate.
   1. Pulse: Check carotid/radial/femoral sites for pulse. If questionable do not delay resuscitative measures, i.e. CPR.
   2. Rhythm: Place defibrillator pads for analysis.
      a. Shockable Rhythms: Ventricular fibrillation, Ventricular Tachycardia, Atrial fibrillation, Atrial Flutter, Re-entry SVT
       i. Perform direct current cardioversion as soon as possible (120-200J with biphasic device.
      b. Unshockable Rhythms: Pulseless Electrical Activity, Asystole
   3. Rate: If pulse is present but patient is bradycardic (HR< 60bpm), consider transcutaneous pacing.
  B. Chest Compressions should be performed until a defibrillator is available and ready to deliver a shock or indefinitely if the rhythm is determined unshockable.
   1. Technique: Place patient on a hard surface. Use the heel of your hand in the center of the chest, along nipple line, to provide compressions at a depth of ~2in at a rate of 100 compressions per minute.
   2. Compression to Breath ratio: [30:2]. Watch for chest rise and fall with each rescue breath lasting 1 second. If there is no chest rise then consider patient positioning being an issue and provide jaw thrust, head tilt, chin lift, oral/nasal airway, LMA, or intubate if experts of airway management are available.
      a. All of these maneuvers should occur with priority being place on limiting duration of interruptions to compressions.
      b. If patient is intubated then continuous ventilation can occur at a rate of 10-12 breaths per minute via an Ambu-bag and 100% FiO_2. Monitor for $EtCO_2$.
   3. Pulse Check: Assess for pulse at the completion of a full CPR cycle [30:2 x 5 cycles] and after cardioversion.
      a. If feasible a pulse should be continuously monitored (A-line wave form or rescuer palpating femoral/radial sites), or monitoring of $EtCO_2$ in order to ensure adequate chest compressions.

II. Airway
  A. Management
   1. Examine oral pharynx for foreign body.
   2. Administer 100% FiO_2 whenever possible.
   3. Monitor $EtCO_2$ if possible.
   4. Supraglottic Airway Techniques: Increased risk of gastric distension & aspiration
      a. Mouth to Mouth
      b. Bag Mask
      c. Oral/Nasal airway
      d. Laryngeal Mask Airway device
   5. Definitive Airway: Allows for continuous ventilation during CPR
      a. Endotracheal Intubation
      b. Tracheostomy

III. Breathing
  A. Position patient for optimal ventilation: jaw thrust, head tilt, chin lift.
  B. Rate:
   1. Supraglottic Airway: [30:2] compressions to breath ratio
   2. Definitive Airway: uninterrupted 10-12 breaths per minute

IV. Defibrillation
  A. Safety:
   1. Make sure no one is touching the patient or connecting surfaces during delivery of shock.
  B. Timing:
   1. It should occur as soon as possible for any shockable rhythm, optimally within 3 minutes of diagnosis.
      a. Shockable Rhythms: Ventricular fibrillation, Ventricular Tachycardia, Atrial fibrillation, Atrial Flutter, Re-entry SVT
       i. Perform direct current cardioversion as soon as possible (120-200J with biphasic device).
      b. Unshockable Rhythms: Pulseless Electrical Activity, Asystole

V. Following Return of Circulation (ROSC)
  A. Management
   1. Optimize Ventilation & Oxygenation (SpO_2>94%, $PEtCO_2$ 35-40mmHg)
   2. Treat Hypotension: Fluids/Vasopressors
  B. Work-up for triggering event
   1. History and Physical
      a. Review Past Medical History
       i. Risk factors for cardiac insult: HTN, HL, DM, male, CHF, CRF, previous stroke
       ii. Risk factors for pulmonary embolus: cancer, smoking, obesity, recent surgery, pregnancy
       iii. Risk factors for neurologic insult which can often present with dysrhymias:

HTN, chronic headaches, trauma, intrancranial hemorrhage
b. Recent Medications
  i. Every medicine has a side-effect and their interactions can result in dysrhythmia.
c. Recent Events
  i. Surgery: Consider volume status/hemorrhagic shock, pulmonary embolus, tamponade (CABG or intrathoracic cases), pneumothorax, sepsis.
  ii. Trauma: Consider volume status/hemorrhagic shock, pulmonary embolus, tamponade (CABG or intrathoracic cases), pneumothorax (is chest tube kinked?).
  iii. Intubation: Consider misplaced endotracheal tube (confirm bilateral breath sounds, $EtCO_2$ monitoring), induction agents (succinyl choline can reult in hyperkalemia).
2. Review Labs
  i. ABG, CMP(comprehensive metabolic panel), CBC, Coag, Glucose, Cardiac enzymes
    b) Often times hypoxia, acidosis, hypo/hyperkalemia, and hypoglycemia are initiating culprits.
3. Imaging/Studies
  a. CXR
    i. Look for signs of pneumothorax or tamponade.
  b. Echo
    i. Focal wall motion abnormalities suggestive of ischemic insult
    ii. Global hypokinesis suggestive of stunned myocardium
    iii. Dilated right ventricle suggestive of pulmonary embolus
    iv. Pericardial effusion and tamponade
  c. EKG
    i. Compare to prior study
    ii. ST elevations:
      a) Diffuse: pericarditis
      b) Anterior MI: leads V1-V4
      c) Inferior MI: II, III, AVF (Q waves and ST elevations)
      d) Lateral MI: I, AVL, V5, V6
      e) Right Heart Strain: inverted T waves V1-V3, right atrial enlargement
      f) Pulmonary Embolus: S1Q3T3
C. Procedures/Intervention:
  1. Induced Hypothermia
    a. Recommended if patient remains unresponsive despite return of circulation after out-of-hospital VF cardiac arrest.
    b. Consider if patient remains unresponsive after return of spontaneous circulation after in-hospital cardiac arrest of any initial rhythm or after out-of-hospital cardiac arrest with an intial rhythm of pulseless electric activity or asystole.
    c. Cool patient to 32-34˚C for12-24 hours
    d. Avoid active rewarming in comatose patients who spontaneously are mildly hypothermic (>32˚C)

    e. Recent multicenter study showing that there may be no significant difference between 36°C versus 33°C in terms of favorable outcomes, but that the active prevention of hyperthermia may be the key
  2. Coronary Reperfusion
    a. Consider if high likelihood of STEMI or MI.

Diagnostic and Treatment Algorithms

The following algorithms serve as reference in the diagnosis and pharmacologic management of the most common arrhythmias encountered in the ICU. They are designed to be reviewed independently of each other.

A. Bradyarrhythmia:
  1. Types:
    a. Sinus Bradycardia: decreased number of impulses arising from SA to AV node
    b. 1st degree AV block: Slowed conduction through the AV node
    c. 2nd degree AV block: Missed beats due to intermittent AV block
      i. Type I (Wenckebach/Mobitz I)
      ii. Type II (Mobitz II)
    d. 3rd degree AV block: complete AV nodal block
  2. Definition:
    a. Stable Bradyarrhythmia: HR <60bpm and asymptomatic
    b. Unstable Bradyarrhythmia: HR <60bpm and signs/symptoms of end organ insult
      i. Hypotensive, complains of chest discomfort, shortness of breath, lightheadedness, nausea/vomiting, altered level of consciousness/mentation, diaphoretic, CXR with signs of acute heart failure (pulmonary edema) or other signs of shock
  3. Common Etiologies:
    a. Medications
      i. negative chronotropes (digoxin, beta blockers, calcium channel blockers), Alpha1 Agonists (phenylephrine), antiarrhythmic drugs (amiodarone), antipsychotic meds (lithium)
    b. Electrolyte disturbances: hyperkalemia, hypermagnesaemia,
    c. Disease processes: elevated ICP, acute MI, increased vagal activity, hypothyroid, protracted hypoxia
  4. Management:
    a. History and Physical exam: CAB's
      i. Auscultate for heart sounds and palpation for distal pulses.
      ii. Evaluate patency of airway.
      iii. Supply supplemental oxygen and provide respiratory support as required to maintain SpO_2>94% and $PEtCO_2$ of 35-45mmHg.
      iv. History: presenting illness, PMHx, medications, allergies, recent labs (CBC, BMP, ABG, etc.)
    b. Monitors:
      i. Continuous EKG, pulse oximetry, blood pressure monitoring, 12 lead EKG
    c. Treatment: Correct reversible causes

i. Stable Bradyarrhythmia:
  a) Continue to monitor and observe for hemodynamic stability.
ii. Unstable Bradyarrhythmia: Consider cardiology consult
  c) Interventions:
    1) Place patient in trendelenburg position.
    2) Establish IV access (bolus 500cc to 1L crystalloid).
  d) Medication:
    3) 1st line: Atropine IV
      i) Initial: 0.5mg bolus IV
      ii) Redose: may repeat 0.5mg IV every 3-5mins up to maximum of 3mg
    4) 2nd line: Chronotropic Augmentation
      i) Dopamine IV infusion 2-10mcg/kg/min
      ii) Epinephrine IV infusion 2-10mcg/kg/min
  e) Transcutaneous/Transvenous pacing

B. Tachyarrhythmia:
  1. Types:
    a. Regular Narrow Complex Tachycardias:
      i. Sinus Tachycardia: increased no. of impulses arising from SA to AV node
      ii. Re-entry Supraventricular Tachycardia (SVT): accessory pathway between atria and ventricle that can allow for a combination of anterograde and retrograde conduction of impulses through to the AV node
    b. Irregular Tachycardias
      i. Atrial Fibrillation: AV node receives signals from multiple foci (commonly originating near the root of pulmonary veins in L. Atrium), each firing disorganized
      electrical impulses (usually 400-600bpm) that the AV node tries to filter out but ultimately still allows conduction of more beats at varying rates and in an irregular pattern to the Ventricles
      ii. Atrial Flutter: Reentry pathway (usually in R. Atrium) that leads to a localized self-perpetuating loop of AV node activation in a regular pattern (~300bpm). Due to the fixed, regular input of signals received, and the longer refractory period of the AV node, not all impulses will be conducted. Results in presence of AV block (2:1, 3:1, 4:1, etc.) and predictable heart rates (150bpm, 100bpm, 75bpm, etc.)
      iii. Multifocal Atrial Tachycardia (MAT): Thought to result from either one foci impulse traveling from atria to AV node via multiple routes OR multiple foci conducting impulses through one route. EKG must show P waves of at least three different morphologies for diagnosis to be made.
    c. Wide-complex tachycardia:
      i. Monomorphic VT: Within a Ventricle (Usually at origin of R. Ventricular Outflow Tract) there is either a single foci that has increased automaticity or a single reentry circuit leading to repetitive depolarizations
      ii. Polymorphic VT: Multiple foci within the ventricle fires impulses or multiple reentry pathways lead to repetitive depolarizations and EKG shows QRS complexes of varying morphology.
  2. Definition:

a. Stable Tachyarrhythmia: HR >100bpm and asymptomatic
b. Unstable Tachyarrhythmia: HR >100bpm & signs/symptoms of end organ insult
  i. Hypotensive, ST segment changes on EKG, complains of chest discomfort, Shortness of breath, lightheadedness, nausea/vomiting, altered level of consciousness/mentation, diaphoretic, CXR with signs of acute heart failure (pulmonary edema) or other signs of shock
3. Common Etiologies:
a. Medications
  i. Stimulants (Nicotine, caffeine, cocaine), anticholinergics, antihistamines, theophylline, digitalis toxicity, sympathomimetics (epinephrine, ephedrine, dopamine)
b. Electrolyte disturbances: hypokalemia, hypomagnesemia, hypocalcemia
c. Stressors: pain, fever, anxiety, hypovolemia, hypoxia, hypercarbia
d. Disease processes: hyperthyroid, sepsis, pulmonary embolus, myocardial infarction, COPD, pheochromocytoma, heart failure
4. Management:
a. History and Physical exam: CAB's
  i. Auscultation for heart sounds and palpation for distal pulses
  ii. Evaluate patency of airway
  iii. Supply supplemental oxygen and provide respiratory support as required to maintain SpO_2>94% and $PEtCO_2$ of 35-45mmHg
  iv. History: presenting illness, PMHx, medications, allergies, recent labs (CBC, BMP, ABG, etc.)
b. Monitors:
  i. Continuous EKG, pulse oximetry, blood pressure monitoring, 12 lead EKG
c. Treatment: Correct reversible causes
  i. Unstable Tachyarrhythmia with Positive Pulses
    a) Interventions:
      1) Establish IV access: consider sedation (versed, fentanyl)
      2) Consider Expert Consultation
    b) Synchronized Cardioversion: Everyone stand clear
      1) Narrow, Regular QRS (<0.12s):
        i) Initial: 50-100J
        ii) Failed: shock increase in a stepwise fashion
          o (50, 100, 150, 200J)
      2) Narrow, Irregular QRS (<0.12s):
        i) Initial: 120-200J Biphasic; 200J Monophasic
        ii) Failed: shock increase in a stepwise fashion
          o (120, 150, 200J)
      3) Wide, Regular QRS (>0.12s):
        i) 100J Biphasic
        ii) Failed: shock increase in a stepwise fashion
          o (100, 150, 200J)
d. Unsynchronized Cardioversion: Everyone stand clear
  i. Wide, Irregular QRS (>0.12s):

a) 150J Biphasic
b) Failed: shock increase in a stepwise fashion
o (150, 200J)
e. Medication:
i. Adenosine IV: Only if Narrow QRS Complex
a) Initial: 6mg rapid IV bolus
b) Redose: 12mg IV bolus if no response from initial bolus within 1-2 min

5. Stable Tachyarrhythmia w/ Regular, Narrow QRS (<0.12s):
[Likely Sinus Tachycardia or Reentry SVT]
a. Interventions:
i. Establish IV access
ii. Vagal Maneuvers
a) Carotid Massage (listen to rule out carotid bruit first, perform on one side at a time)
b) Ask patient to perform Valsalva maneuver
iii. Consider Expert Consultation
b. Medication:
i. Adenosine IV
a) Initial: 6mg rapid IV bolus
b) Redose: 12mg IV bolus if no response from initial bolus within 1-2 min
iii. Beta-Blocker:
a) Esmolol:
1) Initial: 0.5mg/kg IV bolus
2) Redose: 0.5mg/kg IV bolus if no response within 2 min of initial bolus
3) Infusion: 50-300mcg/kg/min
b) Metoprolol:
1) Initial: 5mg IV over 1-2min
2) Redose: 5mg IV q5min to max dose of 15mg
iii. Calcium Channel Blocker:
a) Diltiazem:
1) Initial: 0.25mg/kg IV bolus over 2min
2) Redose: 0.35mg/kg in 15min
3) Infusion: 5-15mg/hr

6. Stable Tachyarrhythmia w/ Irregular, Narrow QRS (<0.12s):
Likely Atrial fibrillation, Atrial flutter, or Multifocal Atrial Tachycardia
a. Interventions:
i. Establish IV access
ii. Vagal Maneuvers
a) Carotid Massage (rule out carotid bruit 1st, perform on one side at a time)
b) Ask patient to perform Valsalva maneuver
iii. Consider Expert Consultation
b. Medication:
i. Beta-Blocker: Avoid in COPD/CHF

a) Esmolol:
1) Initial: 0.5mg/kg IV bolus
2) Redose: 0.5mg/kg IV bolus if no response within 2 min of initial bolus
3) Infusion: 50-300mcg/kg/min
b) Metoprolol:
1) Initial: 5mg IV over 1-2min
2) Redose: 5mg IV q5min to max dose of 15mg
iii. Calcium Channel Blocker:
a) Diltiazem:
1) Initial: 0.25mg/kg IV bolus over 2min
2) Redose: 0.35mg/kg in 15min
3) Infusion: 5-15mg/h
ii. Antiarrhythmic:
a) Amiodarone IV:
1) Initial: 150mg IV over 10min
2) Redose: 150mg IV over 10min q10min if rhythm recurs
3) Infusion: 1mg/min for 1st 6h, followed by 0.5mg/min

7. Stable Tachyarrhythmia w/ Regular, Monomorphic Wide QRS (>0.12s):
a. Interventions:
i. Establish IV access
ii. Consider Expert Consultation
b. Medication:
i. Adenosine IV:
a) Initial: 6mg rapid IV bolus
b) Redose: 12mg IV bolus if no response from initial bolus within 1-2 min
iii. Antiarrhythmic:
a) Amiodarone IV:
1) Initial: 150mg IV over 10min
2) Redose: 150mg IV over 10min q10min if rhythm recurs
3) Infusion: 1mg/min for 1st 6h, followed by 0.5mg/min
b) Procainamide IV: Avoid if prolonged QT/CHF
1) Initial: 20-50mg/min until rhythm abates or hypotension occurs, QRS duration increases >50% or max dose of 17mg/kg given
2) Infusion: 1-4mg/min
c) Sotalol IV: Avoid if prolonged QT
3) Initial: 1.5mg/kg IV over 5min

C. Pulseless Rhythms:
1. Types:
a. Shockable Rhythms:
i. Ventricular Fibrillation: Multiple sites of microreentry pathways within the ventricle that results in electrical pattern with no obvious P wave and lack of properly formed QRS complex.

ii. Pulseless Ventricular Tachycardia: Within a ventricle there is either a single foci that has increased automaticity or a single reentry circuit leading to repetitive depolarizations causing an inability to generate adequate coordination for cardiac output.

   b. Non-Shockable Rhythms:

    i. Asystole: Complete absence of electrical activity on EKG

    ii. Pulseless Electrical Activity (PEA): Evidence of electrical activity on EKG but no resulting mechanical cardiac output, i.e. no pulse or measurable blood pressure

2. Definition:

   a. Shockable Rhythm: Underlying arrhythmia stems from chaotic firing of electrical impulses. Goal of Cardioversion is to supply a shock to "reset" (depolarize) the electrical conduction system so that when the heart again repolarizes the normal electrical conduction system (SA, AV nodes, etc.) can resume command.

   b. Non-Shockable Rhythm: Underlying arrhythmia is not secondary to disorganized electrical impulses but rather the lack of electrical input or electromechanical dissociation. Therefore, applying an electrical shock to "reset" (depolarize the system) would not be of benefit.

3. Common Etiologies:

   a. Medications: Toxins (overdose on beta blockers, calcium channel blockers, opioids, etc.)

   b. Electrolyte disturbances: hyper/hypokalemia, Acidosis

   c. Stressors: hypovolemia, hypoxia, hypothermia

   d. Disease processes: tension pneumothorax, cardiac tamponade, pulmonary embolus, myocardial infarction

4. Management:

   a. History and Physical exam: CAB's

    i. Auscultation for heart sounds and palpation for distal pulses

    ii. Evaluate patency of airway

    iii. Supply supplemental oxygen and provide respiratory support as required to maintain $SpO_2 > 94\%$ and $PEtCO_2$ of 35-45mmHg

    iv. History: presenting illness, PMHx, medications, allergies, recent labs (CBC, BMP, ABG etc)

   b. Monitors:

    i. Continuous EKG, pulse oximetry, blood pressure monitoring, 12 lead EKG

   c. Treatment: Correct reversible causes

    i. Shockable Pulseless Arrhythmias:
    Likely Ventricular Fibrillation or Ventricular Tachycardia

    a) Interventions:

     1) Call Code

     i) Ask for Code Cart with Defibrillator.

     ii) Have available staff obtain IV access and attach defibrillator pads on

patient.

2) Begin CPR Until Defibrillator Available

  i) Confirm placement of CPR board under patient.

  ii) 30 compressions:2 breaths

  iii) Rate of 100 compression/min

  iv) Can attempt to establish definitive airway but this should not delay CPR.

3) Defibrillation

  i) Continue CPR until defibrillator pads attached and ready for rhythm analysis.

  ii) Tell staff to stand clear of patient and contacting surfaces.

  iii) Deliver initial shock of 120-200J.

4) Resume CPR

  i) Complete 5 cycles (~2min)

5) Rhythm Analysis: EKG findings and Pulse Analysis

  i) Return of Circulation:

   — Definition:

   — • Palpable pulse or arterial pressure tracing evident with intra-arterial monitor

   — • Sustained increase in $PEtCO_2$

   — Treatment:

   — • Optimize Ventilation & Oxygenation ($SpO_2 > 94\%$, $PEtCO_2$ 35-40mmHg)

   — • Treat Hypotension: Fluids/Vasopressors

   — Work-up

   — • EKG, CXR

   — • Labs: ABG, BMP, CBC, glucose

   — Procedures/Intervention:

   — • Induced Hypothermia: Consider this if patient remains unresponsive despite return of circulation.

   — • Coronary Reperfusion Tx: Consider if high likelihood of STEMI or MI.

   — Consult Cardiology

ii. Shockable Rhythm: V-Fib or Pulseless V-Tach

  a) Defibrillate 100-200J

  b) Resume CPR x5 cycles (~2min)

   1) During CPR give Epinephrine 1mg IV q3-5 min.

  c) Repeat Rhythm analysis

   1) If Shockable Rhythm, repeat these steps above.

   2) If Return of Circulation, follow previously outline recs.

   3) For Non-Shockable Rhythm, see below.

iv. Non-shockable Rhythm: Asystole or PEA
  a) CPR x 2min
    1) Give Epinephrine 1mg 3-5min during CPR.
  b) Repeat Rhythm Analysis
    1) If Non-Shockable Rhythm, repeat these steps above
    2) If Return of Circulation, follow previously outline recs
    3) If Shockable Rhythm, follow previously outline recs

iii. Non-Shockable Pulseless Arrhythmias:
  Likely Asystole or Pulseless Electrical Activity (PEA)
  a) Interventions:
    1) Call Code
      i) Ask for Code Cart with Defibrillator.
      ii) Have available staff obtain IV access and attach defibrillator pads on patient.
    2) Perform CPR for 2 min
      i) Confirm placement of CPR board under patient.
      ii) 30 compressions:2 breaths
      iii) Rate of 100 compression/min
      iv) Can attempt to establish definitive airway, but this should not delay CPR.
      v) Give Epinephrine 1mg IV q3-5min while performing CPR.
    3) Rhythm Analysis: EKG findings and Pulse Analysis
      i) Return of Circulation:
        — Definition:
        — • Palpable pulse or arterial pressure tracing evident
        — • Sustained increase in PEtCO$_2$
  b) Treatment:
    1) Optimize Ventilation & Oxygenation (SpO$_2$>94%, PEtCO$_2$ 35-40mmHg)
    2) Treat Hypotension: Fluids/Vasopressors
  c) Work-up
    1) EKG, CXR
    2) Labs: ABG, BMP, CBC, glucose
  d) Procedures/Intervention:
    1) Induced Hypothermia: Consider this if patient remains unresponsive despite return of circulation
      i) Coronary Reperfusion Tx: Consider this if high likelihood of STEMI or MI
  e) Consult Cardiology

vi. Shockable Rhythm: V-Fib or Pulseless V-Tach
  a) Defibrillate 100-200J
  b) Resume CPR x5 cycles (~2min)
    1) During CPR give Epinephrine 1mg IV q3-5 min.

c) Repeat Rhythm analysis
  1) If Shockable rhythm, repeat outlined these steps above.
  2) If Return of Circulation, follow previously outline recs.
  3) For Non-Shockable Rhythm, see below.
  4) Non-Shockable Rhythm: Asystole or PEA
d) Resume CPR and repeat above steps

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Questions
5.01 Immediately following elective intubation of a 24yo paraplegic male for airway protection during endoscopy, he is noted to be in asystole. Induction agents included lidocaine, propofol, succinylcholine, and fentanyl. What is the correct sequence of events that should occur during this code?
  E. Confirm placement of ETT, begin chest compressions, give Epi/Calcium/Bicarbonate/Insulin&Glucose
  F. Begin Chest compressions, give Epi, cardiovert as soon as defibrillator is available, confirm placement of ETT
  G. Begin Chest compressions, Confirm placement of ETT, give epi/calcium/bicarbonate/insulin&Glucose
  H. Begin Chest compressions, give Epi, Confirm placement of ETT

5.02 What is the most common cause of cardiac arrest in the pediatric population?
  A. Congenital cardiac malformation
  B. Asphyxia
  C. Hypovolemia
  D. Ischemic insult

5.03 What is the most reliable method of detecting proper Endotracheal Tube placement?
  A. Bilateral breath sounds
  B. ETCO$_2$
  C. Ascultation over stomach
  D. Misting within endotracheal tube

6. Ethical Issues in the ICU

Jessica Reardon DO and Theresa Hartsell MD PhD

Key Points

• The four principles of medical ethics are autonomy, beneficence, non-maleficence, and justice.

• A patient should be assessed for capacity to make decisions. If they are not capable a surrogate decision maker should be appointed.

• Withdrawal of support is not withdrawal of care and patients have the right to refuse or accept life- sustaining treatments.

• The Principle of Double Effect states that an intervention is allowed if the intended outcome is in itself good even if it may have undesirable side effects.

A 55-year-old male collapsed at home and was sent to the emergency department. Upon arriving to the hospital, he was found unresponsive with a Glasgow Coma Score of 6. He was intubated, stabilized, and underwent a CT scan which showed a massive intracerebral hemorrhage. After emergent craniectomy for cerebral decompression, he was sent to the ICU. It has been five days since the event with little change in his clinical picture. A family meeting will occur with physicians, nurses, and social work to discuss goals of care with his wife and daughters.

During the family meeting, the care team discovers that the patient did not have an advance directive. However, his wife, who is now acting as his surrogate decision maker, states that her husband would never have wanted to live chronically on the ventilator with artificial nutrition if there was little chance for recovery. After being updated regarding his overall clinical picture, the wife makes the difficult decision to withdraw ventilator support.

Prior to withdrawal of ventilator support, the patient is examined for neurologic function. It is determined that the patient can be clinically diagnosed as having "brain death." After informing the family, his wife says that her husband is an organ donor and would want to donate his organs to others.

Ethical issues occur frequently in the intensive care unit. For patients who are critically ill or near the end of life, difficult decisions regarding their treatment plan often need to be made. When approaching discussions with the family of a critically ill patient, a care plan should generally be described within 48 hours after admission. There are four core principles in medical ethics that provide a framework to guide the care process of a medical provider: autonomy, beneficence, non-maleficence, and justice. (Table 6.1)

After the initial conversation, a discussion should occur about the patient's beliefs, values, and goals. Updates should be provided to both the patient and his or her family. This will help to build a relationship between the care team (physicians, nurses, social workers, etc.) and the family along with identifying any needs of support for the family.

Patients may often have medical conditions that can preclude them from making "capable" decisions, ultimately affecting their autonomy. In assessing individual patients, the provider will want to make sure that the

patient can communicate, understand the outlined treatment, reason, and comprehend the risks and benefits of accepting treatment.

If the patient is deemed not capable of making his or her own decisions, a surrogate decision maker can be identified to be their "voice." Frequently patients do not have a previously appointed surrogate decision maker. In these cases, relatives are used in the following order (which can vary legally state to state):
 - Spouse (court recognized)
 - Adult child or majority of adult children available to decide
 - Parents
 - Siblings
 - Nearest living relative
 - Close friends.

There can be disputes among relatives as to who is appointed surrogate decision maker. Alternatively, once a surrogate decision maker is appointed, conflict may arise when a treatment plan has been decided. If this is the case, the hospital's ethics committee may be contacted to weigh in on any disagreements that cannot be resolved.

There are various instruments that help guide treatment based upon the pre-determined wishes of the patient. Advance care planning encompasses a wide range of documents whose goal is to outline the patient's wishes when the patient is unable to voice them during a critical illness. These documents help to guide the surrogate decision maker and health care team about what the patient would or would not have wanted. This may place less stress and anxiety on those making the decisions.

Under the tenet of advance care planning, these instruments include a health care proxy or durable power of attorney for health care along with advance directives. A health care proxy is a surrogate designated by the patient on a written document who will make health care related decisions in the event the patient is unable to do so themself. Advance directives include documents like living wills or instructional directives, which can include specific interventions in the event of certain scenarios such as respiratory failure or coma. These interventions relate to the patient's desire for artificial nutrition, cardiopulmonary resuscitation, ventilator support, invasive surgical measures, etc.

With advance care planning, the patient and family need to be pro-active and have discussions about his or her wishes at the end of life prior to a devastating event. Often, however, patients have not had this conversation and their surrogate decision maker and family are left making informed decisions about what the patient would have wanted. This can be an extremely stressful and emotional time for families. The health care team needs to anticipate the emotional stress on the families and help them through the difficult process.

Table 6.1: Principles of Medical Ethics	
Principle	**Explanation**
Autonomy	Patient has the right tho choose or refuse their treatment
Beneficience	Providers deliver care which is in the best interest of the patient
Non-maleficence	In providing care, do no harm to the patient
Justice	Providing "fair" care such as allocating resources equally or systematically among patients

Withdrawal of Life Support

Whether or not an advance directive is present, a patient or their surrogate decision maker has the right to change their preferences regarding care treatments as their clinical condition changes. This allows one to adapt as more information is known. Included in this are decisions to withhold and withdraw specific medical interventions. It is important to keep in mind that withdrawal of support is not withdrawal of care. Providers are still caring for the patient in a different manner. There are often ethical misconceptions about withdrawing or withholding medical support, which include patient abandonment, violation of the principle of beneficence, or sedatives hastening death. (Table 6.2)

Table 6.2: Common Ethical Misconceptions Regarding Foregoing or Withdrawing Support	
Misconception	**Explanation**
Patient Abandonment	In reality, the provider continues to care for the patient with other interventions such as pain control and psychosocial support to make the transition from one intervention to another as comfortable as possible in conjunction with patient or family wishes.
Violates the principle of beneficience	For some patients, letting them die in a manner that is consistent with their end-of-life wishes would carry out their best interest. This may mean withdrawing support, even if without this support it may lead to death sooner.
Administering sedatives or analgesics hastens death	Under the "principle of double effect," administering analgesics for pain control is defensible since the intended act of providing relief is the goal of administration. Side effects such as respiratory depression and possibly death may occur but are not the intention.

The Principle of Double Effect states that an act which may ultimately have undesirable side effects is permissible if the intended outcome is in itself good, is not intended to do harm, and outweighs the bad. This is starkly different from physician-assisted suicide or lethal injection. With few exceptions, the majority of states in the United States do not permit physician-assisted suicide. A physician cannot be actively involved in intentionally causing the death of a patient, even if it is in accordance with the patient's wishes.

In the United States, there is no ethical difference between withholding or withdrawing treatment. It may, however, be hard for families to withdraw life support once it has been initiated. Over the years, there have been several public court cases about withdrawal of life-sustaining support such as Karen Ann Quinlan in the 1970s (involving withdrawal of ventilator support) and more recently Terri Schiavo in 2005 (involving withdrawal of nutritional support). These cases among others have set precedence on current ethical standards in the clinical practice.

Prior to life sustaining therapy being withdrawn, there are several considerations that should be addressed. The family needs to be informed about what to expect, whether that be irregular breathing if taken off of the ventilator or a slower wasting if nutritional

support is withdrawn. It should be emphasized that pain relief will be a primary consideration and a plan for narcotics or sedatives/anxiolytic agents should be available.

In many institutions, there are protocols established to guide withdrawal of life support in the most humane way. Ultimately the amount of time until death after support is withdrawn is difficult to predict. For example, the time to death after withdrawal of mechanical ventilation usually occurs within 24 hours but can range from minutes to days or months or, in extreme cases, years.

Additionally, the family should be prepared emotionally for the dying process. In some facilities a palliative care service should be involved as emotional and psychological support and aid in the bereavement process. Clergy and social work should also be involved to provide spiritual and long-term support. Efforts should be made to contact anyone who would have an interest in seeing the patient prior to withdrawal of life support.

Documentation in the process is also important and a do-not-resuscitate order should be completed. This order will detail what is and is not desired by the family in caring for the patient. This can include the decision to withhold vasoactive medications for blood pressure support, intubation with mechanical ventilation, or cardiopulmonary resuscitation, specifically chest compressions or defibrillation.

Organ Donation

Providers in the intensive care unit must be able to recognize prospective organ donors prior to death. Donated organs can be recovered after the patient meets criteria for brain death or cardiac death. In the United States, over half of the kidneys transplanted and the majority of other solid organs (lungs, heart, liver) are obtained from deceased donors. Legally, organ donation can only be completed when consent is obtained.

Once a potential organ donor has been identified, an organ procurement organization (OPO) referral should be made. While hospital policy varies, a referral to the OPO is usually made prior to withdrawing life support or after meeting criteria for brain death. In accordance with state law variability, disclosure of confidential patient information is allowed per HIPAA to determine eligibility as an organ donor.

The definition of brain death is the irreversible loss of brain functioning. Clinical exam findings and/or neuroimaging have to support an acute central nervous system catastrophe. Reversible conditions such as electrolyte imbalances, acid-base disorders, drug intoxication, anesthetic agents, endocrine disturbances, and hypothermia need to be corrected. Exact limits for core temperature and BP are determined by each state. Additionally, there should be absence of high spinal cord injuries, neuromuscular diseases, or locked-in syndromes.

There are specific diagnostic criteria for brain death and these include unresponsiveness, absence of autonomic reflexes, absence of brainstem reflexes, and apnea. In the United States, rules for determining brain death vary by state and individual hospital policy. Typically two separate physicians, usually in the fields of Neurology, Neurosurgery, Internal medicine, Pediatrics, or Anesthesiology, need to agree upon brain death and sometimes these exams must be a designated number of hours apart, i.e 6. The 2010 updated guidelines on determining Brain Death determined there is insufficient evidence to recommend a minimal observation period and states that one neurologic

exam is sufficient. The criteria for brain death can either be made by clinical exam, see below, or in some places it can be made radiographically, i.e. cerebral blood flow exam. However, according to the 2010 update on determining brain death in adults, there is currently insufficient evidence to demonstrate if ancillary tests can accurately determine brain death. You need to familiarize yourself with your individual hospital policies and state laws. (Table 6.3)

Brain death will cause several pathophysiologic responses and a donor may need to be supported to maintain perfusion and viability of transplantable organs. This may include maintaining hemodynamic stability, administering fluid, medications or vasoactive agents, and maintaining normothermia. While fatal arrhythmias do occur, systemic hypotension is the most common issue in brain death donors. In addition, there is often endocrine-hypothalamic-pituitary dysfunction, which may manifest as diabetes insipidus, hypoglycemia or hypothermia.

Organ donation after cardiac death involves withdrawal of life-sustaining therapies in or near the operating room setting. Families may or may not elect to be present at the

Table 6.3: Basic Findings to Diagnose Brain Death	
Finding	**Explanation**
Unresponsiveness/Coma	Absence of spontaneous or elicited motor activity (i.e. withdrawal, decorticate or decerebrate posturing)
Absence of autonomic response	Absence of change in blood pressure or heart rate to noxious stimulus in all extremities (i.e. nail bed pressure)
Absence of brainstem reflexes	No pupillary constriction to light No oculocephalic reflex No corneal reflex with light touch No grimacing No gag or cough reflex with posterior pharynx stimulation or bronchial suctioning
Apnea	Draw an arterial blood gas prior to disconnect from ventilator, which must show normal pH or normocapnea. Continue monitoring with pulse oximeter, blood pressure cuff/arterial line, and electrocardiography. Disconnect from ventilator and provide oxygen flow through endotracheal tube of 4-10 liters/minute. Repeat arterial blood gas every 5 minutes while off of ventilator. Test can take as long as 15 minutes if there is no respiratory effort, no hypotension (<90 mmHg) or desaturation (SaO_2 <90%). Apnea test is positive if: - No respiratory movements - $PaCO_2$ rises to > 60 mmHg or $PaCO_2$ rises >20 mmHg above initial $PaCO_2$

time of withdrawal of life support. If the family chooses to be present, life support will usually be withdrawn in an induction room where the family may say goodbye after death. A patient is pronounced dead if after five minutes there is an absence of circulation (pulselessness), along with apnea, unresponsiveness, and asystole on electrocardiograph. Once death is certified, the patient is moved to the operating room where organ procurement takes place. No organs can be procured until a physician who is not involved in the transplantation service has certified death.

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Questions

6.1 After you have explained the risks and benefits of chemotherapy to a patient recently diagnosed with leukemia, she has decided not to proceed with chemo and has instead said that she wishes to spend the rest of her days at home with her family. This is an example of which of the four principles of medical ethics?
   A.   Autonomy
   B.   Beneficence
   C.   Non-maleficence
   D.   Justice

6.2 A patient has suffered a massive heart attack and is now intubated and on full support including a balloon pump. He did not have a living will but who of the following would qualify as his surrogate decision maker:
   A.   His mother
   B.   His brother
   C.   His best friend
   D.   His wife

6.3 The Principle of Double Effect justifies:
   A.   The practice of euthanasia with the primary goal of hastening death
   B.   A provider withholding supportive treatment
   C.   A treatment, which will benefit a patient but may have undesirable side effects
   D.   Allocating resources differently among patients

6.4 All of the following are brain stem reflexes used in determining brain death except:
   A.   Oculocephalic reflex
   B.   Corneal reflex
   C.   Gag reflex
   D.   Cervicocollic reflex

6.5 The most common complication seen in patients after brain death is:
   A.   Fatal arrhythmia
   B.   Hypothermia
   C.   Hypotension
   D.   Oliguria

Section 2: Monitoring

Chapters

- **Routine Monitoring**

- **Pulse Wave Monitoring**

- **Ultrasound in the ICU**

- **Point of Care Testing**

7. Routine Monitoring

Ilya Treskov MD, Thomas J Graetz MD and Brian Wessman MD

Key Points

• **Continuous hemodynamic monitoring of the ICU patients is imperative for the early detection of a worsening disease process and a timely response to deterioration.**

• **Standard monitors include EKG, pulse oximetry, blood pressure, temperature as well as capnography on patients who require mechanical ventilation.**

• **Rapid interpretation and integration of the results from the physical exam and various monitors in the ICU setting as well as the knowledge of potential pitfalls is essential for the safe and effective management of critically ill patients.**

A 78 y/o male with h/o CAD, hypertension, poorly controlled Type 2 Diabetes and COPD is admitted to the ICU for the management of respiratory failure and hypotension requiring significant vasopressor support. A-line is placed for blood pressure monitoring and frequent arterial blood sampling. BP is 100/60.

Blood pressure

Manual BP: Indirect measurement of systolic blood pressure (SBP) and diastolic blood pressure (DBP) based on the auscultation of Korotkoff sounds.

• Background:
- An appropriately sized BP cuff is inflated above SBP and slowly deflated
- When the cuff pressure drops below SBP, turbulent flow during systole is auscultated as the first Korotkoff sound
- When the cuff pressure drops below DBP, the cuff no longer compresses the artery and the disappearance of turbulent flow is auscultated as the second Korotkoff sound
- Mean arterial pressure (MAP) is calculated according to the formula
MAP = 1/3 Systolic BP+ 2/3 Diastolic BP

• Caveats:
- An inappropriately sized cuff produces erroneous measurements: A cuff too small over-estimates BP; A cuff to large under-estimates BP.
- BP Cuff width should be about 40% of the limb's circumference. Markings on most BP cuffs confirm appropriate fit.
- BP cuff must be placed at the level of the heart: A cuff too low over-estimates BP; A cuff too high under-estimates BP (error ~ 0.75 mmHg for every cm above or below the heart)
- Avoid placement of BP cuff on the side of radical mastectomy, PICC line, fast-flowing peripheral IV and

AV-fistulas
- A discrepancy between measurements of BP on different limbs may be caused by significant peripheral vascular disease

Automatic BP (Oscillometric method): An indirect measurement of SBP and DBP based on the detection of oscillations within the BP cuff

• Background:
- BP cuff is inflated above SBP and slowly deflated.
- The expansions and contractions of the pulsating artery are transmitted to the BP cuff and detected as pressure oscillations.
- As the cuff deflates, oscillations gradually increase between SBP and MAP and decrease between MAP and DBP.
- The point corresponding to maximum amplitude of oscillations approximates MAP.
- SBP and DPB are calculated according to complex, generally proprietary, algorithms.

• Caveats:
- BP cuff size and position (as above)
- Because automatic BP measurement relies on the detection of oscillations, shivering and excessive movement may lead to erroneous measurements.

Invasive BP: Direct measurement

• Background:
- SBP and DBP are measured via a pressure transducer connected to an arterial catheter with a fluid filled, non-compliant tubing. MAP is obtained by calculating the area under the curve.

• The indications for invasive blood pressure monitoring:
- Ongoing or anticipated hemodynamic instability
- Requirement of significant vasopressor support
- Frequent arterial blood sampling
- Poorly pulsatile blood flow in patients receiving LVAD or ECMO support
- Anatomic reasons making other methods of measurement difficult

• Location:
- Most common: Radial artery
  i. Advantages: superficial anatomical location, relative distance from large veins and nerves as well as considerable collateral circulation
  ii. Disadvantages: Relatively small arterial diameter means the catheter occupies a significant portion of the intraluminal space, impeding the flow and increasing the risk of arterial thrombosis (risk of thrombosis with 18g is increased relative to 20g catheter); a modified Allan's test may be utilized to assess collateral circulation although its utility is disputed.
- Alternatives: Femoral, axillary, brachial, temporal and dorsalis pedis arteries.
- As the arterial line is placed more peripherally, the systolic pressure will be greater and the diastolic pressure slightly lower. The MAP will be the same no matter where the pressure is measured.
- In patients with VA ECMO (particularly peripheral ECMO), the A-line is preferentially placed in the right radial artery to allow for sampling of the arterial blood that reflects oxygen saturation supplied to the brain

• Caveats
- Injection of air bubbles or medications into an A-line may lead to limb ischemia and necrosis.
- The arterial catheter is kept patent by the infusion of fluid (3ml/hr) from a pressure bag; ensure pressure bag remains inflated adequately.
- BP transducer is generally placed at the level of the heart (or other locations, ex: Circle of Willis): If the transducer is too low, the measured pressure over-estimates BP; If the transducer is too high, the measured pressure under-estimates BP.
- An artifactual amplification of pressure waves (whip) or dampening of A-line pressure tracing may result in over-estimation and under-estimation of SBP respectively.

Given the difference in the technique of measuring the manual, oscillometric and invasive BP, some differences between the obtained values are expected. Large disparities in measurements that impact hemodynamic management, however, need to be meticulously investigated to exclude sources of inaccuracy.

Pulse Oximetry
• Background:
- The pulse oximetry probe utilizes LEDs emitting 2 wavelengths:
  • 660nm (Red) – is predominantly absorbed by Deoxy-Hb
  • 940nm (Infrared) – is predominantly absorbed by Oxy-Hb
- Ratio of 660nm/940nm absorbance is the percentage of Hb Saturation
  • Since both arterial and venous blood flows under the pulse-ox probe, the computer calculates arterial Hb saturation by looking for the pulsating, absorbance pattern (thus pulse-ox). The graph of pulsating absorbance is displayed on the monitor next to the oxygen saturation result (Plethysmographic trace).

• Caveats:
- In the absence of an adequate plethysmographic trace, the result of pulse ox may be a random number generator!
- Nail polish (especially blue) may cause inaccuracy in pulse-ox reading
- CO poisoning: Since CO replaces O_2 at the same binding site on Hb molecule, the absorbance of CarboxyHb and OxyHb at 660nm is the same. Therefore, the pulse ox will continue to report adequate saturation despite impaired O_2 transport.
- Methemoglobinemia: Pulse-ox is about 85% with little response to supplemental O_2. List of potential causes is very long! Note:
  - Benzocaine (ingredient of Cetacaine spray)
  - Prilocaine (ingredient of EMLA cream)
  - Nitric Oxide, Nitroglycerin, Sodium Nitroprusside
  - Acetaminophen overdose
  - An injection of dyes such as methylene blue and indigo carmine produces spuriously low readings
- An intense ambient light may interfere with pulse-ox. Cover pulse ox probe to improve plethysmographic trace.
- Since pulse ox is looking for pulsating pattern of light absorption, motion artifact (ex: shivering) is a potential source of inaccuracy

• The integration of information from various monitors may help recognize artifactual readings: If the EKG shows disorganized activity but A-line demonstrates regular pulse, EKG artifact is most likely.

EKG
• Background:
- ICU monitors typically analyze 7 leads: I, II, III, AVF, AVL, AVR and V5
- Placement mnemonic: smoke (black) over fire (red); brown - V5 (5th intercostal space mid-axillary line); white is right; snow (white) on the grass (green)
- V5 is most sensitive to ischemia (followed by V4).
- Lead II is most sensitive to arrhythmia.
- For precise EKG interpretation, get a 12 lead EKG.

• Interpretation:
- Rate: Bradycardia <60bpm; Tachycardia > 100bpm
- Rhythm:
  • Regular or Irregular?
  • P waves before each QRS?
  • Wide or narrow complex? Normal QRS < 120ms
  • Conduction block? Normal PR < 200ms
  • QT interval (prolonged by a variety of drugs) and corrected for heart rate; Normal QTc < 450ms in males and <470ms in females
- Axis:
  • I and AVF are positive, ⇒ axis is normal 👍👍(2 thumbs up!)
  • I ↓ AVF ↓ ⇒ extreme right axis deviation. 👎👎
  • I ↓ AVF ↑ ⇒ right axis deviation 👍👎
  • I ↑ AVF ↓ ⇒ left axis deviation (if lead II is negative) 👍👎
- Ischemia:
  • ≥1 mm ST-segment depression or T-wave inversion – ischemia
  • ≥1 mm ST segment elevation in ≥2 contiguous leads – acute MI

Temperature
• Background:
- Core temperature (PA catheter, tympanic membrane, bladder, rectal, esophageal)
- Surface temperature (skin, oral)

• Hypothermia
- Leads to confusion, delirium, delayed awakening from anesthesia.
- Shivering increases O_2 demand.

• Fever
- Greater than 42°C is associated with dysfunction of endogenous enzymes and multi-organ failure. Patient may require active cooling.
- Is deleterious in patients with ischemic, hemorrhagic or traumatic brain injury, post-cardiac arrest.

Capnometry
• Background:
- Measurement and graphical representation of partial pressure of CO_2 ($ETCO_2$) in expired gas

• Applications: (Figure 7.1)
- Confirmation of endotracheal intubation
- Assessment of cardiac output
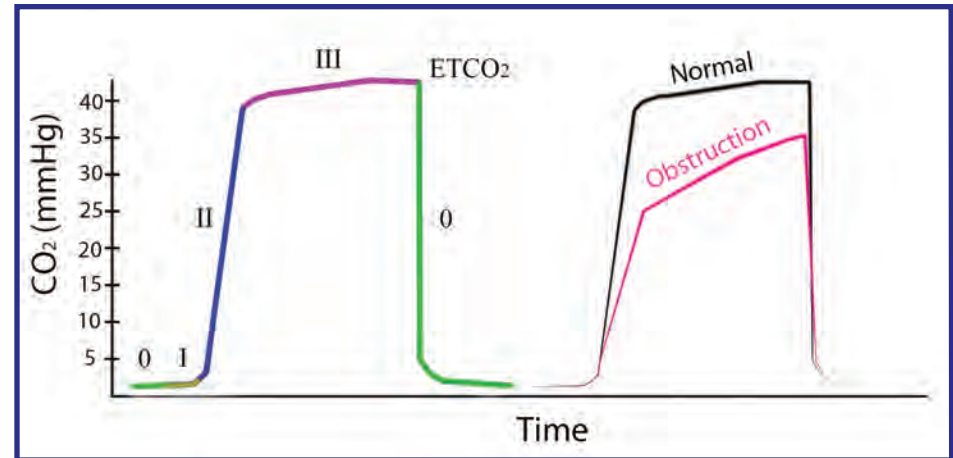
Figure 7.1 Capnogram
0 - Phase 0 (Inspiration); I - Phase I (Anatomical and apparatus dead space); II - Phase II (Mixture of dead space and alveolar gas); III - Phase III (Alveolar plateau)

- Morphology of capnometry waves
• Bronchospasm
• ETT tube occlusion
- Detection of esophageal intubation

• Interpretation of $ETCO_2$ numerical value:
- Normal 35 – 45 mmHg
- Decrease in $ETCO_2$:
  • Ventilation causes:
  - Hyperventilation
  • Circulation causes:
  - Pulmonary embolism
  - Decreased cardiac output
- Minimal or absent $ETCO_2$:
  • Equipment causes:
  - $ETCO_2$ sample line occlusion
  • Ventilation causes:
  - Apnea
  - ETT occlusion
  - Esophageal intubation
  - Bilateral pneumothorax
  • Circulation causes:
  - Catastrophic cardiovascular collapse
  - Massive PE
- Increase in $ETCO_2$:
  • Increase in metabolism/ production of CO_2:
  - Administration of Sodium Bicarbonate
  - Hyper-metabolic state (sepsis, hyperthyroidism)
  • Decrease in elimination:
  - Hypoventilation

In a code situation:
- Confirmation of chest compression effectiveness (goal: ETCO$_2$ 10-20mmHg)
- Detection of the return of spontaneous circulation (sudden rise in ETCO$_2$)

CVP
• Background:
- Measurement of venous blood pressure at the superior vena cava (SVC) – right atrium (RA) junction
- "Normal" CVP ~5-10 cmH2O

• A careful analysis of the CVP trace may aid in diagnosis of a variety of pathological condition including atrial fibrillation, complete AV block, tricuspid valve regurgitation and stenosis.

Figure 7.2 CVP Waveforms
A: Normal EKG; B: Normal CVP tracing; C: CVP tracing in atrial fibrillation;
D: CVP tracing with cannon a-wave, where atrial contraction occurs against a closed tricuspid valve

• CVP waveform: (Figure 7.2)
- a wave: An increase in the venous pressure caused by the right atrial (RA) contraction
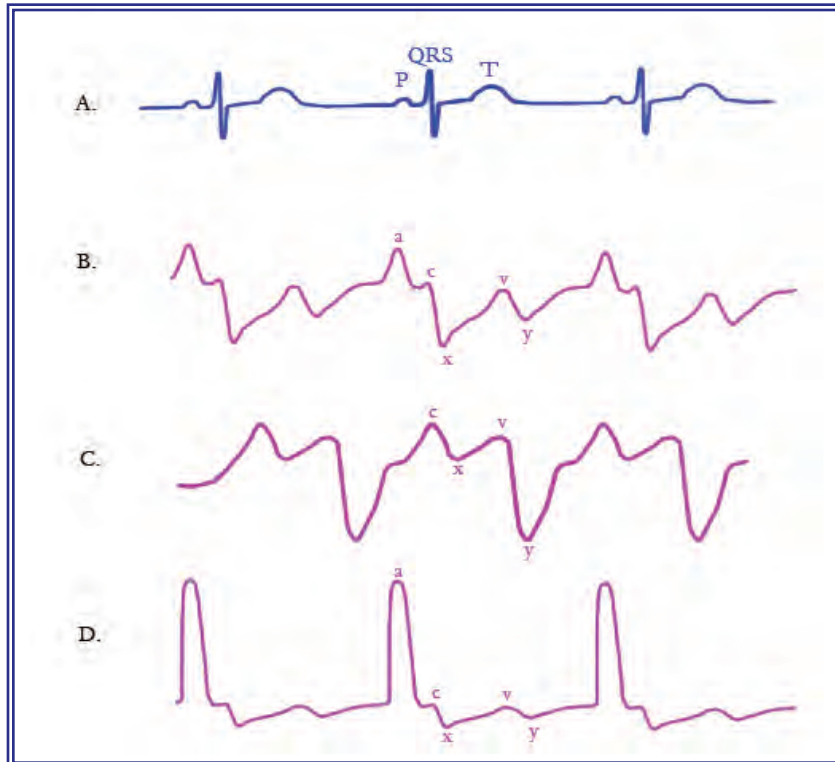- c wave: Motion of the tricuspid valve (TV) toward the RA during early right

ventricular (RV) contraction.
- x-descent: RA relaxation and downward displacement of the TV during systole
- v wave: Venous filling of RA against closed tricuspid valve, generally immediately after peak of T wave on EKG
- y-descent: Emptying of RA upon opening of the tricuspid valve (diastolic filling)

• Abnormal CVP waveforms:
- Atrial Fibrillation: obliteration of the a wave, prominent c wave
- Complete AV block: Cannon a waves

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Questions

7.1 A-line is placed for blood pressure monitoring and frequent arterial blood sampling. BP is 100/60. If the arterial line transducer was accidentally lowered by 80cm, what pressure will be displayed on the monitor?
- A.   180/140 mmHg
- B.   160/120 mmHg
- C.   100/60 mmHg
- D.   60/40 mmHg

7.2 What EKG lead is most sensitive to ischemia?
- A.   V5
- B.   V4
- C.   II
- D.   AVL

7.3 A patient suffers a sudden cardiac arrest and CPR is initiated. What is the best measure of the effectiveness of chest compressions?
- A.   O$_2$ saturation
- B.   BP
- C.   ETCO$_2$
- D.   pH

8. Pulse Wave Monitoring

Aalok Kacha MD PhD

Key Points

• **The adequacy of cardiac output should be based on individual patient assessment**

• **Static pressure measurements such as CVP and PCWP are not an accurate way to determine whether a patient is fluid responsive**

• **PPV and SPV are useful tools to guide fluid therapy in patients who meet criteria for their use**

You are taking care of a 57-year-old man with end-stage liver disease, now newly post-op orthotopic liver transplantation. In the ICU, his heart rate is 90/minute with a blood pressure of 90/50 mmHg with a declining urine output. He remains intubated on cisatracurium, propofol, and norepinephrine infusions. There are multiple invasive monitors in place including a pulmonary artery catheter and an arterial line. His chest X-ray is concerning for an alveolar filling process and you are unsure whether his declining urine output is best managed with administration of additional IV fluid or diuretic medications.

Arterial pressure monitoring

Invasive arterial monitoring is frequently used to measure blood pressure and for serial arterial blood gas analysis. An arterial catheter is connected to rigid fluid-filled tubing of a monitoring system. The fluid column in the tubing carries a mechanical signal created by the arterial pressure wave to the diaphragm of an electrical pressure transducer that converts the mechanical signal into an electrical signal. The electrical signal is transmitted to the monitor and then is amplified and displayed.

In order to assess the accuracy of the arterial pressure waveform, a fast-flush test is used. A brief flush can be applied to the catheter tubing system to determine whether the recording system is distorting the pressure waveform or not. Most systems are equipped with a one-way valve that can be used to deliver a flush from a pressurized fluid bag (usually at 300 mmHg). This flush causes the pressure to increase rapidly with a square wave tracing. Release of the flush should result in a return to baseline after several oscillations. An optimally functioning system has one undershoot and a small overshoot before returning to baseline. An overdamped waveform may be due to the presence of bubbles, clot, lack of flush solution, lack of pressure in the flush system, or excessive bends in the system tubing. Underdamping is usually due to excessive tubing length (> 200 cm) or the use of excessively stiff tubing.

As the pulse travels from the aorta to the periphery, the systolic pressure is amplified by reflected waves from the periphery. This pulse amplification results in distal measurements (e.g., radial artery) having a greater systolic pressure and slightly lower diastolic pressure compared to more proximal measurements (e.g., the femoral artery). The initial upswing (dP/dT) of the arterial waveform is called the anacrotic limb and changes

with cardiac contractility. It is steeper with the use of inotropes and shallower when contractility is impaired. The dicrotic notch signifies aortic valve closure.

Clinical assessment for fluid administration

The need to assess the intravascular volume status of a patient is commonplace in the intensive care unit and operating room. This is often prompted by clinical scenarios such as low urine output, low blood pressure, or high heart rate, suggesting that intravenous fluid therapy may be warranted. Other information such as chest auscultation, chest radiograph, examination of mucous membranes, or skin turgor has been used to guide clinical decision-making regarding fluid therapy. In addition to these clinical assessments, invasive monitoring of filling pressures has been traditionally used to guide fluid therapy in the intensive care unit and operating room.

The most commonly used of these is central venous pressure (CVP), which is readily assessed by transduction of a central venous catheter. The use of CVP monitoring is predicated on the assumption that this measurement reflects right ventricular preload. The assessment of left ventricular preload has traditionally been estimated by an analogous measurement of the pulmonary capillary wedge pressure (PCWP) obtained after placement of a pulmonary artery catheter. These pressure measurements of cardiac filling pressures have not been shown to be an effective tool for guiding fluid therapy. It is likely that this failure reflects the static nature of the measurements as an attempt to estimate preload or blood volume rather than dynamically determining the response to a fluid challenge.

In the clinical scenarios in which one is considering fluid therapy and wants to assess intravascular fluid status, the question that needs to be answered is whether there will be a clinically significant increase in cardiac output if fluids are administered. This question can be answered using the normal changes in stroke volume and cardiac output that occur with positive pressure mechanical ventilation.

Physiologic basis of pulse pressure variation and systolic pressure variation

The stroke volume varies throughout the respiratory cycle due to the interaction between venous return and cardiac function. Changes in pleural pressure affects the circulation by changing right and left ventricular loading and the pressure relationship between intrathoracic and extrathoracic structures.

During positive pressure inspiration, a decrease in vena caval flow is followed by decreases in pulmonary arterial flow and aortic flow. The initial decrease in venous return is likely to due to transmission of the increased pleural pressure to intrathoracic structures causing an increased right atrial pressure (hindering venous return) and compression of the intrathoracic vena cava. This decrease in venous return, via the Frank-Starling relationship, results in a decrease in right-sided cardiac output that results in a delayed (due to the pulmonary transit time of approximately 2 seconds) decrease in left ventricular preload and cardiac output. The left ventricle is also affected by inspiration: the positive pleural pressure decreases the transmural pressure required to eject blood into the aorta and thus effectively decreases left ventricular afterload.

In summary, with the delivery of a positive pressure breath, there is a decrease in venous return to the right ventricle and a decrease in the afterload of the left ventricle. These produce an increase in stroke volume during inspiration, due to the effect of the decreased left ventricular afterload. This increased stroke volume results in an inspiratory increase in systolic blood pressure and a greater pulse pressure (smaller effect on diastolic pressure). Subsequent stroke volumes will decrease, reflecting the previously decreased venous return to the right ventricle. These smaller stroke volumes will result in a delayed (after the positive pressure breath is delivered) decrease in systolic blood pressure and a smaller pulse pressure. For animated slides illustrating the intersection of the venous return and Starling curves, please refer to the supplemental material from Magder, 2004.

The dynamic changes in the interaction between venous return and cardiac function that occur with ventilation can be used clinically. The effects of the varying stroke volumes on beat-to-beat systolic blood pressure and pulse pressure can be observed in patients with an arterial line. Unlike static measures such as CVP and PCWP, the dynamic indices of pulse pressure variation (PPV) and systolic pressure variation (SPV) derived from pulse contour analysis have been demonstrated to be a useful guide to fluid therapy. Although the focus will be on PPV as it is most convenient index to obtain with automatic calculations by modern day monitoring equipment, SPV is readily accessible by examination of the arterial line. Since these phenomena are tied to changes in pleural pressure, they do occur in spontaneously ventilating patients as well, but their use in patients breathing spontaneously has not been completely validated.

Application of PPV

In patients who are fluid responsive, the intersection of the venous return and cardiac function curves is such that patients are on the steep portion of the Frank-Starling curve (Figure 8.1). This leads to larger changes in stroke volume, SPV, and PPV with mechanical ventilation as compared to patients in whom the intersection of the venous return and cardiac function curves occurs on the flat portion of the Starling curve (and who are not fluid responsive).
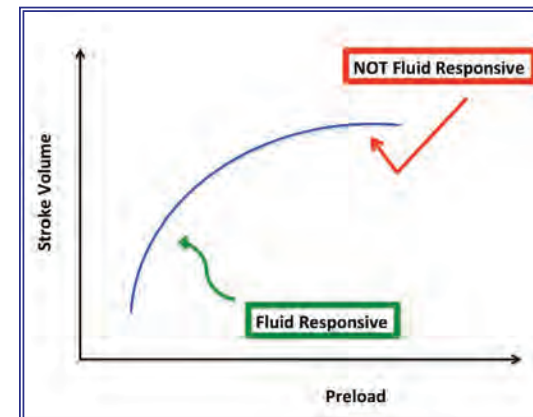
Figure 8.1 Frank Starling curve applied to PPV

The use of PPV to guide fluid therapy has been best characterized in patients with a controlled set of variables. This tool is most useful when all of the following conditions are met.
• Properly functioning arterial line and measurement system
• Regular cardiac rhythm without arrhythmias or extra-systoles
• Mechanical ventilation with tidal volumes of 8 mL/kg
• Passive interaction between patient and ventilator without triggered breaths or dyssynchrony

Pulse pressure variation (Figure 8.2) is calculated as a percentage based on the greatest and least pulse pressures measured during a respiratory cycle:

$$PPV = 100 \times (PP_{max} - PP_{min})/[(PP_{max} + PP_{min})/2].$$

In contrast, SPV is assessed using the end expiratory apneic systolic blood pressure as the baseline. With positive pressure ventilation, an increase in the systolic pressure is

referred to as delta up and a decrease as delta down (which correlates best with preload dependence and fluid responsiveness).

Although precise thresholds for the use of the PPV to determine fluid responsiveness vary, a PPV < 10% suggests that the patient will not be fluid responsive while a PPV > 15% suggests that the patient will be fluid responsive. These values can be used to guide fluid therapy, but consideration must be given to the clinical condition of the patient and the details of the clinical scenario, as differences in physiology may affect the interaction between the ventilator and cardiac output in any particular patient.

There are multiple limitations to the use of PPV that should be considered when using this tool.
• Malfunctioning arterial line and measurement system
• Irregular cardiac rhythm or frequent extra-systoles
• Mechanical ventilation with small tidal volumes (<8 ml/kg)
• Patient-ventilator dyssynchrony or spontaneous breathing
• Open-chest conditions
• Presence of right ventricular failure or pulmonary hypertension
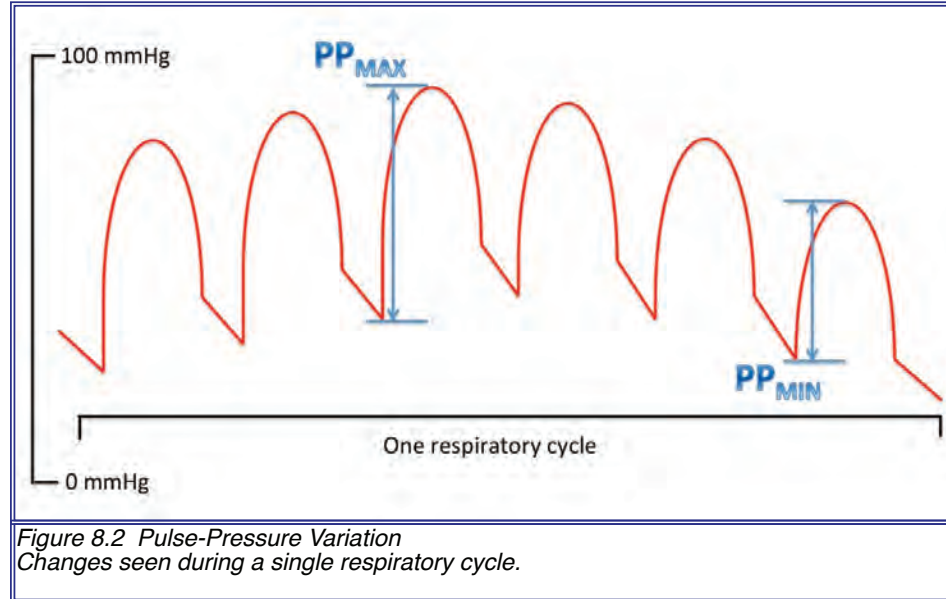

Figure 8.2 Pulse-Pressure Variation
Changes seen during a single respiratory cycle.

This chapter is a revision of the original chapter authored by Lalitha Sundararaman, M.D.

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Questions

8.1 A poor dP/dT on the arterial waveform would favor selection of which of the following drugs?

A. Vasopressin
B. Furosemide
C. Phenylephrine
D. Dobutamine

8.2 Of the following, which is the best to determine fluid responsiveness?

A. CVP
B. PPV
C. PCWP
D. Left ventricular end-diastolic area index

8.3 In a hypotensive patient with a normal cardiac function, which of the following could indicate the need for fluid therapy?

A. CVP 6 cm H_2O
B. PPV > 15%
C. PCWP 10 cm H_2O
D. PPV < 10%

8.4 The delta down on the systolic pressure variation reflects:

A. Preload
B. Afterload dependence
C. Contractility
D. Diastolic dysfunction

9. Ultrasound

Rohit Patel MD

Key Points

• Point of care ultrasound has been shown to make an impact on decision making and improve patient outcomes

• Lung ultrasound has had increased use over the past ten years and continues to have evidence base for use in the critically ill patient

• Reproducibility is probably one of the most important aspects of point of care critical care ultrasound

A 59 year old obese male with a history of pulmonary hypertension arrives to the intensive care unit after coronary artery bypass grafting and mitral and aortic valve replacement. The patient is intubated and receiving therapy with norepinephrine and epinephrine infusions but continues to be hemodynamically unstable with a heart rate of 123, blood pressure of 83/58, and oxygen saturation of 92% on 100% oxygen. Central venous pressure is estimated at 16 and pulmonary pressures are estimated at 57/34 with a pulmonary artery occlusion pressure of 23.

Introduction

Ultrasonography use is becoming an indispensable tool in the practice of critical care medicine. Its safety and portability allow for rapid noninvasive bedside assessment to aid in diagnosis and ongoing management of critically ill patients. In particular the etiology of hemodynamic instability can be difficult to ascertain in patients with cardiac pathophysiology without the use of this diagnostic tool. Other ultrasound modalities useful in the intensive care unit are vascular ultrasound (for access and evaluation of thrombosis), abdominal ultrasound (for evaluation of free fluid, aorta pathology), lung ultrasound (for evaluation of pleura, pneumothorax, interstitial edema, pleural effusion, and consolidations including pneumonia or atelectasis). The American College of Chest Physicians and Society of Critical Care Medicine have made recommendations on critical care ultrasound competencies[1,2]. Resuscitation efforts are frequently redirected based on ultrasound findings. Also it has been shown in recent literature that ultrasound has a high impact on management decisions made in the intensive care unit[3]. Lung ultrasound also has made great advances over the past 10 years and has become more useful in the evaluation of the acute hypoxic patient[4, 5].

Both transthoracic and transesophageal echocardiography can be used to evaluate cardiovascular compromise. Various 'protocols' have been developed in evaluation of the acute hypotensive patient (RUSH, FATE, FEEL, CAUSE, etc), but more importantly it is critical to remember to use the findings and the appropriate clinical setting to make the decision. As the clinician taking care of the patient and the operator of ultrasound image acquisition, the clinician has the advantage of making immediate decisions and impact on patient care. Ultrasound in the ICU has changed from organ specific evaluation to problem based evaluation. A prime example of this is how abdominal evaluation in trauma has been renamed from FAST (Focused Abdominal Sonog-

raphy in Trauma) to FAST (Focused Assessment with Sonography in Trauma), which shows a change from focus of organ (abdomen) to focus of problem (trauma).

The case presentation illustrates the difficulty that can be encountered when treating hemodynamic instability. Despite both epinephrine and norepinephrine infusions the patient continues to exhibit a poor hemodynamic status. Although central venous and pulmonary catheter data are available, the diagnosis remains elusive. The clinical picture is consistent with left ventricular failure but is also compatible with right heart failure, valvular dysfunction or cardiac tamponade. Echocardiography can provide real time images to distinguish between these etiologies.

Ultrasonography, particularly echocardiography, requires a formal education. The outline below simply aims to provide a basic understanding of the use of ultrasonography in the critically ill patient and therefore cannot substitute for formal training in critical care ultrasound[1,2].

More information is available online from the author's fellowship education curriculum site at http://ccm.anest.ufl.edu/education/ultrasound.

Didactics (http://ccm.anest.ufl.edu/education/ultrasound/didactics-self-learning-tests/): the following are applications and particular situations where they may be useful. Refer to more comprehensive resources on each individual topic listed.
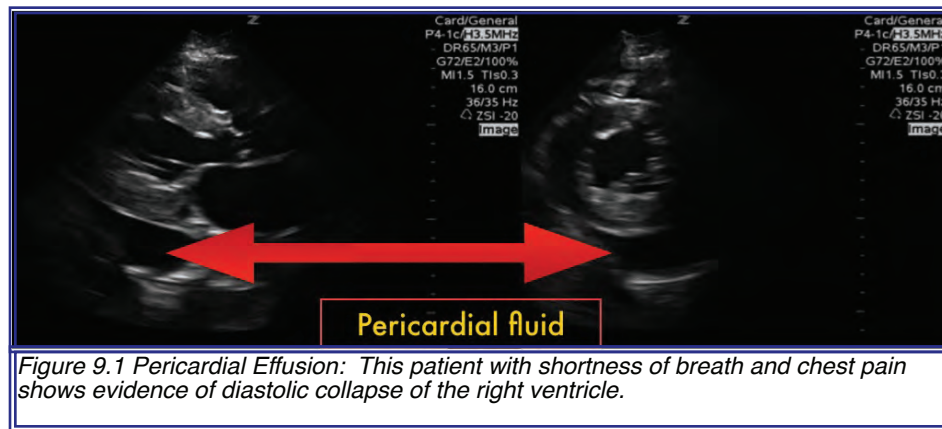
Examinations

Figure 9.1 Pericardial Effusion: This patient with shortness of breath and chest pain shows evidence of diastolic collapse of the right ventricle.

Cardiac
A. Indications
  1. Hemodynamic Instability
    a) Ventricular Failure
    b) Hypovolemia
    c) Pulmonary Embolism
    d) Acute Valvular Dysfunction
    e) Cardiac Tamponade
  2. Complications after Cardiothoracic Surgery
    a) Infective Endocarditis
    b) Suspected Aortic Dissection or Rupture

c) Unexplained Hypoxemia
    d) Sources of Emboli
  3. Chest Trauma with Hemodynamic Compromise
B. Indications for TEE over TTE - High image quality is vital
  1. Aortic Dissection
  2. Endocarditis
  3. Intracardiac Thrombus
  4. Structures that may be inadequately seen on TTE
    a) Thoracic Aorta
    b) LA Appendage
    c) Prosthetic Valves
  5. Patient conditions that prevent image clarity on TTE
    a) Severe Obesity
    b) Emphysema
    c) High PEEP
    d) Surgical drains, Incisions, Dressings
C. TEE Complications
  1. Odynophagia: 0.1%
  2. Dental Injury: 0.03%
  3. Endotracheal Tube Dislodgment: 0.03%
  4. Esophageal Perforation: 0.01%
D. Contraindications to TEE
  1. Absolute
    a) Esophageal Stricture
    b) Esophageal Mass
    c) Esophageal Diverticulum
    d) Mallory-Weiss Tear
    e) Dysphagia/Odynophagia Unevaluated
    f) Cervical Spine Instability
  2. Relative
    a) Esophageal Varices
    b) Recent Esophageal/gastric Surgery
    c) Oropharyngeal Carcinoma
    d) Upper GI Bleeding
    e) Severe Cervical Arthritis
    f) Atlantoaxial Disease
E. Echocardiography findings in hemodynamic instability (LV function best assessed at the parasternal short papillary muscle level) - hypovolemic, cardiogenic, obstructive shock all have specific findings.
F. Hypovolemic Shock
  1. Decreased End-Diastolic Area
  2. "Kissing" Papillary Muscle
  3. Hyperdynamic Function
G. Cardiogenic Shock
  1. Failing Left Ventricle
    a) Decreased Area Change
    b) Increased End-Diastolic Area
    c) Increased End Systolic Area
  2. Failing Right Ventricle
    a) Increased Right Ventricular Size
    b) Intraventricular Septum bulges towards Left Ventricle
    c) Pulmonary Embolus if echogenic density present
  3. Valvular Pathology

a) Mitral Regurgitation
b) Mitral Stenosis
c) Aortic Regurgitation
d) Aortic Stenosis
4. Cardiac Tamponade
a) Pericardial Effusion
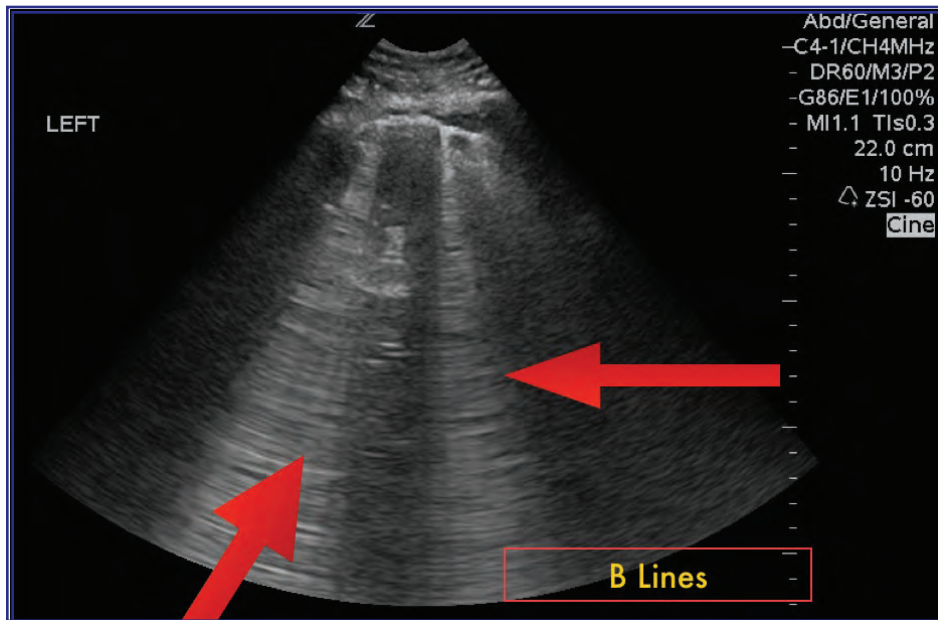b) Diastolic Collapse of Right Ventricle

Figure 9.2 Lung exam: Anterior chest B lines are seen in a patient with hemodynamic pulmonary edema initially suspected to be COPD. Based on this ultrasound, the patient was given diuretics and/or afterload reducing agents to treat the acute exacerbation of CHF with a BP 200/100.

Lung
A. Pleural
  1. Pneumothorax Identification - absence of lung sliding, and lung point which you can see part of the pleura sliding and the other part absent sliding, indicates pneumothorax and can estimate size based on location
  2. Effusion Identification, Characterization and Quantification - quad and sinusoid signs, anechoic space between diaphragm and lung. This can be used to estimate size, and lung pathology
  3. Guidance during Thoracentesis - can use vascular probe to visualize rib space in obese patients, as well as best approach
B. Lung
  1. Identification of Aerated Normal Lung - in respiratory failure patients can signify obstructive lung disease (COPD, asthma) or pulmonary embolism - "A" lines which are horizontal lines and represent reverberation artifacts of the pleural line
  2. Identification of Consolidated Lung with or without Air Bronchograms - can use to differentiate atelectasis from pneumonia - "B" lines without lung sliding can indicate pneumonia
  3. Identification of Pulmonary Edema (Interstitial syndrome) - "B" lines with lung sliding found in anterior lung zones

Vascular
A. Identification of Deep Vein Thrombosis - non-compressible vein
B. Vascular Access (central vein, artery, hemodialysis): Dynamic guidance is when the procedure is performed under direct guidance, with real time view of the needle. Other methods of use include blind and semi-blind techniques.
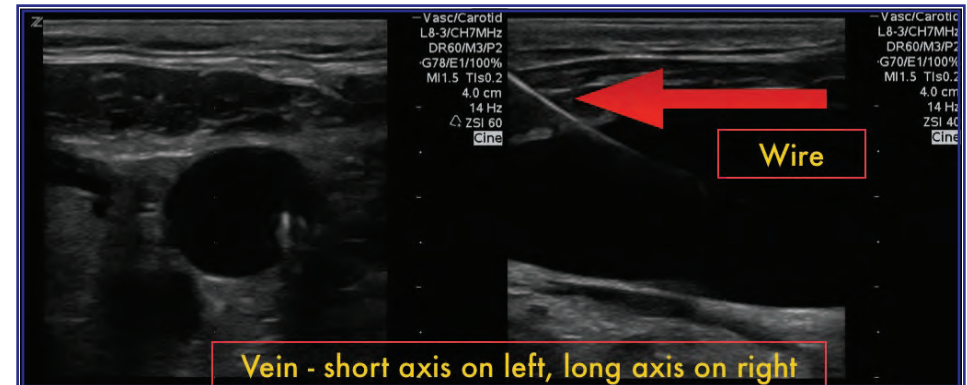
Figure 9.3 CVP Placement: Long and short axis views confirm placement of wire prior to placing CVP catheter in typical ICU patient.

Abdomen
A. Identification, Quantification and Characterization of Intraperitoneal Fluid. This is done routinely during the FAST (Focused Assessment with Sonography for Trauma) exam in the evaluation of the trauma patient.
Areas investigated include hepatorenal, splenorenal, pericardial space, and bladder (posterior to bladder for fluid).
B.Assessment of Urinary Tract
  a)Hydronephrosis
  b)Distended Bladder (ureteral jets)
C. Identification of Abdominal Aortic Aneurysm and Dissection

Tip sheets for all the above modalities can be found at: http://ccm.anest.ufl.edu/education/ultrasound/tip-sheets/
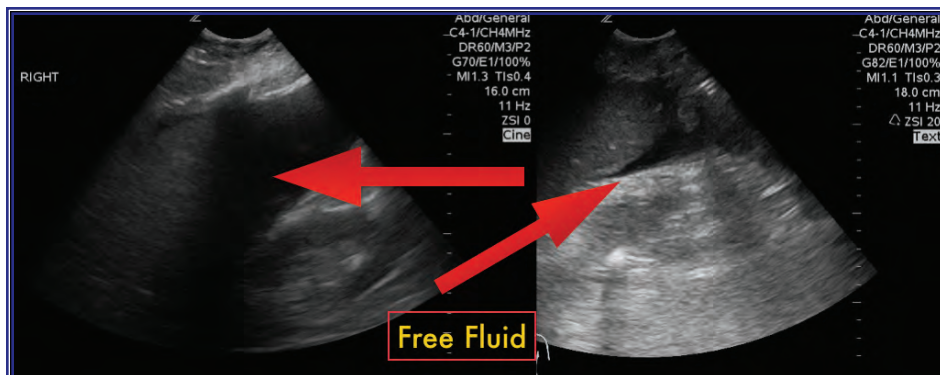
Figure 9.4 FAST Exam for Trauma: Free fluid is seen in this trauma patient with hypotension. There was no obvious cause of bleeding. The patient was found to have a liver laceration on laparotomy.

Conclusion

Ultrasonography provides the critical care physician with a tool to rapidly assess a patient's condition. It is safe and can be used at the patient's bedside. The most important quality of bedside/portable/point of care ultrasound is reproducibility. As the clinician taking care of the patient, you can make interventions and immediately evaluate to see the results of your intervention. With technological advances image quality has improved allowing for the development of new applications for ultrasonography. As experience with this diagnostic modality has increased it is clear that ultrasound use will become ubiquitous with the practice of critical care medicine.

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Questions

9.1 Which of the following is not evaluated during a typical FAST exam?
    A.   Pericardial space
    B.   Hepatorenal space
    C.   Splenorenal space
    D.   Aorta

9.2 Dynamic' approach for line insertion using ultrasound means:
    A.   The procedure is done blindly but after having localized the vein prior to procedure
    B.   The procedure is done with ultrasound in the Doppler mode to see the dynamic blood flow
    C.   The procedure is done with ultrasound after the blind approach fails
    D.   The procedure is performed under direct guidance, with real time view of the needle

9.3 Which pulmonary pathology is ultrasound unable to assess?
    A.   Pneumothorax
    B.   Pulmonary Edema
    C.   Pulmonary Embolism
    D.   Pneumonia
    E.   Ultrasound is able to aid in diagnosis of all of these etiologies

9.4 A middle-aged man is a victim of a stab wound to the chest. He is hypotensive. A bedside TTE is performed and the image below is obtained. What is located by the area indicated by the "X"?
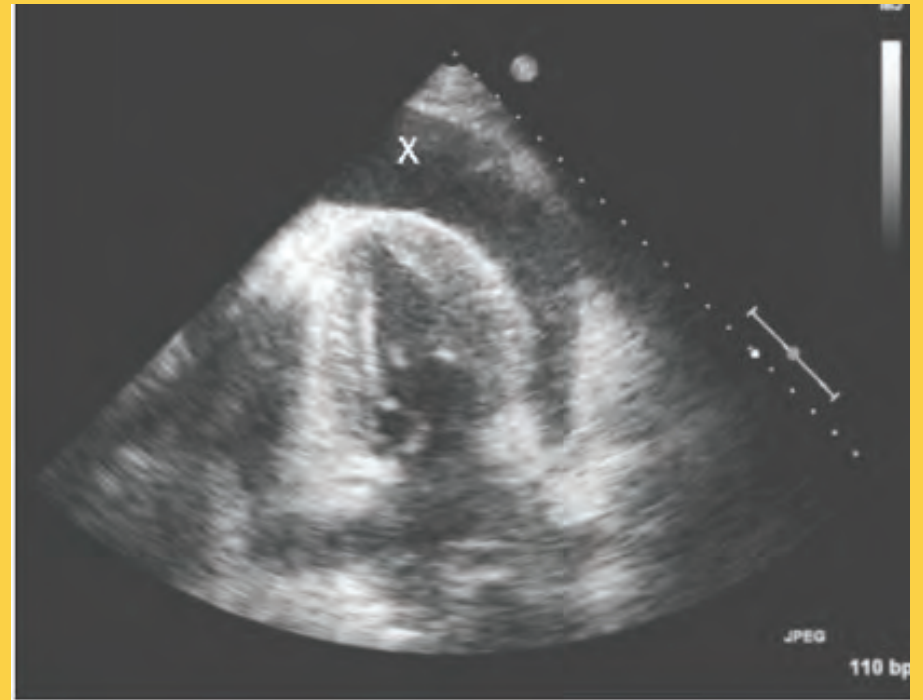
    A.   Left Ventricle
    B.   Right Ventricle
    C.   Lung
    D.   Pericardial effusion
    E.   Liver

10. Point of Care Testing in the ICU

Rebecca Kalman MD and Edward A Bittner MD PhD

Key Points

• Point-of-care testing (POCT) refers to testing performed at or near the patient's bedside, outside of the confines of a centralized clinical laboratory, and has been shown to reduce the therapeutic turn-around time (TTAT).

• The institution of POCT involves staff education in appropriate device use, device maintenance, and device quality control. It does not necessarily correlate to improvements in clinical outcome.

• POCT is available for many laboratory tests commonly obtained in the ICU including glucose, blood gas, electrolytes, lactate, and coagulation studies.

• POCT is more likely to be of benefit in situations where patients' clinical condition changes rapidly or when laboratory values need to be obtained quickly.

A 72 year-old man was transferred to the ICU from the floor for an increasing oxygen requirement and an altered mental status. He was admitted to the hospital two days prior for diverticulitis and has a medical history significant for insulin dependent diabetes, coronary artery disease, and prior stroke. Shortly after arrival to the ICU, his condition worsened and he became hypotensive and unresponsive. He was resuscitated with IV fluids and intubated. Blood was drawn for analysis and an upright KUB was obtained. The KUB revealed free air and he was rushed to the operating room. Twenty minutes after he left the ICU, the laboratory called to report a critical value. The glucose was 26 mg/dL. Would knowledge of this value have changed his management?

Introduction

In taking care of critically ill patients, the time to diagnosis and treatment of life threatening issues can be crucial. Traditionally, most laboratory tests ordered are performed off the unit in a central or STAT laboratory. This involves a multistep process in which tests are ordered, samples are drawn, labeled, and transported to the laboratory. There, they are analyzed and the results then communicated back to the requesting unit/physician (Figure 10.1).[1] These processes take time and the time interval between laboratory test order to treatment decision is referred to as the therapeutic turnaround time (TTAT). In the ICU, the clinical condition of unstable patients can change quickly and rapid turnaround in laboratory tests is required for prompt diagnosis, early therapy, and changes in management. Consequently, delays causing an increase in TTAT may have detrimental effects.

Point-of-care test(ing), commonly referred to as POCT, is testing performed at or near the patient's bedside, outside of the confines of a centralized clinical laboratory. POCT is usually performed on whole blood with user-friendly devices located either directly at the patient's bedside or within the ICU. Studies have shown that POCT, when compared to central laboratory testing, reduces TTAT.[2,3] In one randomized, controlled trial performed in an emergency department, patients' blood was randomly allocated to POCT versus testing by the hospital's central laboratory. In the POCT group, there was a reduction in TTAT and overall time needed to make decisions regarding patient management. In addition, time to treatment was reduced for patients with conditions where timing was considered to be critical. However, these changes did not affect clinical outcome.[3]

Advantages and Disadvantages of POCT

One of the biggest advantages of POCT is in the reduction of TTAT leading to rapid data availability, and faster real-time patient management and clinical decision-making. There is, also, a decreased chance for errors associated with specimen handling, labeling, and transport. Most POCT require smaller blood volumes, thus decreasing iatrogenic blood loss. In addition, POCT is often cost saving.

Potential disadvantages of POCT include less consistent sample handling, poor analytic performance, unauthorized testing, potential for transcription, communication, and documentation lapses due to less formal protocols, inadequate training of personnel performing the test, validation error of test results, limited test menu, and lack of a notification system or documentation for critical values.

POCT devices and tests

Figure 10.1 Different steps in testing with POC vs Central Laboratory
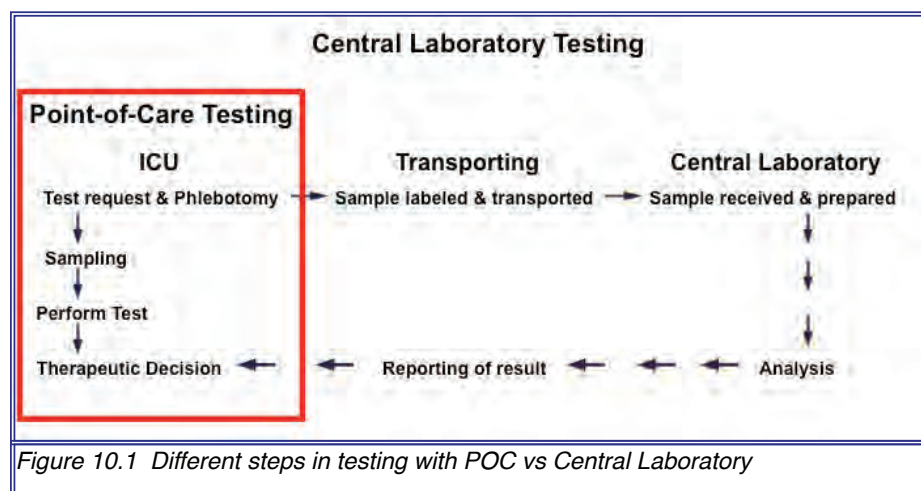
There are a variety of POCT devices and tests. Most POCT devices require blood to be drawn from the patient, similar to samples sent to the lab. However, some POCT can be performed in vivo allowing testing on whole blood without removing it from the body. An example is the use of fiberoptic pulmonary artery catheters to continuously measure mixed venous oxygen saturation (SvO_2). Other in vivo tests include subcutaneous real-time glucose monitoring or measurement of arterial blood gas via intra-arterial sensors.[1]

Specific situations in which POCT may be helpful in the ICU include the monitoring of glucose, electrolytes, blood gas, lactate, and coagulation studies. They are described in more detail below.

GLUCOSE
Glucose control is an integral part of ICU care as both hyper- and hypoglycemia are associated with increased morbidity and mortality.[4] Critically ill patients can have large fluctuations in blood glucose levels influenced by stress, medications, and co-morbidities. Given that there are time dependent risks associated with both hyper- and hypoglycemia, bedside glucometers are the standard in many ICUs. However, glucose values obtained with a point-of-care device can differ significantly from those obtained by laboratory analysis. Laboratory or plasma glucose levels are usually higher than whole blood POCT results due to differing ratios of water content in the samples. For this reason, a calibration factor is incorporated into POCT devices. In addition, values drawn from a central venous catheter can differ from those obtained from a finger stick. Other factors affecting the accuracy of POCT glucose results include a patient's hematocrit and enzyme degradation of testing strips. [5]

BLOOD GAS
Oxygenation, ventilation, and acid-base status are of major concern in the critically ill patient. Life threatening changes in these parameters can occur suddenly and rapid results are often key to diagnosis and treatment. POCT has the potential to decrease TTAT for these crucial values. Blood gas testing has been mentioned as the most-often needed POCT in the ICU. In fact, there is some evidence that POC blood gas testing leads to improved clinical outcomes when there is a reduction in TTAT. However, these results were not consistent across all studies.   For example, in a report of one center's experience with POCT for blood gas analysis, inaccuracies in pCO_2 measurements were identified that eventually led to the discontinuation of the POCT. It was eventually determined that the discrepancies were due to incompatibility between testing syringes and the device, illustrating the complexity of implementing POCT in the critical care setting.[6]

ELECTROLYTES
In the ICU, many conditions can lead to electrolyte abnormalities and these can be life-threatening if not detected and treated. When a microanalyzer was implemented to analyze electrolytes and blood gases, on trauma patients in the emergency room, the reported laboratory values were accurate and fast and provided more information for evaluation and management of the patient. They were specifically found to be helpful in patients requiring urgent or emergent operative intervention as laboratory data obtained via POCT were more likely to be available pre-operatively.[7]

LACTATE
Recognizing an elevated lactate level leads to the diagnosis and treatment of tissue hypo-perfusion whether it be related to sepsis, vascular ischemia, or hemorrhage. The use of lactate POCT has been reported to improve mortality in neonates and other high-risk patients undergoing congenital heart surgery.[8]

COAGULATION STUDIES
Critically ill patients may have disorders of coagulation related to their underlying illness, hemorrhage, fluid administration, or medications. Timely evaluation of coagulation status can facilitate appropriate use of blood products and related medications. Traditional methods of monitoring coagulation, including the prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR), platelet count, and fibrinogen levels, may be time consuming to obtain and do not fully characterize the risk of bleeding.

Activated clotting time (ACT) is a common POCT used to evaluate the intrinsic or common pathway of coagulation. A whole blood sample is added to an activator (diatomaceous earth or clay) and the time to clot formation is measured. It is often used in the

operating room when monitoring the effect of heparin therapy or anticoagulation by direct thrombin inhibitors such as argatroban, bivalirudin, and lepirudin.

Thromboelastography (TEG) is a POCT method that evaluates multiple levels of the coagulation cascade. It measures the movement of a pin placed in a rotating cup filled with whole blood mixed with kaolin. As clot forms, the freely hanging pin becomes bound to the rotating cup and movement of the pin is recorded to produce a graph with parameters (Figure 10.2). TEG has been reported to accurately predict peri-operative and post-operative bleeding and can have value in targeting coagulation treatment. (9) Its use has also been associated with a decrease in blood product use after elective coronary artery bypass grafting.[10] Precise sample handling and aliquot transfer is important to ensure accurate TEG measurements. In addition, evaluation of platelet function can be inaccurate in the presence of platelet inhibitors.[11]

There are several POCT devices available for the testing of platelet function. Some devices provide standard complete blood counts, including platelet count and evaluation of platelet function such as aggregation and inhibition. Other POCT devices measure platelet responsiveness to antiplatelet medications, such as aspirin and clopidogrel, or are able to detect inherited and acquired platelet dysfunction, such as von Willebrand's disease.
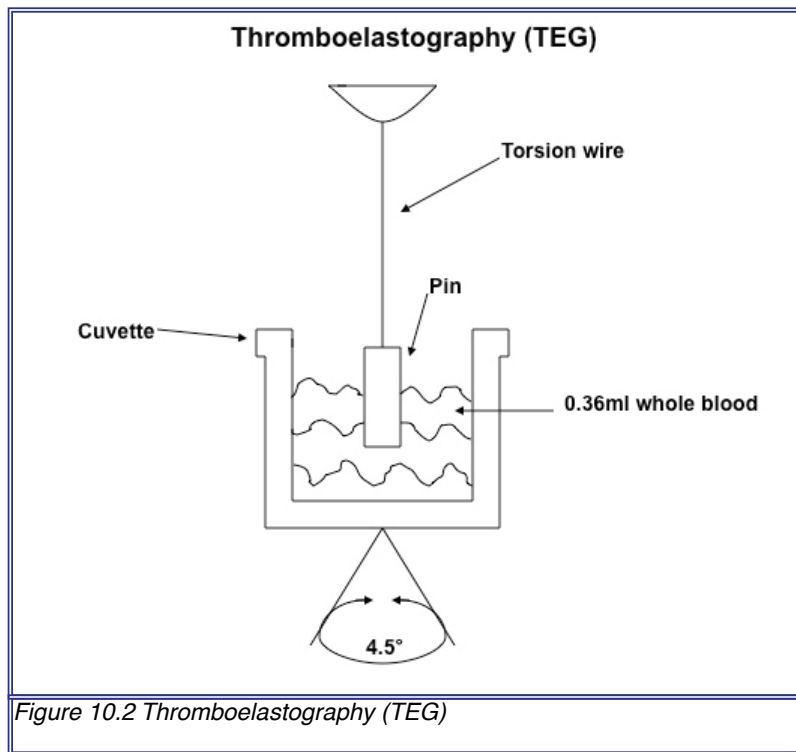
Quality issues with POCT

Figure 10.2 Thromboelastography (TEG)

Since POCT generates information leading to clinical decisions, it is essential to ensure a proper quality management program overseeing its use. A close, ongoing relationship with the central laboratory is key since many characteristics of POCT must be checked and continuously monitored by the laboratory including the choice of methods, initial and ongoing staff training, proper equipment maintenance, and management of consumables. An internal quality control program performed at least once daily with monthly reviews of performance as well as periodic quality assessment of each instrument and appropriate procedures for recording results are other essential components of a POCT quality assurance program.

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Questions

10.1 Point of care testing:
    A.   Reduces therapeutic turn around time
    B.   Has been consistently show to improve patient outcomes
    C.   Involves a multi-step process in which tests are ordered, samples drawn, labeled, and transported to the lab.
    D.   Is always subject to a set of formal protocols, training, and documentation.

10.2. Advantages of POCT include all of the following EXCEPT:
    A.   Reduction in therapeutic turn around time
    B.   Use of smaller blood volumes minimizing of iatrogenic blood loss
    C.   No need for critical values notification system
    D.   Cost savings

10.3. Regarding POCT of coagulation studies, all of the following are true EXCEPT:
    A.   Activated clotting time (ACT) is often used in the operating room when monitoring the effect of heparin therapy.
    B.   Thromboelastography (TEG) is a POCT that evaluates multiple levels of the coagulation cascade and has been shown to accurately predict peri-operative and post-operative bleeding in certain patient populations.
    C.   There are many POCTs available that test platelet function.
    D.   Traditional tests of coagulation (INR, PTT, platelet count, fibrinogen) allow complete evaluation of the clotting cascade.

Section 3: Neuro Critical Care
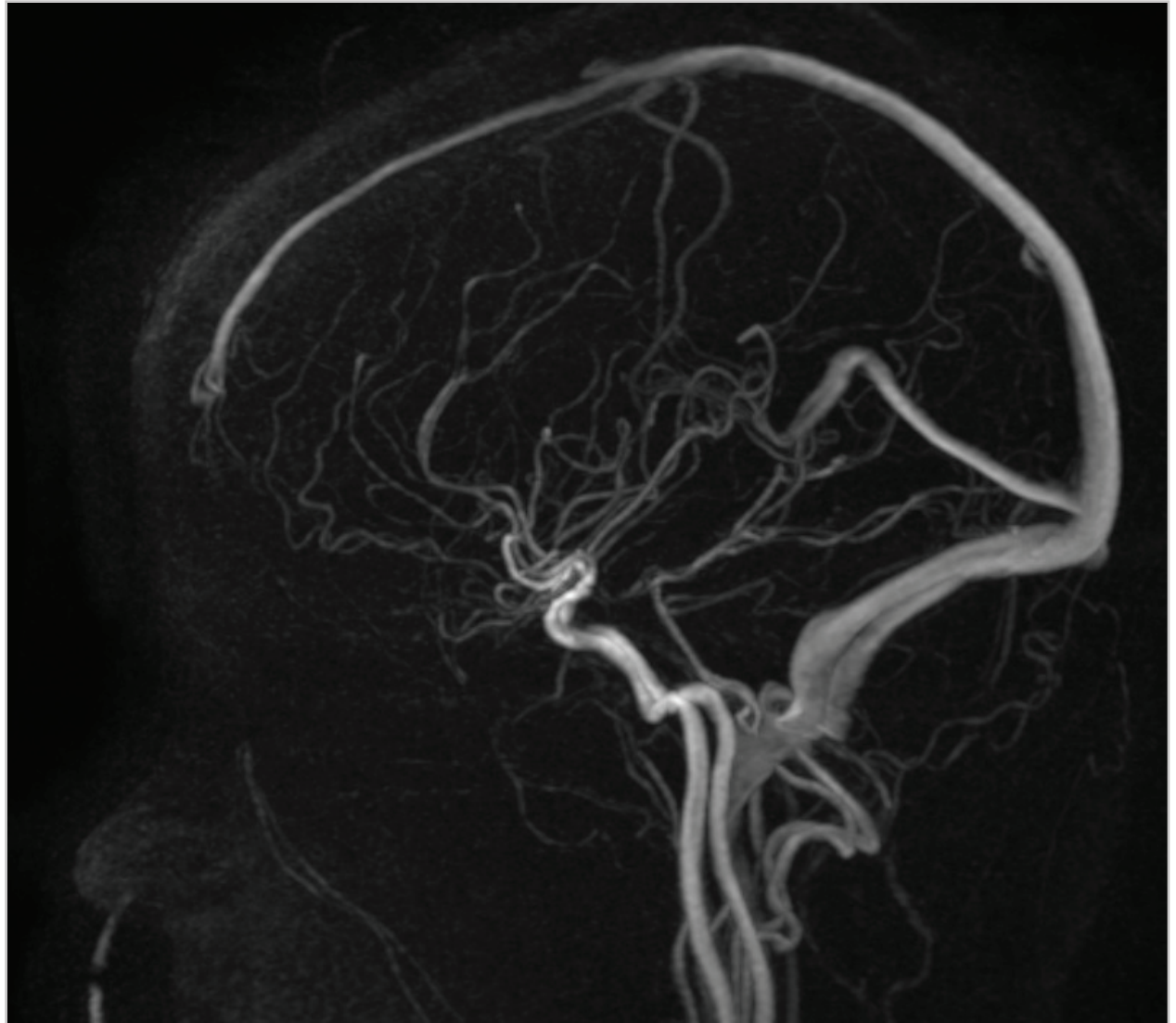
11. Neurocritical Care

Peggy White MD

Key Points

• Elevated ICP is managed by manipulation of CSF, blood, interstitial fluid, bony skull or neuronal cellular activity.

• Mortality and morbidity in SAH patients is increased significantly by re-bleeding, vasospasm and hyponatremia.

• Ischemic stroke treated by tPA or mechanical thrombectomy should have blood pressure control below 180/110. Cytotoxic edema occurs from 2-5 days post ischemia and can cause significant brain swelling and possibly herniation.

• Patients with myasthenia gravis can safely receive a depolarizing muscle relaxant.

You are called to evaluate a patient for emergent c-section. The parturient is a 29 year old G2P1 who has a history of myasthenia gravis, status post thymectomy 10 years ago and has since received plasmapheresis on two separate occasions for exacerbation of her disease. She takes pyridostigmine and prenatal vitamins. She had clear liquids 6 hours ago, otherwise her last meal was more than 8 hours ago.

Neuroanatomy and physiology

The central nervous system is made of the brain, spinal cord, cerebral spinal fluid (CSF) and supporting cells. The adult human brain weighs approximately 1350 grams and receives between 12-18% of the total cardiac output. In an average sized adult with a cardiac output of 5 liters per minute, this is about 750 ml of blood per minute circulating through the four main cerebral arteries to the cranial vault. (Figure 11.1) Global flow is 50ml/100 grams/min, ischemia occurs at 20 ml/100 grams/minute. If the delivery falls below this, the cells will shift to anaerobic metabolism and pyruvate production will lead to acidosis and cell death. The brain oxygen utilization 3.5 ml/100 grams/min.[1]

Neurons, supporting glia cells, blood vessels and CSF are compartmentalized inside the protective skull. CSF is produced by the choroid plexus, mostly found in the lateral ventricles, the fluid flows from the lateral ventricles through the two foramens of Monroe into the third ventricle, through the cerebral aqueduct into the fourth ventricle, and finally through the foramen of Magendie and two foramens of Luschka. CSF is absorbed via the arachnoid granulations found on the inner surface of the dura. In the adult, the total CSF volume at any given time is 150 ml, with an average production of 450 – 750 ml of CSF per day.[1,2]

Cerebral autoregulation is maintained by several factors and comprehensive discussion is too detailed for this review. However, three pertinent factors are: pCO_2, pO_2, and mean arterial pressure. Cerebral vasoconstriction (and thus a decrease in intracranial pressure, ICP) occurs with lowering of pCO_2 levels. A decrease in pCO_2 below 25 mmHg causes intense cerebral vasoconstriction resulting in ischemia.[2] However in times of impend-

ing herniation, a moderate lowering of pCO_2 to 30 mmHg can be life saving until other ICP reducing measures are taken.

The main effect of arterial oxygenation is noted at pO_2 levels below 60 mmHg. At this level there is intense vasoconstriction that may lead to cerebral ischemia. Levels above 60 mmHg cause little effect on cerebral vaso-responsiveness.

Cerebral perfusion pressure is calculated by mean arterial pressure (MAP) minus ICP. The cerebral vasculature will constrict and relax to maintain perfusion at MAPs between 50 – 70 and 150 mmHg. If the MAP decreases below 50 – 70 mmHg, intense cerebral

Figure11.1 Circle of Willis

vasodilatation occurs. A MAP above 150 mmHg will result in cerebral vasoconstriction.

Increased ICP

The Monroe-Kellie hypothesis describes the relationship between three substances: blood, CSF and brain tissue, all contained in a bony box (the skull). Any increase in one of the components will increase the intracranial pressure and compromise the other two components. Lowering of ICP can be controlled by manipulation of the bony skull, neuronal cellular activity, or fluid volume (interstitial, CSF or blood).

Cerebral blood volume can be decreased by decreasing neuronal cellular activity or cerebral metabolic rate of oxygen ($CMRO_2$). $CMRO_2$ can be slowed through the use of hypothermia, barbituates, propofol and avoiding circumstances that may increase cellular activity such as hyperthermia and seizures. A reduction in $CMRO_2$ by 6 – 7% can be achieved for each degree Celsius of temperature reduction. Hypothermia can cause complete burst suppression at 18 – 20 °C.[1] The cerebral blood compartment can also be decreased by facilitation of venous drainage, which is accomplished by elevation of head of bed, avoiding internal jugular cannulation, avoiding extreme flexion of the neck and any constricting devices around the neck. In extreme circumstances muscle relaxation can be used to decrease muscular resistance to venous outflow.

The brain tissue compartment can by decreased by hypertonic saline or osmotic diuresis, which decreases intracellular fluid volume.

The CSF compartment can be decreased via neurosurgical intervention with CSF diversion via an extra ventricular drain (EVD). As a last resort a craniectomy, or removal of skull flap, can be performed to allow for controlled herniation out of the cranial vault.

Subarachnoid Hemorrhage

In the U.S. the incidence of subarachnoid hemorrhage (SAH) is estimated at 10 per 100,000.[4] The true incidence is difficult to determine, since a quarter of patients die prior to or en route to the hospital. Half of the patients who make it to the hospital will be left with significant disabilities.[3]

The hallmark sign of an acute SAH is the thunderclap, worst headache of their life with photophobia 80% of the time. Other symptoms include: nausea, vomiting, meningismus, brief loss of consciousness and focal neurological deficits.[3]

Initial work up consists of a non-contrast CT scan. Once subarachnoid blood is identified on CT scan, a CT angiogram or IR angiography should be completed to identify the location, size, and type of aneurysm to aid in operative planning (open craniotomy versus endovascular). The aneurysm needs to be secured as soon as possible, usually in the first 24 to 48 hours. (Table 11.1 and 11.2)

Grading scales are used to estimate the risk for vasospasm and predicted morbidity. The Fisher score predicts risk of vasospasm, and Hunt-Hess grade predicts patient mortality and morbidity.

Mortality increases to approximately 80-90% if the aneurysm re-bleeds. Strict blood pressure control is pivotal.[3] The SAH guidelines do not state an absolute blood pressure goal but, at our institution, a systolic pressure below 140 mmHg is maintained until the
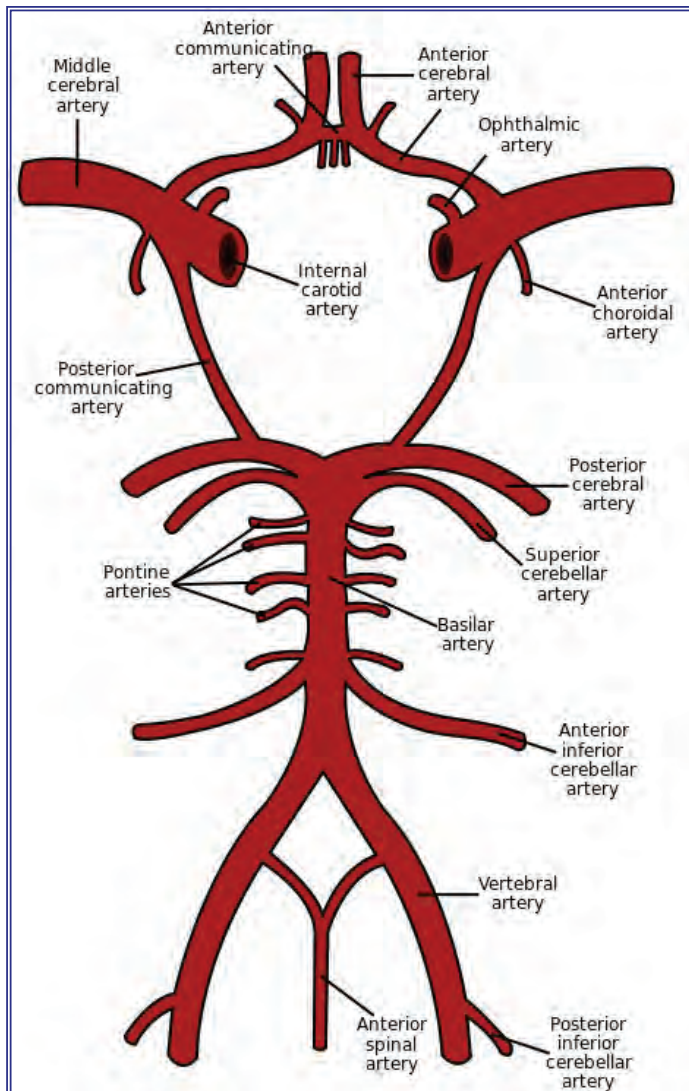
aneurysm can be secured. Many agents can be used to reach this blood pressure goal. Nicardipine infusion is preferred for its quick onset and offset, with minimal effect on heart rate. However, labetalol or nitroprusside could also be used. Keep in mind that nitrates can cause reflex tachycardia and headache, which may complicate care. The use of an antifibrinolytic for clot stabilization can also be used for 24 hours while awaiting definitive intervention.

The decision to clip (surgery) or coil (endovascular) the aneurysm is based on several

Table 11.1 Hunt-Hess Grade	
Grade	Clinical Findings
1	Asymptomatic or mild headache +/- nuchal rigidity
2	CN palsy, moderate to severe headache, nuchal rigidity
3	Mild focal deficit, lethargy or confusion
4	Stupor, moderate to severe hemiparesis, early decerebrate rigidity
5	Deep coma, decerebrate rigidity
Add 1 grade for serious systemic disease or severe vasospasm	
Adapted from Rosen, et al[4]	

patient factors. Aneurysm location, neck size and aneurysm characteristics (saccular, fusiform or blister) will help guide these decisions.

Complications from SAH

Hydrocephalus: CSF diversion via extraventricular drain (EVD) or by serial lumbar punctures can improve the neurologic exam and relieve the hydrocephalus. The mechanism of hydrocephalus can be secondary to obstruction from mass effect occluding the ventricle, a thick clot obstructing the ventricle or from dysfunctional CSF reabsorption via arachnoid granulations.

Vasospasm: The theorized mechanism is irritation to the arteries caused by blood products or inflammatory mediators in the subarachnoid space. It can occur in any of the cerebral arteries. The peak incidence of vasospasm is post bleed day 3 – 10, but patients remain at risk up to 21 days. Typically patients are monitored for vasospasm and cerebral ischemia with hourly neurological examination, transcranial Doppler and if indicated, CT angiography. Oral nimodipine 60 mg every 4 hours has been shown to reduce the incidence and long-term morbidity from vasospasm. Other measures shown to reduce morbidity include: statins, 5-7 days of antiepileptic medications, maintenance of euvolemia (avoidance of hypovolemia).[3]

Hyponatremia: from cerebral salt wasting (CSW), or SIADH. SIADH is euvolemic hyponatremia and CSW is hypovolemic hyponatremia. For both diagnoses the goals of treatment are the same: to maintain euvolemia and normonatremia via hypertonic saline or a mineralocorticoid.

Intracerebral hemorrhage

Hemorrhagic stroke is the second most common form of stroke. It is difficult to differentiate between hemorrhagic and ischemic stroke based on physical exam. The diagnosis must be confirmed by non-contrasted CT (the gold standard). Increased risk for hematoma expansion is highest during the first three hours of symptom onset. Therefore, care is focused around early diagnosis and management to prevent expansion of hematoma and subsequent decline in neurological status. Management during these crucial hours includes; reversal of any anticoagulation, maintenance of ventilation, oxygenation, hemodynamic support and avoidance of hypertension. The AHA stroke guidelines state systolic blood pressure below 140 mmHg, but there is no conclusive evidence to support a specific goal.[5]

There remains some controversy on medical versus surgical management. Surgical intervention is recommended for posterior fossa hematomas, which compromise brainstem function and for large peripheral hematomas. Surgical management is often left to the discretion of the neurosurgeon and depends on patient age, neurological deficit, size and location of the hematoma.

Once the patient is stabilized, management should focus on prevention of secondary

Table 11.2 Fisher Grade	
Grade	CT Findings
1	No subarachnoid blood
2	Diffuse or vertical layers < 1mm
3	Localized clot and/or vertical layer ≥ 1mm
4	Intracerebral extension or intraventricular clot
Adapted from Rosen, et al[4]	

injury such as: maintenance of euglycemia, avoidance of hyperthermia, continued correction of any coagulopathies, and CSF diversion for hydrocephalus. Patients are admitted to the ICU for frequent neurological exams. For patients with Glascow coma scale (GCS) at or below 8, AHA guidelines recommend ICP monitoring and maintenance of CPP above 50 – 70 mmHg.[5]

Ischemic Stroke

Ischemic stroke is the most common form of stroke and the incidence is increasing as our population ages. The development of the AHA ischemic stroke guidelines has increased awareness and improved patient survival.

Any patient with a focal neurological deficit suspicious of ischemic stroke should have an immediate non-contrasted CT of the head to rule out a bleed and identify tissue at risk with perfusion weighted imaging. If the stroke onset has been within the last 3 hours (4.5 hours with some exceptions), and there is no mass lesion or ICH, the patient may qualify for systemic intravenous tissue plasminogen activator, tPA. The decision to administer tPA is largely governed by the time from onset of symptoms, NIH stroke scale and other coexisting diseases. Common absolute contraindications to receiving tPA include: persistent hypertension above 185/110, INR above 1.7 or receiving antico-

agulants recent stroke in past month, surgical procedures, and seizures.[6]

After tPA infusion, there is a 24 hour window where no anticoagulation (including DVT prophylaxis) or antiplatelet therapy is given. After this period, all patients should receive aspirin. Some patients may benefit from GpIIb/IIIa inhibitor therapy, but this should be decided on a case by case basis.[6]

Medical management of ischemic stroke includes continuous hemodynamic and telemetry monitoring, supplemental oxygen to keep SpO2 above 94% (with intubation if necessary), and maintenance of euglycemia (goal of 140-180 mg/dL). There is no conclusive evidence for blood pressure management. However, the AHA guidelines recommend lowering blood pressure by 15% in the first 24 hours, if the patient did not receive fibrinolysis and the blood pressure is above 220/120. If tPA has been given, the blood pressure should be controlled below 180/110.[6]

Complications of ischemic stroke include hemorrhagic conversion and cerebral edema. Typically these complications occur with large strokes, such as proximal middle cerebral artery (MCA) occlusion. Edema usually occurs between post ischemic day $2 - 5$. During this time, it is crucial to monitor neurological status and serum sodium. Hypertonic saline can be used to push serum sodium to $145 - 150$ mEq/L in an attempt to reduce edema. Measures to prevent secondary injury as discussed above should be implemented.

Status epilepticus
According to the neurocritical care guidelines, status epilepticus is defined as a seizure lasting longer than 5 minutes clinically or on EEG, or recurrent seizure activity without recovery to baseline between seizures. The incidence of status epilepticus in the general ICU population is around 10%, in the neuro ICU the incidence is around $12 - 25$%. Status epilepticus can be classified as: convulsive, non-convulsive or refractory status epilepticus.

Convulsive status epilepticus presents with rhythmic tonic-clonic movements, mental status change, or focal neurological deficits in the post ictal period.[7]

Non-convulsive status epilepticus (NCSE) is categorized as seizures on EEG without clinical features. They can be described as the "wandering confused" or the acutely ill with severely impaired mental status. The latter of which is seen in critically ill patients who are sedated and intubated for other reasons. NCSE can further be divided into positive (agitation, delirium, perseveration) and negative symptoms (aphasia, catatonia, coma, confusion).

Patients who don't respond to standard treatment (consisting of a benzodiazepine and one antiepileptic durg) are considered non-responders to standard treatment and are considered to be in refractory status epilepticus (RSE).[7]

Initial treatment for seizures should be focused on maintenance of oxygenation, ventilation and hemodynamics. Initial management does not always necessitate intubation and it may actually complicate the neurological exam after the seizures have been controlled. However, if the patient's oxygenation and ventilation is compromised the airway should be secured.

Simultaneous seizure abortive therapy should also be immediately given. First line therapy is lorazepam, which has the most attractive pharmacokinetic profile. However, midazolam and less favorably valium could be used depending on the clinical situation. Early aggressive seizure abortive therapy is imperative, because the longer the seizure continues, the higher the likelihood for development of status epilepticus.

If an identifiable correctable cause of the seizure can be identified, such as hypoglycemia or drug toxicity, the patient does not need maintenance antiepileptic therapy. Otherwise, the patient should be started on maintenance antiepileptic therapy most appropriate for the type of seizure.

Guillian-Barre
Guillian-Barre (GBS) is an acute immune mediated polyradiculoneuropathy that usually presents $2 - 4$ weeks after upper respiratory or gastrointestinal infections. Classical presentation is ascending sensory and motor deficits. Respiratory, bulbar and cranial nerve function can be impaired requiring intubation and mechanical ventilation. Autonomic instability may complicate care and usually occurs at weeks $2 - 4$ at peak weakness. Symptomatology centers around the pathophysiology of myelin destruction by macrophages and lymphocytes.[8]

Diagnosis is made by nerve conduction studies and lumbar puncture. Lumbar puncture shows increased protein with normal glucose and minimal white blood cells. Prompt diagnosis is essential, because therapeutic intervention should be started as soon as possible. Treatment includes plasmapheresis or IVIG as well as supportive care. There is no benefit in combining plasma exchange with IVIG.[8]

Acute respiratory failure secondary to muscle weakness can occur rapidly. Depolarizing muscle relaxants are contraindicated because of the risk of hyperkalemia. Nondepolarizers can be used, but should be done with great caution as their use may result in prolonged weakness.[1]

Myasthenia Gravis
Myasthenia gravis is an autoimmune disorder where autoantibodies are formed against the acetylcholine receptor on the post-synaptic neuromuscular junction. This results in generalized and/or bulbar weakness and fatigue, but not autonomic instability. There is a strong association of MG with thymus hyperplasia or thymomas.

The clinical history and exam provide the first clue to the diagnosis. Three studies can be used for the diagnosis, anti-AChR antibody titers, the Tensilon test, and electromyography. The tensilon test involves administration of a short acting acetylcholinesterase inhibitor (edrophonium) and then following for any improvement in symptoms. MG patients can safely receive depolarizing muscle relaxants, but will likely require a larger dose. Caution should be used when administering nondepolarizers, as MG patients are at risk for prolonged profound weakness.[1]

A paraneoplastic form of MG, called Eaton Lambert, results in weakness, but the patho-

genesis is autoantibodies formed against the presynaptic calcium channel.

Acute management of MG begins with the institution of IVIG, acetylcholinesterase inhibitors and steroids. These patients often become too weak to manage their secretions and hypoventilate. Once the decision is made to secure the airway, the use of a sedative often is enough to create optimal intubation conditions. If a neuromuscular blocker (NMB) is required, succinylcholine is the agent of choice, as non-depolarizering NMB can cause prolonged weakness.[1]

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Questions:

11.1 For the patient in the case presentation, which of the following options would be the BEST choice for GETA?

    A.   There is no indication for neuromuscular relaxation in myasthenia gravis patients.
    B.   RSI with Succinylcholine and propofol.
    C.   RSI with rocuronium and propofol.
    D.   She will need an awake fiberoptic intubation.

11.2 A 57 year old woman with a SAH is post bleed day 5, and post embolization day 4. Transcranial dopplers show elevated velocity with a high lindegaard ratio consistent with vasospasm. Her serum sodium has decreased from 140 to 131 mEq/L in the last 36 hours. Her CVP is 6 cm H_2O and she is one liter negative for her hospital stay.   Urine Na is 60 mEq/L and urine osm >100 mOsm/Kg. What is the next best intervention?

    A.   3% saline bolus
    B.   23.4% saline bolus
    C.   Fludrocortisone
    D.   Furosemide

11.3.You are called to the bedside of a TBI patient with elevated ICP of 30 mmHg for the past 10 minutes. Which of the following is the next BEST thing to do?
    A.   Furosemide
    B.   Mannitol bolus
    C.   23.4% Saline
    D.   Elevate the head of bed

12. Management of Increased ICP

Matthew R Hallman MD

Key Points

• Initial evaluation and management of an individual suspected of having an elevated intracranial pressure (ICP) is targeted at prompt identification and correction of abnormalities in airway, breathing and circulation (ABC's).

• Recognizing an elevated ICP relies on physical examination (Glasgow Coma Score), neuro-imaging (CT/MRI of the head), and invasive pressure monitors (predominantly intraventricular drains, intraparenchymal and subdural microtransducers).

• Treatment of an elevated ICP is directed at maintaining a favorable balance between cerebral oxygen supply and demand. This involves maintaining cerebral blood flow by ensuring adequate cardiac output, reducing cerebral vascular resistance through removal of intracranial components (blood, cerebral spinal fluid, intracellular/extracellular water), and reducing cerebral oxygen demands through control of fever, seizure, pain and agitation.

A 24 year-old man presents to the hospital following a motorcycle crash. He was not wearing a helmet. His vital signs are HR 120 bpm, BP 88/50 mmHg, RR 24/min, SpO$_2$ 96% on ambient air, and T 37.1°C. On exam, he is noted to have obvious facial trauma and scalp abrasions, breath sounds bilaterally, normal heart sounds, weak pulses, GCS of 7 (E1 V2 M4) and both pupils are 5mm and reactive to light.

Physiology

Normal adult intracranial pressure (ICP) is 8-12 mmHg.[1] The rigid cranium contains stable amounts of brain parenchyma, blood and cerebral spinal fluid (CSF) that exist in equilibrium. An increase of any of the normal physiologic components or the addition of a pathologic component without simultaneously reducing the volume of another component results in an elevated ICP. This concept is known as the Monroe-Kellie Doctrine.

Parenchymal volume is controlled primarily through regulation of vascular permeability and osmotic gradients across the blood brain barrier (BBB). Cerebral edema results when the BBB is disrupted or overwhelmed, and water accumulates within brain parenchyma. Cerebral edema is categorized as either cytotoxic or vasogenic. Cytotoxic edema occurs from direct neural injury and cell lysis when osmoles enter and accumulate in the intracellular compartment. This may occur following traumatic brain injury (TBI) or ischemic stroke. As water follows the osmotic gradient, swelling results. Similarly, if serum osmolality falls rapidly, the BBB may be overwhelmed resulting in net movement of water from the intravascular to extravascular space. Vasogenic edema results when hydrostatic forces favor water flow from the intravascular to the extravascular space as may happen with increased intravascular pressure following a venous outflow obstruction, or when inflammation causes increased vascular permeability such as occurs in perineoplastic territories.

Normally, CSF production (approximately 20 ml/hour by the choroid plexus in the ventricles) is in equilibrium with CSF absorption (approximately 20 ml/hour by the arachnoid villi in the subarachnoid cisterns).(1,2) When production surpasses absorption, hydrocephalus results. Communicating hydrocephalus results from

the malfunction of the arachnoid villi, whereas obstructive hydrocephalus results from the interruption of CSF flow from the choroid plexus to the arachnoid villi. Blood in the subarachnoid space may cause communicating hydrocephalus, while mass lesions and intraventricular blood often cause obstructive hydrocephalus. Transependymal flow of CSF from the ventricles to the parenchyma occurs with elevated intraventricular pressure. This may also cause cerebral edema.

Cerebral blood flow (CBF) and cerebral blood volume (CBV) are dynamic and occur on a minute-to-minute basis. Four major mechanisms regulate CBF: 1) flow-metabolism coupling; 2) pressure autoregulation; 3) CO_2 reactivity; and 4) O_2 reactivity.[1,2] Flow-metabolism coupling allows increased cerebral metabolic demands, as occurs with fever and seizures, to be met with cerebral vascular dilation and increased CBF and CBV. Conversely, resting states see less CBF and CBV. Pressure autoregulation allows constant CBF over a wide range of systemic mean arterial pressures (MAP). Higher MAP cause cerebral vasoconstriction whereas lower MAP cause cerebral vasodilation. This occurs over the MAP range of 65 – 150 mmHg in most people. The net effect is relatively constant CBF over the entire range of pressures, but variable CBV (lower CBV at higher MAP and vice versa). When pressure autoregulation is disrupted, higher MAP result in increased CBV. Cerebral vascular CO_2 reactivity causes vasodilation or vasoconstriction. An increase in $PaCO_2$ leads to an increase in CBF and CBV while the converse occurs in a low $PaCO_2$. This occurs over a $PaCO_2$ range of 25–70 mmHg. However, this is a short-lived effect and CBF will return to baseline over the next 6-8 hours despite the $PaCO_2$. Oxygen reactivity is similar, but vasodilation does not start until PaO_2 falls below 60 mmHg. Below this level both CBF and CBV rise sharply. When any of these control mechanisms fail it is possible for CBF to rise inappropriately resulting in increased cerebral blood volume and an elevated ICP.

Finally, ICP will rise when pathologic components such as hemorrhage and tumor are present in the cranium. While small volume increases may be tolerated as CSF is pushed into the extracranial thecal sac, the elastance ($\Delta P/\Delta V$) curve quickly steepens resulting in large ICP rises with small subsequent volume increases.

Monitoring

Optimal ICP and cerebral perfusion pressure (CPP) targets are not clear. Treatment is generally indicated for ICP > 20 – 25 mmHg for 15 minutes or more. Maintenance of a CPP of 50 – 70 mmHg is recommended for most conditions.(1-3) However, ICP values > 20 mmHg may be tolerated without problems in patients with normal CT-head imaging, a fact that underscores the need to avoid simply treating numbers.(4) The same type of physiologic rationale supports the avoidance of systemic hypotension, but specific targets remain difficult to define outside of the broad recommendations to maintain a sufficient MAP to keep a CPP of 50 - 70 mmHg at any given ICP. The utility of an accurate ICP assessment is therefore easy to understand.

There are a number of theoretical methods for non-invasive ICP assessment, but CT imaging is most commonly utilized. CT findings suggestive of elevated ICP include midline shift, hydrocephalus, cistern compression, edema, hemorrhage and other mass effects. Whenever imaging findings or clinical exam raise suspicion for ICP elevation, invasive monitoring is the gold standard. Table 12.1 summarizes common indications

for invasive ICP monitoring.

The three most commonly used methods for invasive ICP monitoring are the externalized ventricular drain (EVD), intraparenchymal microtransducer, and subdural microtransducer. An EVD allows for therapeutic drainage of CSF and in vivo calibration. However, there is a risk of infection and hemorrhage, and placement may be difficult in patients with small ventricles. Intraparenchymal microtransducers, do not allow in vivo calibration, but appear to be more accurate than subdural microtransducers. They carry a small risk of bleeding and infection. Device choice depends largely on the suspected etiology of the ICP elevation as well as imaging findings (e.g. in subarachnoid hemorrhage and cases of hydrocephalus the ability to drain CSF is important and EVDs are typically placed). In TBI, the ventricles may be displaced or compressed causing a difficult EVD placement. Therefore, an intraparenchymal or subdural microtransducer is often used. If there is an elevated bleeding risk, the subdural microtransducer is often selected as it carries the smallest risk of hemorrhage. Placing the monitor in an area of the brain that accurately reflects the conditions in the brain, as a whole, is a challenge with all devices. The falx cerebri and tentorium cerebellum are physical barriers in pressure transmission across varying areas of the brain. Monitoring on one side may not detect pressure elevations on the other. Hematomas and tumors may similarly limit pressure transduction necessitating careful evaluation of the quality of data returned from the monitors.

Table 12.1. Indications for Invasive ICP Monitoring
Traumatic Brain Injury: GCS < 9 after initial resuscitation AND an abnormal head CT OR a normal head CT AND two of the following: age > 40 years, SBP < 90 mmHg or any motor posturing
Subarachnoid Hemorrhage
Symptomatic Hydrocephalus
Massive Hemispheric Stroke
Acute Liver Failure
Imaging consistent with elevated ICP (cerebral edema, midline shift, compression of cisterms)

Management

Matching cerebral metabolic rate of oxygen consumption ($CMRO_2$) to oxygen supply is the primary goal when ICP is elevated. Ensuring adequate cardiac output (CO) and hemoglobin (Hgb) is very important. While no specific CO targets exist, avoiding SBP < 90 mmHg is advised in most cases as deviation below this level is associated with worse outcomes in TBI.[3] Likewise, no specific Hgb target is supported by robust evidence, but levels less than 7 g/dl, and possibly higher in some situations, should be avoided.

Seizures, hyperthermia and agitation significantly increase $CMRO_2$, and should be aggressively corrected.[5] There is mixed evidence to support therapeutic hypothermia. Any potential benefit to cooling a patient must be weighed against the potential for other complications. Pain and agitation increase $CMRO_2$ and also lead to ventilator dysynchrony and increased ICP. As sedative and analgesic agents may obscure the neurological exam, they should be titrated to the minimum effective dosage, but should

not be witheld.[6] When sedation/analgesia alone is not effective in controlling ventilator dysynchrony it may be necessary to administer neuromuscular blockade (NMB).[6] NMB should not be instituted without concomitant sedation as this can lead to significant anxiety and increased $CMRO_2$ despite an outwardly calm patient.

Positioning the patient's head above heart level is one of the least invasive ways to acutely lower ICP.[5] Similarly, ensuring good cerebral venous drainage by placing the head in a midline position avoids vascular congestion that may contribute to an elevated ICP.[5] Recommendations to avoid placement of venous catheters in the internal jugular vein over concerns of impeding venous outflow are not evidence based. As most patients are mechanically ventilated it is important to consider that high levels of positive end expiratory pressure (PEEP) and large tidal volumes may impede cerebral venous drainage.[5]

The anti-inflammatory effects of glucocorticoids are of theoretical benefit in patients with cerebral edema. In the setting of peri-tumor edema, they are in fact quite effective at reducing swelling and lowering ICP.[6] However, they carry a risk of infection and hyperglycemia and have been proven harmful in other settings such as TBI where they should be avoided.[3,6]

Acute hyperventilation causes cerebral vasoconstriction, resulting in a decrease in CBV and lower ICP. Conversely, hypoventilation and hypoxemia both lead to cerebral vasodilatation and increased CBV. While hyperventilation lowers ICP for short periods, the reduction in CBF may be harmful if maintained for too long. Further, the effect is lost over 6-8 hours, and rebound acute respiratory acidosis with the associated cerebral vasodilatation and increased ICP may occur upon return to normoventilation. Hyperventilation is, therefore, only recommended as a temporizing maneuver, but hypoventilation and hypoxemia should be aggressively corrected.[5]

Of the pharmacologic interventions, mannitol and hypertonic saline (HS) are most commonly used to acutely lower ICP.[6] While they may also have rheological properties that improve microcirculatory flow, their primary mechanism of action is the establishment of an osmolar gradient favoring water egress from brain tissue. It is not clear which solution is more effective. The choice of mannitol or HS is often guided by patient specific factors such as the starting serum sodium and intravascular volume status. Serum osmolality should be monitored with hyperosmolar therapy, as serum osmole loads greater than 320 – 330 mOsm may be harmful, and serum sodium should generally not be allowed to go above 160 mEq/L.[6]

When the above interventions fail to control ICP, more aggressive measures may be employed. Electroencephalographic burst-suppression most commonly utilizes propofol or barbiturates to maximally decrease $CMRO_2$.[6] Both are associated with a significant incidence of hypotension and neither have been shown to improve outcomes. Regardless of the agent chosen, continuous EEG monitoring is recommended in order to assess burst-suppression and minimize sedative doses.

Surgical management may be necessary when ICP is refractory to all medical interventions, when the initial presentation includes a pending herniation syndrome, or where waiting for non-invasive measures to be effective is not considered reasonable.[3,5] These procedures are reserved for only the worst cases as they are not themselves without

risk. Figure 12.1 suggests a step-wise approach to the management of patients with an elevated ICP.
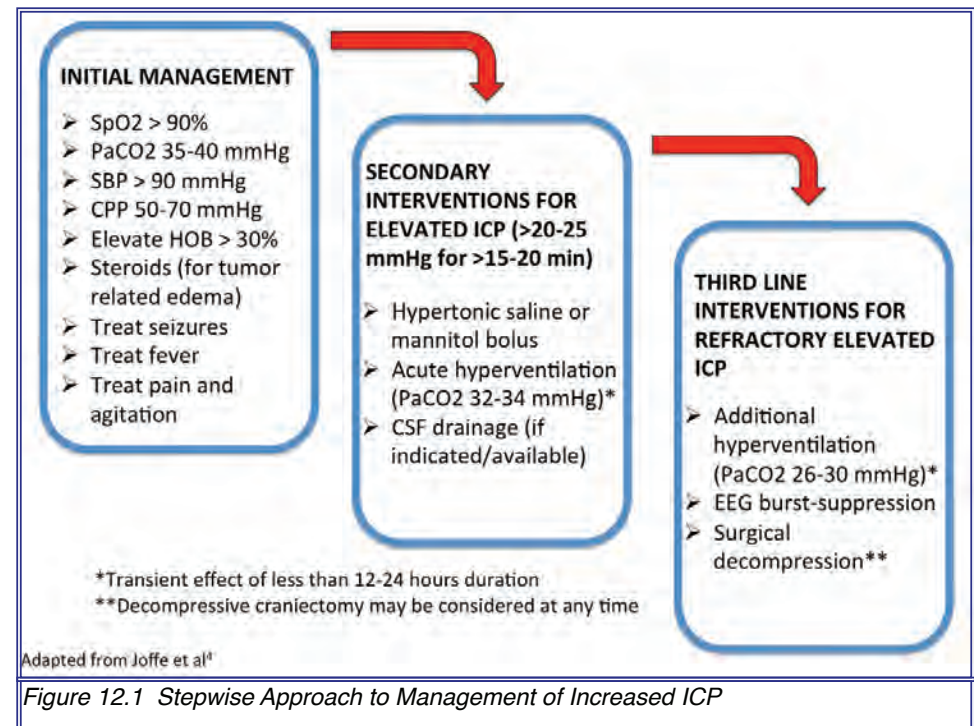
Figure 12.1 Stepwise Approach to Management of Increased ICP

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Questions:

12.1 Considering the patient in the case presentation at the start of this chapter, of the following interventions, which is the MOST appropriate initial intervention?
   A. Obtain CT imaging of the head
   B. Place an ICP monitoring bolt
   C. Initiate cooling measures
   D. Administer a fluid bolus

12.2 Of the following interventions, which is LEAST likely to increase ICP in a patient with a traumatic brain injury?
   A. Placing a central venous catheter in the internal jugular vein
   B. Initiating a lung protective ventilator strategy (low tidal volume, high PEEP)
   C. Placing the bed in Trendelenburg position for placement of a central line
   D. Reducing a femoral fracture

12.3.   In which of the following instances is administration of systemic glucocorticoids MOST appropriate?
   A. Subarachnoid hemorrhage with elevated ICP
   B. Communicating hydrocephalus with elevated ICP
   C. Traumatic brain injury with elevated ICP
   D. Intracerebral tumor with elevated ICP

13. Delirium

Jace Perkerson MD and Ansgar Brambrink MD PhD

Key Points

• Delirium is commonly seen in ICU patients; it is characterized by inattention, impaired cognition, and a fluctuating course.

• Critically ill patients that develop delirium have increased mortality rates, increased hospital length of stay, cost of care, days requiring mechanical ventilation, and increased rates of long term cognitive impairment.

• All ICU patients should be screened daily for the presence of delirium.

• Prevention of ICU delirium is achieved by limiting modifiable risks, judicious use of all deliriogenic medications, early mobilization, and promotion of a healthy sleeping environment.

A 70 year old man with CAD, HTN, and NIDDM, is admitted to the ICU for E. coli bacteremia and sepsis. He requires a norepinephrine infusion at 5 mcg/min to maintain MAPs > 60 mm Hg. On HD #2, ICU nurses note that the patient is agitated. He pulls out his IV twice and tries to get out of bed without assistance. He has angry outbursts and claims the staff is trying to harm him. On exam he is lethargic. It takes several attempts to gain his attention to answer questions. Once focused on a question he rambles and his speech is incoherent. There are no focal neurological deficits.

Delirium is a very common problem among patients in the ICU. Due to its dramatic negative impact on patient outcomes, it is important that all ICU providers be familiar with the clinical syndrome and its inherent challenges. This article is intended to provide a brief overview about the clinical presentation and possible interventions for prevention and treatment of ICU delirium.

What is delirium and why is it important?

Delirium is an acute clinical syndrome often seen in ICU patients. It is a form of organ dysfunction characterized by altered consciousness, impaired cognition, and a fluctuating course. Three subtypes of delirium have been described: hypoactive, hyperactive, and mixed. Hyperactive delirium is characterized by agitation, irritability, perseveration and hypervigilance. Hypoactive is common among elderly patients, is easily missed by ICU practitioners, and carries a poor prognosis when compared to the other subtypes. Hypoactive delirium is notable for features such as slowed speech, lethargy, and diminished alertness. Elements of both, hyperactive and hypoactive delirium characterize the mixed subtype.

Delirium is common in the ICU. The prevalence varies widely with different patient populations. For example, nearly 80% of patients requiring mechanical ventilation are diagnosed with delirium while non-intubated patients have an incidence closer to 20%. Overall prevalence ranges from 45% to 87%. Many adverse outcomes have been associated with delirium in the ICU. These include increased risk of death during hospitalization, prolonged mechanical ventilation, increased rates of unplanned extubation, and increased healthcare costs. In addition, patients diagnosed with delirium in the ICU often have increased rates of cognitive deficits

and increased rates of death up to one year later.

What causes delirium?

The pathophysiology of delirium is not well understood. Multiple hypotheses exist for mechanisms. Some research suggests decreased cholinergic activity in the development of delirium. Other studies suggest alterations of the immune system may trigger delirium based on observation of high levels of inflammatory mediators (TNF-1) at the onset of ICU delirium. Increased dopaminergic activity and an imbalance in serotonin levels have also been implicated. Due to the complex nature of cognition it is likely that the etiology of ICU delirium is multifactorial. Future research will likely allow better understanding of the biological bases of the clinical syndrome.

Numerous factors have been identified that place an ICU patient at increased risk for the development of delirium. Some factors are patient-related, such as age, medical history, and conditions related to the acute illness, and can alert the clinician to a patient "at risk". Other factors may prove to be targets for prevention or treatment of delirium. For example, the knowledge that daily interruption of pharmacological sedation in the ICU is associated with decreased rates of delirium has led to change in how respective medications are used. Good examples are the current recommendations regarding the use of benzodiazepines.[1] Table 13.1 summarizes known risk factors, and Table 13.2 cites medications that have been associated with ICU delirium. Considering this information may aid the ICU provider in strategies to decrease the incidence of delirium in their patients.

Table 13.1 Risk Factors for ICU Delirium		
Patient Related Factors	**Acute Illness Factors**	**Hospitalization / Treatment Related Factors**
Alcohol/Tobacco Use	Sepsis	Impaired Sleep/Noisy Environments
Increased Age	Fever	Medications (see Table 13.2)
Depression	Shock	Foley Catheters
Dementia	Anemia	Gastric Tubes
	Respiratory Disease	Immobility
	Medical Disease	Lack of hearing aids, glasses, dentures
	Electrolyte Abnormalities	

How is delirium diagnosed?

Patients with delirium exhibit both, impaired cognition and abnormal behavior. These abnormalities can be mild, moderate or severe, and their presence and course can vary during the progression of the disease. Impaired cognition is often the first sign. Patients are noted to be disoriented to person, place, or time. Other signs are impaired memory and reduced level of consciousness. Alteration in the sleep-wake cycle, paranoid delu-

Figure 13.1 CAM-ICU Worksheet

sions, and hallucinations are also common features of delirium.

In current ICU practice, affected patients remain often unrecognized, particularly those with the hypoactive subtype of delirium. A number of clinical tools have been developed to aid in diagnosis. While at least six different scales have been validated, cur-

rently the most commonly used instrument is the 'Confusion Assessment Method for the Intensive Care Unit' (CAM-ICU) that was specifically developed for use in nonverbal ICU patients. While initially complex appearing, the instrument is quite easy to use, and it takes only minutes to assess a patient. With > 90% sensitivity and specificity, this assessment tool is highly reliable for clinical use.[2] CAM-ICU looks for the presence or absence of four key features of delirium:

1. Acute or fluctuating course
2. Inattention
3. Altered level of consciousness, and
4. Disorganized thought.

Based on the results, a given patient is deemed either CAM-ICU positive (delirium present) or CAM-ICU negative (no delirium). Figure 13.1 shows a typical CAM-ICU assessment sheet (available in multiple languages).

Routine use of a validated screening instrument such as the CAM-ICU will help the clinician to avoid undiagnosed and, therefore, untreated ICU delirium.

How can delirium be prevented?

Day-to-day clinical practice in the ICU should include considerations regarding delirium prevention. Clinicians can aim to avoid medications, which are known to cause, or are associated with an increased rate of delirium. Nevertheless, immediate patient care needs may present obstacles to this goal. For example, the requirements for adequate sedation and pain relief need to be balanced against the risk for inducing delirium. While sedatives and analgesics frequently cannot be avoided completely in the critically ill, the clinician can try reducing the dose or frequency as best as possible. Recent evidence suggests that daily stoppage of sedatives, when combined with a spontaneous breathing trial, decreases the rate of ICU delirium.[1]

Table 13.2 Medications Commonly Associated with ICU Delirium	
Prescription	**Over-The-Counter**
benzodiazepines	diphenhydramine
barbiturates	mandrake
narcotics	henbane
antiparkinson agents	jimson weed
antihistamines	belladonna extract
H2 blockers	valerian
scopolamine	loperamide
fluoroquinolones	
tricyclic antidepressants	
lithium	
digitalis	
beta-blockers	
muscle relaxants	
steroids	

Similarly, clinicians can try avoiding specific drugs that alone, or in combination with others, increase the risk for delirium. Strong evidence suggests that benzodiazepines (e.g. midazolam, lorazepam) can cause delirium. Therefore, sedation strategies that avoid benzodiazepines likely will decrease the rate of delirium in the ICU setting.

A specific conundrum is the treatment of pain. While inadequate pain management has been shown to be a risk factor for ICU delirium, opioids, the most potent analgesics, have been closely associated with promoting ICU delirium. Equally well documented is that opioids, strictly used as analgesics, actually decrease the prevalence of delirium. Clinicians should therefore frequently assess ICU patients for pain and treat with potent analgesics including opioids as needed. Accurately assessing pain and distinguishing it from ICU delirium is particularly challenging in the non-verbal patients as the 2 diagnoses often present with similar symptoms, e.g. restlessness, agitation or anxiety. For practical purposes, the available evidence suggest that opioids, when used for the treatment of pain and not for the treatment of agitation or anxiety are safe and apparently do not trigger delirium in ICU patients.

Numerous non-pharmacologic strategies have been suggested to reduce the risk for delirium in the ICU. Some examples are: early mobilization, physiologic sleep-wake rhythm and noise control.

Most patients in the ICU are confined to their beds, and while physical and occupational therapy in the past were deemed unsafe for critically ill patients (especially those requiring mechanical ventilation), early mobilization today is considered standard of care and identified as a means to reduce the incidence of delirium.[1]

ICU patients are exposed to an environment that does not promote healthy sleep patterns unless this issue is specifically considered by the treatment team. Numerous alarms, communication between personnel, illuminated rooms, hallways and monitors, as well as repeated oral medications will reduce the amount and quality of sleep. Encouraging a quiet, calm environment that employs lighting strategies to simulate a day-night cycle, thereby promoting adequate sleep, can further reduce delirium in ICU patients.

In addition to reducing or eliminating deliriogenic medications and employing non-pharmacologic methods, options for prophylactic medical treatment have been explored. Among the drugs tested, the anti-dopaminergic, antipsychotic haloperidol has been studied most intensely with mixed results. While some studies suggested a significant effect in delirium prevention compared to placebo, others did not observe any benefit resulting from preemptive haloperidol medication.[2] Based on these results, prophylactic anti-delirium treatment using antipsychotic drugs are currently not recommended.

Once diagnosed, how is delirium treated?

First and foremost, the treatment of ICU delirium starts by addressing critical illness. Significant imbalances in volume status, electrolytes, glucose, nutrition status, and oxygen delivery should be optimized first. Next, drugs that are known triggers of delirium should be discontinued or their dosages decreased if possible. Protecting the patient from self-injury is another important aspect in the management of this syndrome. While physical restraints may sometimes be indicated for safety, their use also has been linked to an increased incidence of delirium. Therefore restraint use should be viewed as a last resort, and other techniques for behavior management should be employed. Close observation by a nurse, family member, or other healthcare provider ('sitter') is often very

effective.

Medications are often used for the treatment of ICU delirium, although solid evidence proving their effectiveness is lacking. Nevertheless, haloperidol is currently most commonly used as the first line therapy for the hyperactive form of delirium. In addition, newer antipsychotics (so called 'atypicals') have recently received great attention. While the data is still inconclusive, agents like risperidone, olanzapine, and quetiapine are currently considered effective treatment alternatives.

As a matter of principle, the potential benefit of antipsychotics must always be balanced against their inherent risk for QT prolongation, cardiac arrhythmia and other side effects relevant to the critically ill patient. Due to the lack of tangible evidence, current practice guidelines published by the Society of Critical Care Medicine make no specific recommendation for the use of these agents for the treatment of ICU delirium. Rather, they recommend against the use of these agents in patients who are at risk for torsades de pointes.[3]

Benzodiazepines and cholinesterase inhibitors are counterproductive in the management of delirium for the reasons mentioned above, and should be avoided.

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Questions

13.1 Of the following subtypes of ICU delirium, which carries the worst prognosis?

A.   Hyperactive
B.   Hypoactive
C.   Mixed
D.   Organic

13.2 Which of the pairings below are BOTH known to be risk factors for the development of ICU delirium?

A.   Depression AND IV potassium
B.   Mechanical ventilation AND early rehabilitation
C.   Benzodiazepines AND foley catheters
D.   Steroids AND analgesic therapy for post-surgical pain

13.3. Of the following, which can help prevent the onset of delirium in the ICU?

A.   Avoidance of benzodiazepines
B.   Adequate analgesia
C.   Promotion of a normal sleep/wake cycle
D.   Early mobilization and rehabilitation
E.   All of the above

13.4 Of the following medications commonly used in the treatment of delirium, which agent should be avoided in the hemodynamically unstable patient?

A.   Haloperidol
B.   Olanzapine
C.   Quetiapine
D.   Risperidone
E.   Dexmedetomidine

Section 4: Airway and Pulmonary
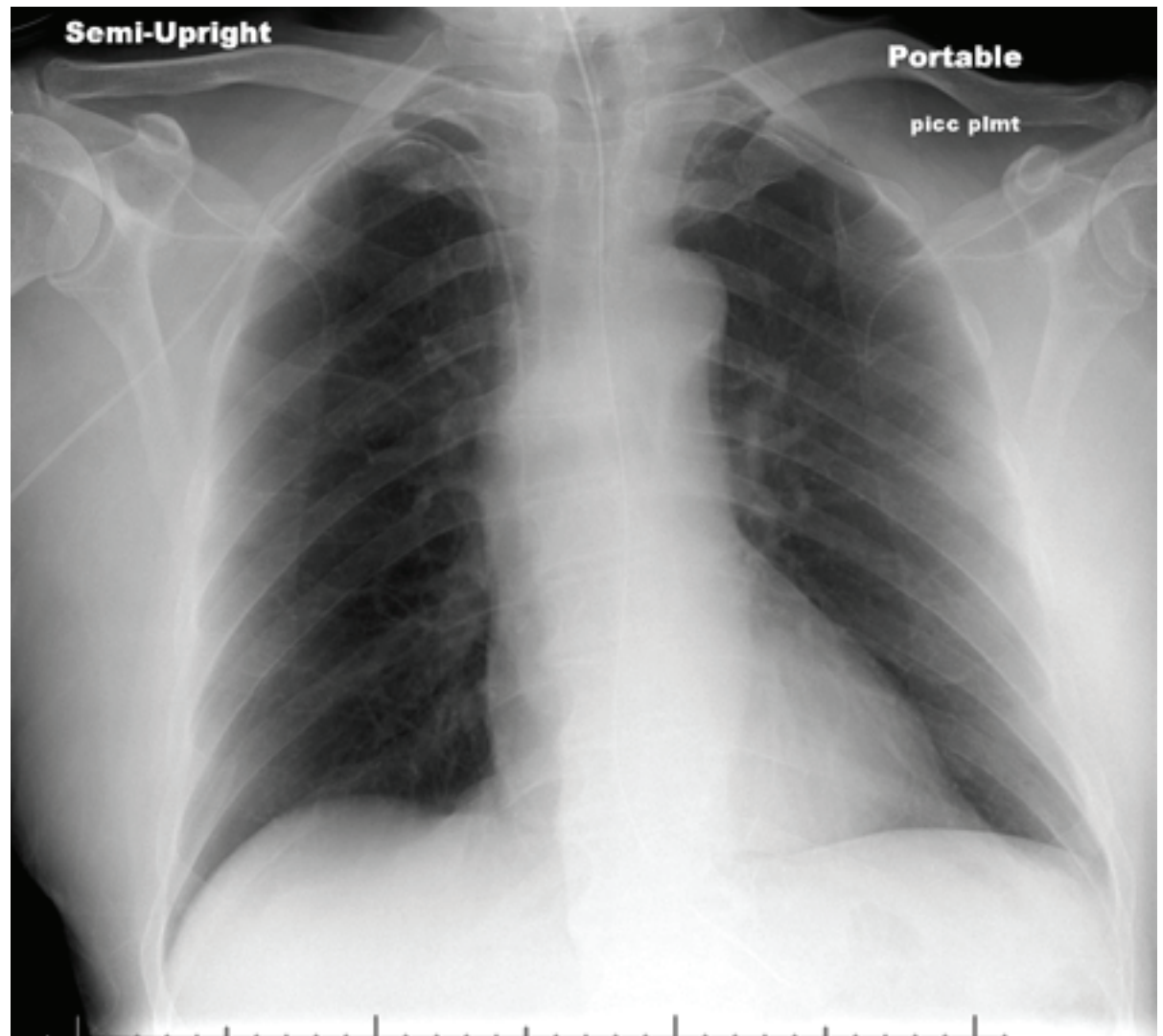
14. Airway Management

Elizabeth Hankinson MD and Aaron Joffe DO

Key Points

• The 3 major indications for airway management in the ICU are need to: (1) deliver a high FIO2; (2) positive pressure ventilation; and/or (3) provide an artificial airway/ to secure an airway

• There are various instruments and methods available to place an endotracheal tube. Available equipment, patient factors, and provider preference will ultimately dictate the final course of action.

• Always be familiar with a 'back-up' plan should the first plan be unsuccessful.

• Complications in the ICU are more common than in the operating room.

A 22-year-old male is involved in a motor vehicle accident and arrives to the hospital with a suspected C4 vertebral fracture. He is admitted to the ICU for neurologic evaluation and airway management. The patient is 87 kg and 182 cm with good mouth opening. He is currently in a cervical collar and his Mallampati score is 2. An awake fiberoptic technique is selected and his airway is topicalized with aerosolized and viscous lidocaine. An infusion of dexmedetomidine is started during the topicalization and he is placed on nasal cannula at 4L/min. He is sedated yet spontaneously ventilating while a fiberoptic bronchoscope is passed through the mouth and the vocal cords. An 8.0 cuffed endotracheal tube is passed over the bronchoscope.

Institution of invasive mechanical ventilation can be a lifesaving procedure in critically ill patients. It should be noted, however, that the reported incidence of airway related morbidity and mortality is several fold higher when performed emergently outside of the operating room. This is not surprising in that critically ill patients frequently have limited physiologic reserve. Additionally, the primary indication for the procedure is often hemodynamic instability, hypoxic or hypercapnic respiratory failure, or the need for an artificial airway consequent to airway edema, copious secretions, altered mental status, or injuries to the head and neck. Thus, awakening the patient after induction or deferring the procedure until conditions are more optimal is not an option.

Indications for Invasive Airway Management

The indications for invasive airway management can be broadly categorized into three categories: the need to deliver a high fraction of inspired oxygen (FiO_2), the need for positive pressure ventilation, or need of an artificial airway/secure an airway (Table 14.1). These categories are not necessarily mutually exclusive. For example, a patient suffering neuromuscular weakness due to Guillain-Barré syndrome may have atelectasis, a decreased FRC, elevated intrapulmonary shunt fraction, and increased elastic work of breathing (need for positive pressure). Additionally, bellows fatigue may result in alveolar hypoventilation (need for ventilation) while cranial nerve involvement can severely impair the ability to control and coordinate the muscles of the upper airway (need for an artificial airway).

Table 14.1: Indications for Airway Management

Need for high FiO2	Need for Ventilation	Need for Artificial Airway
- hypoxemic respiratory failure - CHF - pulmonary contusion - ALI/ARDS - Morbid obesity	- hypercapneic respiratory failure - neuromuscular disease - cervical spinal cord injury - diaphragmatic paralysis - COPD exacerbation - severe asthma exacerbation - drug intoxication	- airway obstruction - suppressed upper airway reflexes - facial or neck trauma - oropharyngeal or laryngeal edema - TBI, stroke, SAH - GCS < 9 - sustained seizure activity - copious secretions

Airway Examination

The external airway exam has poor positive and negative predictive value. For the purposes of procedural planning, airway difficulty should be expected. Nonetheless, a rapid but thorough examination of the airway should be done whenever possible prior to airway management. Traditionally reported risk factors for difficult mask ventilation and difficult intubation are presented in Table 14.2. More recently, a seven item score was shown to be accurate and precise in identifying patients at risk for difficult intubation in the ICU (Table 14.3). Mallampati grading is presented in Figure 14.1. Examination is classically performed with the patient sitting upright, neck extended and tongue protruding without phonation. However, assessment of the patient in recumbent position, as may be necessary in the critically ill, is at least as good.

Table 14.2: Characteristics Predictive of Difficulty Ventilating or Intubating

Predictors of Difficult Ventilation	Predictors of Difficult Intubation
- BMI > 30 - macroglossia - edentulous - facial trauma/swelling - snoring - limited jaw protrusion	- facial trauma/swelling - airway swelling or bleeding - anatomical anomalies - thyromental distance < 3FB - mouth opening < 2FB - decreased neck ROM - significant overbite - short, thick neck - Mallampati class III or IV

BMI: body mass index; FB: fingerbreadths; ROM: range of motion

Intubation in the ICU

The first step is to determine the urgency of the clinical situation. Whenever possible, an evaluation of the airway should be performed and the patient's vital signs, medications, allergies, recent labs and mental status reviewed. The ICU staff and respiratory therapist should be notified of an impending intubation. Following an intubation checklist (See example of one in Figure 14.2) will ensure a standardized approach to the setup and communication surrounding the procedure. Such an intubation "bundle" has been shown to reduce severe hypoxemia and cardiovascular collapse in the ICU (Table 14.4)

ICU patients may be obtunded and require little or no medication in order to induce anesthesia for tracheal intubation. If medications are required, consider the patient's hemodynamic status, renal function and electrolytes. The intensivist should understand the

pharmacologic profile of the medications chosen, the side effects, and how to counter them.

A variety of techniques may be used to secure the airway. However, orotracheal intubation using some type of (modified) rapid sequence induction/intubation (RSI) is by far the most common. Routine asleep intubation is performed when the provider feels confident that the airway can be secured after induction. Optimal patient position is the "sniffing" position with the neck flexed and the head extended at the atlanto-occipital joint to align the oral, pharyngeal and laryngeal axes.
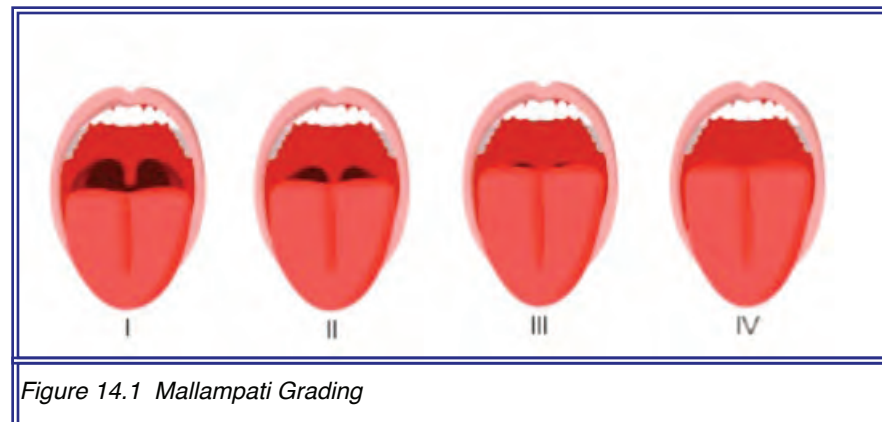
Figure 14.1 Mallampati Grading

After induction, the ability to bag-mask-ventilate is verified. A neuromuscular blocking agent (NMBA) is then given with bag-mask-ventilation continued until the airway is secured with the placement of the endotracheal tube. This step of "test ventilating" prior to administration of the neuromuscular blocking drug is commonly omitted when rapid sequence induction/intubation techniques are used. Securing the airway can be facilitated via direct or video laryngoscopy, intubating LMA, Eschmann stylet or a flexible fiberoptic bronchoscope. Direct laryngoscopy is the most common initial method when

Table 14.3: MACOCHA Score for Predicting Difficult Intubation

	Factors	Points
Patient	Mallampati Score III or IV	5
	Obstructive Sleep Apnea	2
	Cervical Spine Immobility	1
	Mouth Opening < 3cm	1
Disease	Coma	1
	Hypoxemia	1
Practitioner Experience	Non-Anesthesiologist	1

Total scored from 0-12, with higher scores predicting increased difficulty.
Adapted from deJong, et al.[9]

EMERGENCY INDUCTION CHECKLIST

Prepare Patient	Prepare Equipment	Prepare Team	Prepare for difficulty
❑ Is preoxygenation optimal?	❑ What monitoring is applied?	❑ Who is ...?	❑ If the airway is difficult, could we wake the patient up?
	❑ ECG	❑ Team leader	
	❑ Blood pressure	❑ First Intubator	
❑ Is the patient's position optimal?	❑ Sats probe	❑ Second Intubator	
	❑ Capnography	❑ Cricoid Pressure	❑ If the intubation is difficult, how will you maintain oxygenation? (Plans A,B,C,D)
		❑ Intubator's Assistant	
		❑ Drugs	
		❑ MILS (if indicated)	
❑ Can the patient's condition be optimised any further before intubation?	❑ What equipment is checked and available?	❑ How do we contact further help if required?	❑ Where is the relevant equipment, including alternative airway?
	❑ Self-inflating bag		
	❑ Suction		
	❑ 2 ET tubes		
	❑ 2 laryngoscopes		❑ Are any specific complications anticipated?
❑ How will anaesthesia be maintained after induction?	❑ Bougie		
	❑ Do you have all the drugs required, including vasopressors?		

This Checklist is not intended to be a comprehensive guide to preparation for induction

RTIC Severn

taken from saferintubation.com

Figure 14.2 Emergency Induction Checklist

the external airway examination is reassuring. Regardless, the immediate availability of adjunct airway equipment is of vital importance and should not be overlooked.

When a grade 1 view is acquired, the tube can be directly inserted. This may not be the case with a grade 2 view and an Eschmann stylet may be employed. When a grade 3 view is acquired, the Eschmann stylet is recommended, but may not be sufficient and the operator may need to move to another technique altogether, whereas with a grade 4

Table 14.4: ICU Intubation Bundle Worksheet

PRIOR to intubation:
- two operators available
- small fluid bolus (250-500ml) in the absence of cardiogenic pulmonary edema
- long-term sedation available
- pre-oxygenation with 100% oxygen for 3-5 minutes if time allows

INTUBATION:
- RSI: propofol, etomidate or ketamine, followed immediately by succinylcholine (in the absence of hyperkalemia, severe acidosis, neuromuscular disease, spinal cord trauma or burn injury over 48h, in which case rocuronium may be substituted)
- Cricoid pressure (Sellick maneuver) until confirmation of secure airway

AFTER intubation:
- confirmation with capnography* followed by CXR
- initiation of long-term sedation
- initiation of mechanical ventilation (initial Vt 6-8ml/kg)

*capnography may be inaccurate if cardiac output is extremely low or non-existent such as in cardiac arrest. RSI: rapid sequence induction; CXR: chest x-ray; Vt: tidal volume

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view, an alternative technique should be immediately employed. (Figure 14.3) "Blind" intubation techniques are discouraged, unless there is no other option.

Patient's requiring emergent intubations are often not NPO and need a rapid intubation process to protect against aspiration of gastric contents during induction referred to as rapid sequence induction. Rapid sequence induction is done by administering the induction agent, immediately followed by a rapid-acting neuromuscular blocking agent while applying cricoid pressure (Sellick maneuver) with no attempts at bag mask ventilation prior to securing the airway.

An awake intubation is reserved for patients with airway pathology resulting in significantly increased risk of failed intubation and/or ventilation after induction. This includes patients with significant face and neck pathology, oropharyngeal obstruction, and those with severely limited mouth opening. The sensory nerves of the airway - glossopharyngeal, superior laryngeal and the recurrent laryngeal – can be anesthetized prior to the procedure to prevent excessive gagging and coughing. An awake intubation is performed in a variety of ways, including blind nasal, direct laryngoscopy, or most commonly, with a flexible fiberoptic bronchoscope. This technique takes time and requires a patient who is somewhat cooperative and stable. Sedation with minimal changes in respiratory drive or muscle tone can be achieved with low-dose infusions of either dexmedetomidine or remifentanil.

Airway management outside of the OR (i.e., the ICU) is often more challenging and has

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an increased rate of complications. Every healthcare provider should be prepared with appropriate anesthetic agents, vasopressors and difficult airway equipment, have the most experienced personnel available, have appropriate staff present and have a backup plan prepared.   When faced with a difficult airway, either anticipated or discovered after induction, the managing physician should have some familiarity with the difficult airway algorithm endorsed by the ASA (Figure 14.4).

Complications of Endotracheal Intubation

The incidence of complications associated with endotracheal intubation is quite small when done electively in a controlled environment. However, there is a several fold increase when done emergently on critically ill patients outside the operating room. Complications associated with endotracheal intubation can occur either during intubation or after the endotracheal tube is in place (Table 14.5).
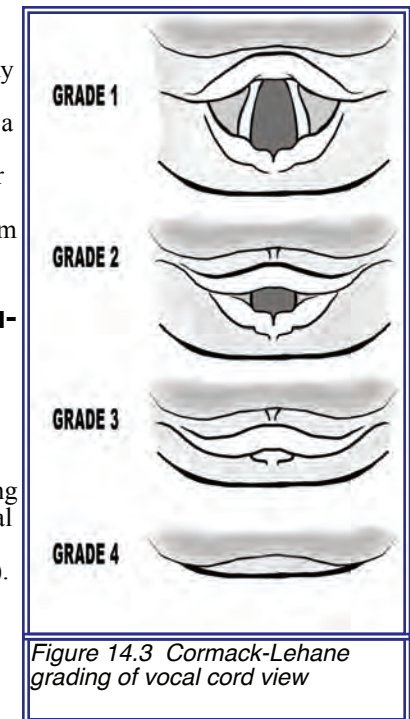
Figure 14.3 Cormack-Lehane grading of vocal cord view

Table 14.5: Complications of Endotracheal Intubation

During Intubation

Trauma: dental, lip or oral mucosa, perforation or dislocation of pharyngeal, laryngeal or tracheal structures

Pulmonary: hypoxia, esophageal intubation, laryngospasm, bronchospasm

Cardiovascular: hypotension, hypertension, arrhythmias

Neurologic: increased ICP, passage of tube into cranial vault during nasal intubation in patient with basilar skull fracture

Post Intubation

kinking or blockage of tube

misplacement/displacement of tube

ischemia of tracheal tissue

vocal cord injury

sinusitis (nasal intubation)

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Questions

14.1 After administering intravenous medications for a rapid sequence induction, you attempt to intubate the patient via direct laryngoscopy. You have a grade 4 view and are unable to successfully intubate the trachea on your first attempt. The patient's saturation is now 84%. After calling for help, what is your next step in airway management?
  A. Placement of an LMA
  B. Attempt to intubate with a different blade (i.e. Macintosh to Miller)
  C. Fiberoptic intubation
  D. Attempt face mask ventilation

14.2 Which of the following statements regarding cricoid pressure for rapid sequence intubation is true?
  A. Despite adequate cricoid pressure, aspiration may still occur, particularly in patients withfull stomachs or active vomiting.
  B. Cricoid pressure should be released immediately after the endotracheal tube is inserted.
  C. When applied correctly, cricoid pressure will always prevent aspiration during intubation.
  D. None of the above

14.3 A man is admitted to the ICU following a motor vehicle collision with blunt trauma to the face, head, and neck. Although still protecting his airway, he does have a decreasing mental status. You decide to electively intubate this patient. Which of the following statements regarding the management of this patient's airway is true?
  A. An awake blind nasal intubation is an acceptable method and route.
  B. An asleep intubation via direct laryngoscopy with propofol and vecuronium is not unreasonable.
  C. An awake fiberoptic intubation through the mouth is safe.
  D. A rapid sequence induction is not indicated for an asleep intubation.

14.4 A 37 year-old woman presents to the ER 2 hours after sustaining a 3rd degree burn to 45% of her body in a house fire. On exam, you observe soot in the airway and singed nasal hairs. She is awake, alert, and oriented to person, place, and time. Her voice is clear and easy to understand. Which of the following is most appropriate?
  A. Clear the patient for discharge
  B. Continue to monitor the patient in the ER
  C. Electively intubate this patient
  D. Electively administer ketamine

14.5 You are called to the ICU to intubate a patient with respiratory distress. The patient is a 27 year-old woman G1P0 at 30-weeks gestational age. She has a history of cystic fibrosis, chronic hypertension, and newly diagnosed gestational diabetes. Her last meal was 10 hours ago. You prepare your equipment for intubation. Which of the following is most accurate regarding your airway management?
  A. A standard induction using a slower-acting neuromuscular blocking agent is appropriate since the patient's last meal was over 8 hours ago.
  B. Patients with diabetes always have delayed gastric emptying and therfore should receive a rapid sequence induction.
  C. Pregnancy places this patient at risk for aspiration and a rapid sequence induction is safest.
  D. Pregnancy causes dilation of the airway and a larger endotracheal tube is recommended.

Figure 14.4 ASA Difficult Airway Algorithm, 2013 [7]

AWAKE INTUBATION

Airway approached by Noninvasive intubation

Invasive Airway Access[b]*

Succeed*

FAIL

Cancel Case

Consider feasibility of other options[a]

Invasive airway access[b]*

INTUBATION AFTER INDUCTION OF GENERAL ANESTHESIA

Initial intubation attempts successful*

Initial intubation Attempts UNSUCCESSFUL

FROM THIS POINT ONWARDS CONSIDER:
1. Calling for help.
2. Returning to spontaneous ventilation.
3. Awakening the patient.

FACE MASK VENTILATION ADEQUATE

FACE MASK VENTILATION NOT ADEQUATE

CONSIDER/ATTEMPT SGA

SGA ADEQUATE*

SGA NOT ADEQUATE OR NOT FEASIBLE

NONEMERGENCY PATHWAY
Ventilation adequate, intubation unsuccessful

EMERGENCY PATHWAY
Ventilation not adequate, intubation unsuccessful

Alternative approaches to intubation[c]

IF BOTH FACE MASK AND SGA VENTILATION BECOME INADEQUATE

Call for help

Emergency noninvasive airway ventilation[a]

Successful Intubation*

FAIL after multiple attempts

Successful ventilation*

FAIL

Invasive airway access[b]*

Consider feasibility of other options[a]

Awaken patient[d]

Emergency invasive airway access[b]*

15. Tracheostomy Management

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Key Points

• There are no major outcome differences between surgical versus percutaneous tracheostomies

• No consistent evidence for major outcome benefits to early (prior to 10 days) versus late (after 10 days) tracheostomy

• A decannulated fresh (within 7 days of tube insertion) tracheostomy is an airway emergency and generally the first maneuver should be securing the airway via oro-tracheal intubation.

A 26 year-old man, intubated in the emergency department for a GCS of 5 following a motor vehicle crash, is admitted to the intensive care unit. Persistently elevated intracranial pressures requiring deep sedation and paralysis, ventilator-associated pneumonia, and acute lung injury complicate his ICU course. On ICU day 9, he remains intubated due to continued encephalopathy. An uncomplicated percutaneous bedside tracheostomy is performed with placement of a size 6 cuffed, unfenestrated Shiley tracheostomy tube. On post-procedure day 2, his tracheostomy tube is accidentally dislodged. His airway is re-secured via oral endotracheal intubation. His Shiley tracheostomy tube is then replaced under bronchoscopic guidance.

Introduction

A tracheostomy is the creation of an opening into the trachea such that the tracheal mucosa is continuous with the external epithelium. It is an increasingly popular procedure that may be performed open (surgically) in the operating room or percutaneously at the bedside. A tracheostomy decreases the work of breathing by decreasing the volume of dead space and increases the ease of respiratory care (e.g., tracheal suctioning). However, it results in the loss of some upper airway functions, such as filtration and humidification of inspired air. Tracheostomies are commonly seen in the ICU for patients requiring prolonged mechanical ventilation.

Indications

Clinical indications for tracheostomy include the following.[1]

- Prolonged or expected prolonged intubation/mechanical ventilation
- Upper airway obstruction
- Inability to manage secretions (including aspiration or excessive broncho-pulmonary secretions)
- Ventilator support to facilitate rehabilitation
- Inability to be orally or nasally intubated
- As an adjunct to manage head and neck surgery or significant head and neck trauma

• Chronic mechanical ventilation due to chronic respiratory failure

The benefit of early (within one week of endotracheal intubation) versus late tracheostomy remains an issue for debate. Tracheostomy placement may improve patient comfort while decreasing the use of sedatives, and facilitating weaning from mechanical ventilation. It may also reduce trauma to the upper airway, the incidence of nosocomial pneumonia, and ICU or hospital length of stay. A 2005 systematic review and meta-analysis suggested that early tracheostomy reduced the duration of mechanical ventilation and hospital stay yet it failed to demonstrate an improvement in mortality or the occurrence of nosocomial pneumonia.[2] A 2012 Cochrane review drew similar conclusions, but noted that available data is limited and could lead to bias.[3] To address this question, a recent large randomized controlled trial (TracMan) comparing early (≤ 4 days) to late (≥ 10 days) tracheostomy was performed. Again, there was failure to demonstrate improvement in 30-day mortality, 2-year mortality or ICU length of stay.[4] These studies also commented on the difficulty in accurately predicting patients who will require long-term endotracheal intubation.

Contraindications[5]

• Patient or surrogate refusal to consent
• Infection at the site of potential tracheostomy placement
• Anatomic aberrations obscuring neck anatomy,
• Patient instability, including high oxygen requirements or ventilator settings
• Coagulopathy

Technique

The tracheotomy is typically performed between the 2nd and 3rd or 3rd and 4th tracheal ring interspace. (Figure 15.1) Placement too high increases the risk of subglottic stenosis. Placement too low increases the risk of damaging vascular structures (the brachiocephalic vein or innominate artery) and accidental decannulation in the early postoperative period.[5]

Open (surgical) tracheostomies typically involve transport of the patient to the operating room where pre-tracheal tissues are surgically dissected and the tracheostomy tube is inserted into the trachea under direct vision. Percutaneous tracheostomies can be done at the bedside and employ a Seldinger technique followed by blunt dilation over a wire to open pre-tracheal tissues for the passage of a tracheostomy tube. Wire cannulation and tube placement are usually visualized in real-time with bronchoscopy. Research has yielded conflicting results regarding the superiority of open or percutaneous tracheostomies, thus the choice of technique is typically based on institution and surgeon preference. A recent meta-analysis suggests that percutaneous tracheostomies may have a lower occurrence for wound infection (OR 0.28, 95% confidence interval 0.16 to 0.49, p < 0.0005) with otherwise equal incidence of bleeding, major peri-procedural and long-term complications.[6]

Tracheostomy Tube Types and Management

Tracheostomy tubes vary based on material used for construction, length, diameter, and presence or absence of an inner cannula, cuff and fenestrations.[7] Components of a
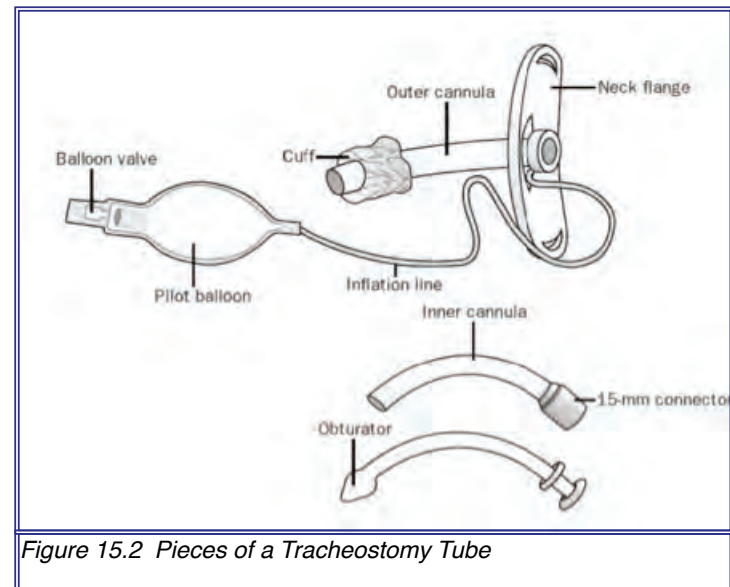
Figure 15.2 Pieces of a Tracheostomy Tube

Figure 15.1 Anatomy of Tracheostomy Site

tracheostomy include the following (Figure 15.2):

- Single cannula
- Double cannula (inner and outer cannulas)
- Neck flange
- Obturator
- Cuff
- Pilot Balloon

Tubes with variable lengths proximal and distal to their bend accommodate variations in tracheal tissue depth and anatomy. A longer proximal portion or an adjustable flange will accommodate patients with thicker pre-tracheal tissues, while a longer distal portion may facilitate ventilation in patients with tracheal anomalies. Tube diameter, defined both by inner and outer cannula diameters, affects resistance to airflow and work of breathing. Although an inner cannula decreases the effective diameter and thus increases resistance to airflow, the removable cannula allows for convenient respiratory care, as inspissated mucous can be removed with a simple inner cannula exchange or cleaning.

- There are no major outcome differences between surgical versus percutaneous tracheostomies
- No consistent evidence for major outcome benefits to early (prior to 10 days) versus late (after 10 days) tracheostomy
- A decannulated fresh (within 7 days of tube insertion) tracheostomy is an airway emergency and generally the first maneuver should be securing the airway via oro-tracheal intubation.

Nearly all tubes in the ICU, especially newly placed ones, will have an inflatable cuff to facilitate positive pressure ventilation. As weaning from mechanical ventilation occurs, the cuff may be deflated or the tube exchanged for a cuffless, fenestrated, and/or smaller diameter tube; however, tubes should only be exchanged 7 days following initial cannulation to ensure epithelialization of the tracheostomy site. Tube fenestrations increase the ease of airflow around and through the tube. A smaller diameter tube may improve a patient's ability to phonate with the use of a Passy-Muir valve, which is a one-way valve attached to a tracheostomy that allows inhalation through the tracheostomy but blocks airflow during exhalation and thus forces air through the vocal cords. It is contraindicated to have a tracheostomy cuff inflated with a 1-way valve in place, as this renders the patient unable to exhale. Eventually, if the indications for initial tracheostomy have been reversed, decannulation of the tracheostomy can be considered. In general, a mature stoma can close up to 50% within 12 hours and up to 90% within 24 hours; complete closure may take up to 2 weeks.[8]

Complications
Complications of tracheostomy can occur intraoperatively and during the early or late postoperative periods. The three most common tracheostomy emergencies are the following.[8]

- Major bleeding
- Tube dislodgment
- Tube obstruction

Intraoperative complications include bleeding, injury to surrounding structures (the thyroid, esophagus, recurrent laryngeal nerves, and surrounding vasculature), pneumothorax, and air embolism. Bleeding is the most common complication, typically the result of injury to the anterior jugular veins or thyroid isthmus.[5] Care is taken to remain midline during tracheostomy and, where applicable, perform suture ligation of the thyroid isthmus. Other structures at risk when straying off midline during tracheostomy include the recurrent laryngeal nerves, carotid sheath and internal jugular vein. Injury to the internal jugular vein may result in the rare complication of air embolism. Injury to the posterior tracheal wall may result in a trachea-esophageal fistula.

Early postoperative infection as a complication of tracheostomy is rare; prophylactic antibiotics are not typically used during this procedure.[5, 7, 8] Subcutaneous emphysema can be a result of excessive positive pressure ventilation or false lumen passage. Mucus plugging leading to acute airway obstruction is a common occurrence with new tracheostomies. Deep suctioning, warm humidified air/oxygen, or nebulized normal saline treatments may decrease this occurrence.

Early tracheostomy tube displacement is an airway emergency as the tracheostomy tract is not yet epithelialized and blind recannulation may result in the creation of a false lumen. The first approach after accidental early decannulation should be oro-tracheal intubation.[7, 8] Experienced providers should only undertake the passage of a tube through the tracheostomy site when tracheal rings may be visualized. Dislodged tracheostomies older than 7 days can usually be blindly recannulated with a tracheostomy tube (facilitated by an obturator) or an endotracheal tube placed through the tracheostomy site.

Late postoperative complications include the following:

- Granuloma formation with tracheal stenosis
- Tracheomalacia
- Fistula formation with multiple adjacent structures.

Granulomatous tissue formation leading to tracheal stenosis occurs due to the body's innate reaction to foreign bodies. Such findings may be asymptomatic, but occasionally require intervention such as correcting the tube size, cautery of granulation tissue, and/or laser ablation.[5] Tracheomalacia results from cuff over-inflation or excessive traction by ventilator tubing with resultant tissue ischemia and necrosis. Fistula formation, a rare late complication of tracheostomies, may form between the trachea and the esophagus, skin, and innominate artery. Tracheo-esophageal fistulas can present as tube feeds in the tracheostomy tube; other signs and symptoms include copious secretions, air leak, gastric distention, dyspnea and aspiration.[8] Tracheo-cutaneous fistulas occur when a tracheostomy tract becomes completely epithelialized. This can lead to delayed tracheostomy closure following decannulation. Tracheo-esophageal and -cutaneous fistulas require surgical intervention.

A rare but catastrophic late complication of tracheostomy is tracheo-arterial fistula, most commonly between the trachea and the innominate artery. The incidence is estimated at 0.6-0.7%, and even when urgently treated only about 20% of patients survive.[7] It

is typically a result of direct pressure of the tracheostomy tube against the innominate artery. Risk factors include low tracheostomy placement and high cuff pressures. 70% of tracheo-arterial fistulas occur within 3 weeks of tracheostomy.[7, 8] Emergent intervention - typically surgical, although there are some reports of successful treatment with embolization - is required.[8] While awaiting definitive intervention, temporizing treatment includes occlusion of the fistula with tracheal tube pressure - or if unsuccessful, tube removal and anterior digital pressure.

Conclusion

Tracheostomy placement is a common surgical procedure encountered in the ICU. Although multiple indications exist, the most common reason is failure to wean from mechanical ventilation. Unfortunately, at this point in time, no conclusive evidence exists for early versus late tracheostomy placement in the ICU population. Multiple complications, both early and late, may occur in patients with tracheostomies. As a result, patients should be closely monitored in a critical care setting in the immediate post-procedure setting. Not specifically discussed in this chapter, tracheostomy weaning, possible for many patients, occurs via a step-wise management plan and is relatively straightforward.

This chapter is a revision of the original chapter authored by Sherif Afifi, MD.

Questions

15.1 Chronic complications of tracheostomies include all of the following except:
- A. swallowing dysfunction
- B. tracheomalacia
- C. stomal erosion
- D. innominate artery – tracheal fistula
- E. pneumothorax

15.2 The timing of tracheostomy
- A. may impact success of weaning from mechanical ventilation.
- B. is considered late if conducted 10 days after oro-tracheal intubation for respiratory failure.
- C. depends on whether an open or a percutaneous tracheostomy is planned.
- D. ideally should be on the 4th day following an oro-tracheal intubation for respiratory failure due to pneumonia.
- E. has no relevance to any patient outcomes.

15.3 Which of the following is not an indication for tracheostomy?
- A. a patient with myasthenia gravis unresponsive to medical therapy and has a pH of 7.20 and PaCO2 of 80; the patient has a history of failed oro-tracheal intubation and refuses awake intubation.
- B. stridor in a patient with supraglottitis
- C. PaCO2 of 62 in a COPD patient with a respiratory rate of 24 on nasal cannula
- D. Absence of swallow reflex in a patient with a large sub-arachnoid hemorrhage who was oro-tracheally intubated 7 days ago

15.4 The following are considered emergent complications of tracheostomy tube placement except:
- A. accidental decannulation
- B. pneumothorax
- C. pneumo-mediastinum
- D. swallowing dysfunction
- E. stomal hemorrhage

15.5 The most common sequence towards removal of a tracheostomy tube is:
- A. weaned mechanical ventilation > vocalization > downsizing > plugging > decannulation
- B. down-sizing > vocalization > weaned mechanical ventilation > plugging > decannulation
- C. plugging > decannulation > vocalization > down-sizing > weaned mechanical ventilation
- D. weaned mechanical ventilation > plugging > downsizing > decannulation > vocalization
- E. decannulation > downsizing > plugging > vocalization > weaned mechanical ventilation

16. Management of Mechanical Ventilation

Daniel W Johnson MD and Edward A Bittner MD PhD

Key Points

• In Assist-Control every breath, whether mandatory or spontaneous, has the same level and type of support.

• Extrinsic PEEP maintains alveolar recruitment, increases FRC, decreases pulmonary shunt, may improve lung compliance, and may decrease the patient work of breathing.

• Peak airway pressure is the pressure required to overcome airway resistance and the elastic properties of the lung. Whereas, plateau pressure is an estimate of peak alveolar pressure, an indicator of alveolar distention.

A 66-year-old man with a history of CAD and COPD is admitted to the ICU after an open AAA repair. Overnight he remains on full ventilator support (Assist Control, Vt=500 mL, freq=18, FiO_2=0.4, PEEP=5). His fluid requirements decrease, and he is hemodynamically stable in the morning. He has an ABG of pH 7.38 / pCO_2 37 / pO_2 92 and an actual respiratory rate of 20. He is heavily sedated on propofol and hydromorphone. How would you proceed towards extubation? Spontaneous breathing trial (SBT)? Pressure support ventilation (PSV)? Synchronized intermittent mandatory ventilation (SIMV)?

Mechanical ventilatory support is commonly encountered in the ICU. At present, numerous techniques exist for the initial control and subsequent support of the respiratory system. A thorough understanding of these techniques leads to individualized treatment strategies and reduction of complications.

Ventilators

Positive pressure ventilators operate by applying positive pressure (via flow of O_2 and/or air) to the airways during inspiration. In the ICU, mechanical ventilation is almost exclusively positive pressure ventilation.

Negative pressure ventilators create intermittent negative pressure around the thorax and abdomen. The "iron lung," popular during polio outbreaks in the 1940s-50s, is the prototypical example. In modern ICUs, negative pressure ventilators are almost never used.

Modes of Ventilation

The mode of mechanical ventilation describes the control (volume, pressure, flow, time) and phase variables (trigger, limit, cycle), which define how ventilation is provided. The trigger variable is adjusted to sense patient effort (by negative pressure or by flow at the proximal airway) for the initiation of inspiration. The limit variable rises no higher than a given preset value or increases to a preset value before inspiration ends.

Cycle is the variable that terminates inspiration (commonly volume, time or flow).

Note that in the absence of patient respiratory effort (e.g. in the setting of deep sedation or neuromuscular weakness or paralysis), there is essentially no difference between the modes described below: IMV, SIMV and A-C. In the absence of patient effort, these modes utilize a preset frequency (f) and the preset inspiratory pressure (P_i) or tidal volume (Vt) to provide full respiratory support. In other words, the differences between IMV, SIMV and A-C are essentially differences in patient-ventilator interaction.

A. Intermittent mandatory ventilation (IMV): In this mode, the intensivist sets the mandatory frequency and tidal volume (if Volume Control) or inspiratory pressure (if Pressure Control) and the ventilator delivers breaths while allowing the patient to take spontaneous breaths at any time during the respiratory cycle. IMV allows the patient to take spontaneous breaths, but all spontaneous breaths are totally unsupported; and IMV has no mechanism for coordinating patient breaths with mandatory breaths. If a patient is taking a spontaneous breath when the IMV ventilator is scheduled to give a mechanical breath, dyssynchrony or "breathstacking" will occur (the full preset Vt will be delivered on top of the patient's spontaneous V_t). For example, if the ventilator is set for IMV with a frequency of 10, the ventilator will initiate a mandatory breath every 6 seconds regardless of whether the patient is taking zero or 25 spontaneous breaths per minute.

B. Synchronized IMV (SIMV): This improvement on IMV allows the ventilator to detect the patient's spontaneous breath so that the mandatory mechanical breaths can be delivered in synchrony with spontaneous breaths. SIMV was an improvement on IMV because it reduces the risk of dyssynchrony and "breath stacking." With early SIMV ventilators, spontaneous breaths between mandatory breaths received no support from the ventilator. Modern SIMV ventilators can provide varying levels of pressure support (see below) for the breaths between mandatory breaths.

If a patient is on SIMV with a mandatory rate of 10, the ventilator will deliver the mandatory breaths at times when the patient makes an inspiratory effort. If the patient makes no inspiratory effort within a 6 second interval, the mandatory breath will simply be delivered.

C. Assist-control (A-C): In assist-control, *every* breath, whether it is a mandatory breath initiated by the ventilator or a patient-triggered breath, receives the same *full* support that is prescribed for mandatory breaths. For example, if the A-C ventilator is set at V_t=600mL and freq=8 and the patient makes 30 inspiratory efforts per minute, the ventilator will deliver 600mL x 30, or 18 L/min of ventilation.

Volume Control, Pressure Control and Dual Control
Independent of the mode (IMV, SIMV, A-C), mechanical ventilation is either volume control (a set tidal volume is delivered during every mandatory breath, resulting in variable airway pressures), pressure control (a set airway pressure is maintained throughout every mandatory breath, resulting in variable tidal volumes) or dual control (a combination of volume and pressure control). This can be confusing for residents in the ICU. Remember that a patient can be on Assist Control with Volume Control, SIMV with

Volume Control, Assist Control with Pressure Control, or SIMV with Pressure Control.

A. Volume Control: A set tidal volume is delivered with a set peak inspiratory flow resulting in rising and variable airway pressure during the breath. In SIMV with volume control, only the mandatory breaths are obligated to equal the set tidal volume. In A-C with volume control, *all* breaths (ventilator initiated *and* patient triggered) are obligated to equal the set tidal volume.

B. Pressure control: A specific peak airway pressure and an inspiratory time are set. In order to maintain a constant airway pressure during inspiration, the inspiratory flow waveform is decelerating. The amount of flow necessary to maintain a constant airway pressure is affected by the airway resistance and the compliance of the lungs and chest wall. For example, the ventilator might be set at 20 cmH$_2$O for 2 seconds per breath. This might result in large tidal volumes in patients with compliant lungs and small tidal volumes in patients with non-compliant lungs.

C. Dual Control (or Adaptive Control) was designed to combine the features of volume control and pressure control. Vendors use different names to describe this mode of ventilation: "Pressure Regulated Volume Control," "Auto-Flow," and "Volume Control Plus" are examples of vendor names for dual/adaptive control. In this mode, the desired tidal volume is set and the ventilator delivers pressure control breaths in order to achieve the tidal volume. In dual control mode, the flow pattern is initially high and then decelerates just as it is during pressure control mode. The ventilator analyzes the delivered tidal volume of the previous breath and adjusts up or down the necessary airway pressure to be delivered during the next breath. For example, if the set tidal volume is 500 mL and the current breath has an airway pressure of 15 resulting in an actual tidal volume of 420 mL, the ventilator will automatically adjust the airway pressure up on the next breath in an attempt to achieve 500 mL.

Other modes
A. Pressure support (PSV): Unlike IMV or A-C, pressure support does not provide full ventilator support to an apneic patient. It is a pressure-preset, flow-cycled mode used to support the patient's spontaneous respiratory efforts. With each inspiratory effort the patient triggers the ventilator, which maintains the preset pressure in the circuit throughout inspiration. The inspiratory cycle ends when the flow rate has decreased to a pre-determined level (usually 25% of the peak flow rate).

B. Inverse ratio ventilation (IRV): This mode increases the mean airway pressure by prolonging the inspiratory to expiratory (I:E) ratio. The prolonged inflation time can help prevent alveolar collapse, resulting in improved oxygenation. Heavy sedation with or without neuromuscular blockade is usually required for patients to remain on IRV.

C. Airway pressure release ventilation (APRV): APRV cycles between a high continuous positive airway pressure (HCPAP) and a low continuous positive airway pressure (LCPAP) while allowing the patient to breathe spontaneously at all times. Transition from HCPAP to LCPAP allows deflation and transition from LCPAP to HCPAP allows inflation. APRV can improve oxygenation by maximizing alveolar recruitment and reducing shunt.

D. Proportional assist ventilation (PAV): PAV is synchronized partial ventilatory support

in which the ventilator generates pressure in proportion to the patient's instantaneous inspiratory effort. In PAV, the more effort a patient makes, the more support the ventilator provides. PAV was created to more closely mimic the body's innate communication between the nervous system and the respiratory system. It is sometimes used in the ICU as an alternative to pressure support ventilation.

E. Noninvasive Positive Pressure Ventilation (NPPV): NPPV is the delivery of mechanically assisted or generated breaths without an endotracheal or tracheostomy tube. Ventilation is delivered via face mask, nasal mask or helmet. Advantages of NPPV include: avoiding the risks of intubation, reduced need for sedation and lower rates of healthcare-associated pneumonia. Disadvantages include: lack of protection against massive aspiration, less airway pressure tolerated, and lack of access to the airways for suctioning. NPPV is most beneficial for patients with acute COPD exacerbations and patients with acute cardiogenic pulmonary edema. Other uses include post-extubation support, obesity-hypoventilation syndrome, acute post-operative respiratory failure, and for patients who are not candidates for intubation (DNI order).

1. Continuous positive airway pressure (CPAP): CPAP works by generating a continuous flow of oxygen and/or air that maintains a continuous positive pressure to the respiratory system during inspiration and expiration thus preventing airway and alveolar collapse. CPAP may improve alveolar ventilation and oxygenation by reversing atelectasis, maintaining greater end expiratory lung volume, and preventing obstruction of the airways.

2. Bi-level positive airway pressure (BiPAP): BiPAP involves independently set inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP). Vt results from the combination of patient effort and the difference between IPAP and EPAP. BiPAP can be used as a strategy to reduce $PaCO_2$.

F. Positive end expiratory pressure (PEEP): PEEP may increase oxygenation in lung diseases characterized by lung collapse.

1. Extrinsic PEEP (PEEP set on the ventilator) is essentially CPAP in between inspiratory cycles. It maintains alveolar recruitment, increases FRC, decreases pulmonary shunt, may improve lung compliance, and may decrease patient work of breathing. The application of PEEP may have disadvantages: it increases intra-thoracic pressure, which can decrease venous return and can compromise cardiac output. In addition, because PEEP has the greatest effect on compliant regions of the lung, over distention can occur, resulting in increased dead space. High levels of PEEP may contribute to ventilator-induced lung injury (VILI).

2. Intrinsic PEEP or auto-PEEP results from pressure developing from gas trapping (dynamic hyperinflation) due to insufficient expiratory time and/or excessive expiratory airway resistance. Increasing expiratory time, reducing airway resistance, and reducing minute ventilation (by reducing tidal volume and/or reducing frequency) are methods for reducing auto-PEEP.

G. Recruitment maneuvers refer to the application of elevated pressures and volumes for variable duration, magnitude and frequency in an effort to recruit atelectatic lung

H. Permissive hypercapnia is an approach to limit ventilator-induced lung injury through deliberate tolerance of elevated PCO_2 in the setting of hypoventilation. Contraindications include elevated ICP, right ventricular failure, and severe ongoing acidemia.

Complications of mechanical ventilation

A. Ventilator-induced lung injury (VILI) occurs when the lung is directly damaged by the action of mechanical ventilation. "Barotrauma" is alveolar overdistention/rupture related to high inspiratory pressures. Pneumothorax, pneumomediastinum and pneumoperitoneum can occur in this setting. "Volutrauma" is lung injury from excessive volume rather than excessive pressure. "Atelectrauma" refers to the possibility of injury to the lung secondary to the cyclic opening and closing of alveoli during mechanical ventilation. "Biotrauma" refers to the release of inflammatory mediators related to mechanical ventilation.
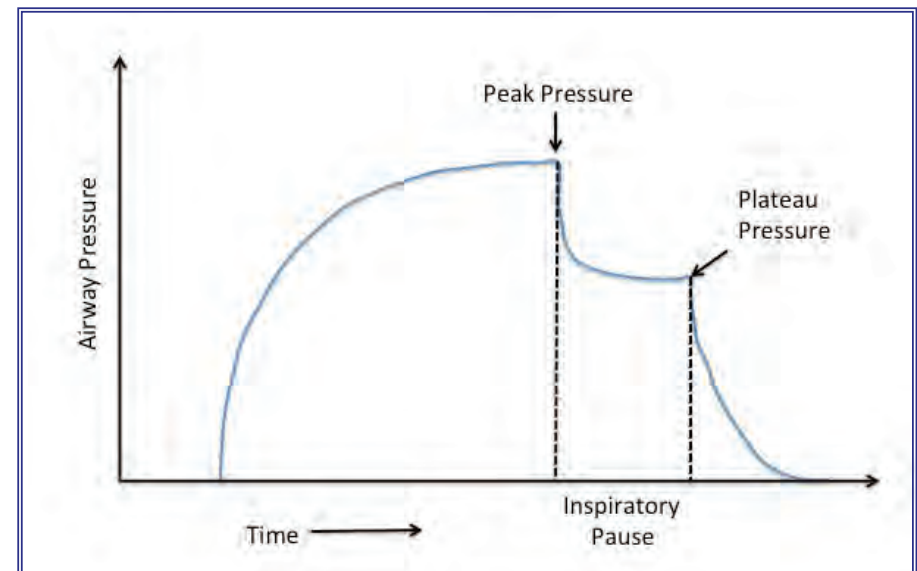

Figure 16.1 Ventilator Pressures

B. Oxygen toxicity: Prolonged exposure to high concentrations of oxygen may cause lung damage. Normal lung units are at highest risk for oxygen toxicity because these areas receive the most ventilation. The FiO_2 should be reduced when possible provided that arterial oxygenation is adequate. In adults, an FiO_2 of less than 0.5 is considered safe.

Mechanics

A. Airway pressures (Figure 16.1)

1. Peak (P_{peak}) is the pressure reached at end inspiration during positive pressure volume control ventilation. P_{peak} is the sum of the pressure required to overcome airway resistance and the pressure required to overcome the elastic properties of the lung/chest.

2. Plateau (P_{plat}) reflects the pressure required to overcome the elastic properties of the lung/chest. The P_{plat} is an estimate of the peak alveolar pressure, which is an indicator of alveolar distention. Measurement of P_{plat} requires the absence of patient effort and is obtained during a short inspiratory hold at end inspiration.

3. Mean pressure is the average pressure within the airway during one complete respiratory cycle. It is related to inspiratory time, freq, P_{peak} and PEEP.

B. Compliance is change in volume divided by the change in pressure.

1. Static compliance is measured when airflow is absent. It is calculated by $C_{stat} = V_t / (P_{plat} - PEEP)$. When airflow is absent, the airways resistance is not a factor. Thus static compliance reflects the distensibility of the lung/chest only.

2. Dynamic compliance is measured when airflow is present at end inspiration. Since airflow is present, airways resistance contributes to C_{dyn}. It is calculated by $C_{dyn} = V_t / (P_{peak} - PEEP)$

3. Comparing static and dynamic compliance can help identify the cause(s) for difficulty with ventilation or difficulty with discontinuing the ventilator. C_{dyn} is decreased by conditions where airways resistance is increased (e.g. bronchospasm), while the C_{stat} is unaffected by such conditions.

4. Resistance (R) is the change in pressure divided by the flow. It is calculated by $R = (P_{peak} - P_{plat}) / F$ where F is the peak inspiratory flow rate

C. Pressure- flow relationships

1. Flow of air into the alveolus is driven by trans-pulmonary pressure (P_L), or the difference between alveolar pressure and pleural pressure. P_L is calculated by $P_L = P_A - P_{pl}$. P_L is transpulmonary pressure; P_A is alveolar pressure; and P_{pl} is pleural pressure. Flow, transpulmonary pressure and resistance relationships are summarized by Flow = P_L / R, where $P_L = P_A - P_{pl}$ Because P_A and P_{pl} are difficult to measure directly, they are estimated by P_{plat} and esophageal pressure (P_{es}) respectively in clinical practice. Hence, Flow = $(P_{plat} - P_{es})/R$.

2. Esophageal pressure *changes* reflect pleural pressure *changes* (the absolute P_{es} does not reflect absolute pleural pressure). P_{es} is measured with a thin walled balloon in the lower esophagus. Changes in P_{es} can be used to assess chest wall compliance during full ventilator support and to assess respiratory effort, work of breathing and auto-PEEP during spontaneous breathing and patient-triggered modes of ventilation. In severe lung disease (e.g. severe ARDS), esophageal manometers can be used to estimate P_{pl} so that P_L can be estimated and ventilator settings adjusted accordingly.

3. Work of breathing: To achieve ventilation, work is performed to overcome the elastic and frictional resistances of the lung and chest wall. Work of breathing can be calculated by multiplying the change in transpulmonary pressure (P_L) times the change in tidal volume.

Monitoring and physiology

A. Oxygenation

1. Pulse oximetry is a standard ICU monitor that provides noninvasive measurement of the oxygen saturation of hemoglobin using differential light absorption characteristics in oxyhemoglobin versus deoxyhemoglobin. Two wavelengths of light, red (660 nm) and infrared (900-940 nm) are passed through a pulsating vascular bed (e.g. a fingertip) to a photo detector. The relative amounts of red and infrared light reaching the photo detector provide information about the relative ratio of deoxyhemoglobin and oxyhemoglobin. These data are compared (by a computer) to calibration curves developed in studies of healthy volunteers to give an oxygen saturation reading, denoted SpO_2. The actual arterial oxygen saturation, SaO_2, correlates well with the SpO_2 when the SaO_2 is greater than 80%. At lower SaO_2 values, the accuracy is diminished. Other causes of inaccurate SpO_2 include dyshemoglobinemias, dyes, pigments, low perfusion, motion, abnormal pulse, extreme anemia and external light sources.

2. Arterial blood gas (ABG) analysis provides (among other data) a measurement of the partial pressure of oxygen (PaO_2), which represents the amount of oxygen dissolved in arterial blood. It is important to remember that dissolved oxygen (represented by PaO_2) makes up a small portion of the total arterial oxygen content. The oxygen content of arterial blood (CaO_2) consists of two components: oxygen bound to hemoglobin (which determines the SaO_2) and the oxygen dissolved in plasma (which determines the PaO_2). CaO_2 is described by $CaO_2 = [1.34 * Hgb * SaO_2] + [PaO_2 * 0.003]$ where 1.34 mL O_2 per gram Hgb is a constant, Hgb is hemoglobin in g/dL, SaO_2 is the arterial oxygen saturation and should be in decimal form (e.g. 98% is written 0.98), PaO_2 is in mmHg, and 0.003 mL O_2 per mmHg per dL is a constant

a) Intermittent ABG: A sample of arterial blood is inserted into a blood gas analyzer intermittently and results are displayed within a few minutes

b) Continuous ABG monitors detect variations in light and fluorescence to allow the continuous display of ABG results. These monitors are subject to a variety of artifacts and are not routinely used in the ICU.

3. Transcutaneous oxygen tension monitoring uses the polarographic principle to measure PO_2 at a warmed skin surface. This monitor is particularly useful in neonates and infants, but due to technical and physiologic limitations in adult patients, it is rarely used in the adult ICU.

4. The shunt fraction is the proportion of the cardiac output that does not participate in gas exchange. Normal shunt fraction is approximately 3-8% and is mostly due to the bronchial circulation. The degree of shunt can be estimated by the shunt equation: $Qs/Qt = (CcO_2 - CaO_2) / (CcO_2 - CvO_2)$ where Qs is shunt, Qt is total cardiac output,

CcO$_2$ is end-capillary O$_2$ content, CaO$_2$ is arterial O$_2$ content and CvO$_2$ is mixed venous O$_2$ content

5. Global oxygen delivery (DO2) is the product of arterial O$_2$ content and the cardiac output: $DO_2 = CaO_2 * CO * 10$ where DO$_2$ is in mL/min, CaO$_2$ is in mL/dL, CO is cardiac output in L/min, and 10 converts L into dL.

6. Oxygen consumption (VO$_2$) is calculated by the Fick equation $VO_2 = CO * (CaO_2 - CvO_2)$ where VO$_2$ and CO are in L/min.

B. Ventilation

1. Capnometry/capnography: The capnometer is a device that measures CO$_2$ in exhaled gas and the capnograph provides a display and ability to track changes in CO$_2$. Quantitative capnometers measure CO$_2$ using infrared spectroscopy, Raman spectroscopy or mass spectroscopy. Quantitative capnometers and capnography are standard monitors in the operating room and can be used in the ICU to non-invasively estimate/track the PaCO$_2$. In the setting of lung disease, capnometry is less accurate in its estimate of PaCO$_2$. Non-quantitative capnometers indicate the presence of CO$_2$ by color change of an indicator material (e.g. for confirmation of endotracheal tube placement).

2. ABG: the arterial partial pressure of CO$_2$ reflects the balance between CO$_2$ production and the alveolar ventilation. PaCO$_2$ varies directly with CO$_2$ production (VCO$_2$) and inversely with alveolar ventilation (VA) as described by: $PaCO_2 = VCO_2 / VA$. Minute ventilation (VE) affects the PaCO$_2$ only to the extent that it affects the alveolar ventilation (VA).

3. CO$_2$ production is a function of O$_2$ consumption and CO$_2$ that is liberated in the buffering of H$^+$ ions. In normal physiology, increased CO$_2$ production is rapidly followed by an increase in alveolar ventilation to eliminate excess CO$_2$ and maintain normal PaCO$_2$. In patients with impaired ability to increase alveolar ventilation (e.g. sedation, weakness or lung disease), an increase in CO$_2$ production can result in an increase in PaCO$_2$. Overfeeding is a recognized cause of hypercapnia in patients with respiratory failure. Overfeeding with carbohydrates is especially problematic because metabolism of carbohydrates generates more CO$_2$ than do lipids or proteins.

4. Dead space (Vd) refers to ventilation that does not participate in gas exchange. The dead space ratio is calculated from the Bohr equation which measures the ratio of dead space to tidal volume: $Vd / Vt = (PaCO_2 - PeCO_2) / PaCO_2$ where PeCO$_2$ is the CO$_2$ concentration in mixed expired gas, NOT end-tidal CO$_2$, though end-tidal CO$_2$ is sometimes used as an estimate. The normal dead space to tidal volume ratio is 0.3 to 0.4. High dead space ratio can be predictive of failure to successfully discontinue mechanical ventilation.

5. Transcutaneous CO$_2$ monitoring has been used in the neonatal ICU but has had limited acceptance in the adult ICU.

Cardiopulmonary interactions

A. Venous return: Administration of positive pressure ventilation causes increased intrathoracic pressure, which can cause decreased venous return leading to reduction in cardiac output. Administration of intravascular fluid may counteract the negative hemodynamic effects of positive pressure ventilation.

B. Afterload reduction: Lung expansion increases extramural pressure, which helps to pump blood out of the thorax and thereby reduce LV afterload. In conditions where cardiac function is mainly determined by changes in afterload rather than preload (e.g. hypervolemic patient with systolic heart failure), positive pressure ventilation may be associated with improved cardiac output.

C. Shunt effects: In patients with right-to-left intra-cardiac shunts, positive pressure ventilation and PEEP may increase right-to-left shunt and worsen systemic hypoxemia. The mechanism of increased shunt is likely Valsalva-like activity (e.g. breathing against the ventilator) or an increase in pulmonary vascular resistance secondary to PEEP.

Miscellaneous

A. Hyperbaric oxygen (HBO, HBOT) therapy involves breathing 100% oxygen at > 1 atmosphere of pressure. HBOT is administered in specialized chambers under close patient monitoring. Mechanisms of action of HBO therapy stem from 2 types of effects: hyperoxygenation of perfused tissues and reduction of gas bubble volume. Indications include:

1. Air embolism: The effect of HBO is predicted by Boyle's Law, which states that the volume of air (mostly nitrogen) bubbles is inversely proportional to the pressure exerted on them. Nitrogen bubble size is further reduced by replacement of nitrogen with oxygen, which is rapidly used in cellular metabolism. Air embolism can result from procedures (e.g. central line placement) or operations (e.g. sitting craniotomy) in which air can be entrained through a disrupted vascular wall.

2. Decompression sickness ("the bends"): Divers breathing compressed air who return to the surface too rapidly are at risk for decompression sickness, which occurs when bubble formation in blood and tissues occurs as the partial pressure of inert gas (nitrogen) exceeds that of ambient air. HBO is the primary treatment for decompression sickness through its effects on bubble size and relief of hypoxia.

3. Carbon monoxide (CO) poisoning: HBO significantly reduces the half-life of carboxyhemoglobin, which may prevent the late neurocognitive defects associated with severe CO poisoning.

4. Soft tissue infections: HBO has been used as an adjunct therapy for severe life or limb threatening infections such as clostridial myonecrosis, necrotizing fasciitis and Fournier's gangrene.

B. Independent lung ventilation (ILV): Patients with severe unilateral lung disease may require different ventilation strategies applied to each lung. Indications for independent lung ventilation include: unilateral pulmonary contusion, bronchopleural fistula, massive hemoptysis from a single lung, or following single lung transplantation (though ILV is not routinely used for any of these conditions). A double lumen tube and two

ventilators facilitate ILV.

C. Heliox is a gas mixture of helium and oxygen that is used in conditions of high airflow resistance. Helium is less dense than air and flows more readily through regions of reduced cross-sectional area where flow is turbulent. (Turbulent flow is dependent on the fluid or substance's density. This is in contrast to laminar flow, which is dependent on viscosity). Heliox may be useful in acute exacerbations of asthma / COPD or in tracheal obstruction. Heliox is generally well tolerated but its use is frequently limited by the high concentration of helium required, which limits FiO_2 delivery. Most studies use a helium:oxygen mixture of 80:20 or 70:30 to achieve benefit. Many ICU patients can not tolerate an FiO_2 of 0.2 or 0.3 due to hypoxemia.

D. High frequency ventilation achieves gas exchange by combining very high respiratory rates with very low tidal volumes (smaller than anatomic dead space). Potential advantages include a lower risk of barotrauma due to small tidal volumes and improved gas exchange due to more uniform distribution of ventilation and greater alveolar recruitment.

1. High frequency jet ventilation (HFJV) delivers pulses of gas at high velocity and frequency into the trachea through a small catheter. The high velocity jet pulse creates an area of reduced pressure, which entrains additional gas and produces a mixing effect. Exhalation is a passive process. HFJV has been used in ARDS patients with the goal of reducing airway pressures and ventilator induced lung injury.

2. High frequency oscillatory ventilation (HFOV) delivers low tidal volumes at very high frequency using a pump so that airway pressure oscillates slightly about a mean airway pressure. This allows maintenance of alveolar recruitment while avoiding high peak airway pressure. HFOV has been used primarily in children and neonates where its use is associated with improved oxygenation and reduced barotrauma.

Future directions
A. Improvement in ventilator technology has allowed for the recent development of a variety of modes (e.g. Neurally Adjusted Ventilatory Assist, or NAVA) with increased emphasis on patient ventilator interactions. The goal is to mimic the complex interplay of the central nervous system, peripheral nervous system and respiratory system exhibited during normal breathing.

B. Alternatives to traditional positive pressure mechanical ventilation, including pumpless extracorporeal gas-exchange devices driven by the patient's blood pressure, continue to attract more attention as intensivists seek to minimize ventilator induced lung injury.

Discussion
Proper management of mechanical ventilation requires a thorough understanding of respiratory and cardiovascular physiology and pathophysiology of critical illness. While a wide variety of ventilator modes exist, the recovery of patients in respiratory failure depends mostly on clinicians' vigilance and ability to modify therapy appropriately.

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QUESTIONS:

16.1 Static compliance will be independently affected by:
A. Pulmonary edema
B. Bronchospasm
C. Kinked endotracheal tube
D. Mucus plugging

16.2 Goals of adding PEEP to routine ventilation settings might include all of the following EXCEPT:
A. Improved lung compliance
B. Improved PaO_2
C. Decreased work of breathing
D. Reduced dead space

16.3 A contraindication to permissive hypercapnia is:
A. Hypoxia
B. Plateau pressure > 25 cm H_2O
C. Brain injury with very high intra-cranial pressures
D. ARDS

17. Weaning from Mechanical Ventilation

Jarett Skirball MD and Peter M Schulman MD

Key Points

• **Prolonged mechanical ventilation is associated with adverse outcomes such as higher rates of pneumonia, longer intensive care unit stays, and increased mortality.**

• **The weaning process constitutes a significant proportion of time critically ill patients spend receiving mechanical ventilation.**

• **A proactive approach to ventilator weaning is critical. Clinicians should make a daily determination of weaning readiness, initiate the weaning process as soon as predetermined criteria are met, and liberate patients from mechanical ventilation as quickly as possible.**

• **Protocol directed weaning strategies with daily spontaneous breathing trials shorten the duration of mechanical ventilation.**

• **Weaning failure should prompt a thorough evaluation for potentially reversible causes.**

A 73 year-old man was admitted to the ICU for aspiration pneumonia. Over the next 36 hours, he developed worsening hypoxic respiratory failure requiring non-invasive bilevel positive airway pressure, and ultimately intubation and mechanical ventilation.)n volume-assist control ventilation (AC) with a tidal volume of 6 ml/kg based on predicted ideal body weight, he required a FiO_2 of 0.7 with PEEP of 12 cmH_2O to maintain a SpO_2 greater than 90%.

On ICU day 5, his sedation was discontinued but he remained minimally responsive. Ventilator settings were AC, FiO_2 0.4 PEEP 8. Hemodynamic indices were stable. He was noted to gag and cough with endotracheal suctioning and had minimal respiratory secretions. An ABG demonstrated pH 7.33/$PaCO_2$ 52/PaO_2 80. He was then placed on a spontaneous breathing trial with pressure support 5 cmH_2O and PEEP 5 cmH_2O. However, after 17 minutes, his breathing became more labored and his RR increased from 22 to 37.

Introduction

In the United States, approximately 800,000 patients per year require mechanical ventilation (MV).[1] When prolonged, MV is associated with adverse outcomes such as higher rates of pneumonia, longer intensive care unit (ICU) and hospital stays, and increased mortality.[2]

Weaning is the process of liberating a patient from MV. It encompasses a continuum of care that starts once the underlying cause for intubation has been addressed. It involves improving the strength-to-load ratio of the respiratory system by stepping down the level of mechanical support and encouraging spontaneous breathing prior to extubation.[1] For the majority of patients, this process is uncomplicated and can be accomplished expeditiously (e.g. routine postoperative extubation). However, in the setting of acute or chronic respiratory failure, minimizing the duration of MV is an important goal. Evidence based strategies to improve outcomes and reduce the duration of MV include small tidal volume ventilation in patients with or at risk for acute respiratory distress syndrome, daily interruption of sedatives or the avoidance of sedatives altogether, early physical and occupational therapy, conservative fluid management, and the prevention of ventilator associated pneumonia.[1]

In terms of reducing the duration of MV, shortening the weaning process is another key consideration, as weaning accounts for an average of 40-50% of the time spent receiving MV.[3] It is therefore critical to continuously assess readiness for weaning, start the weaning process as soon as is appropriate, liberate patients from mechanical ventilation as soon as extubation criteria are met, and take steps to prevent reintubation whenever

possible. A proactive, protocol driven, evidence-based approach to the weaning process will dramatically shorten the duration of mechanical ventilation and improve outcomes. [1,4-6]

Categorizing the Weaning Process

Different classification systems have been proposed to categorize the weaning process based on its duration and the number of spontaneous breathing trials (SBT) required, as well as to assist clinicians in risk stratifying mechanically ventilated patients. One such system, developed by an international task force in 2007, is as follows: [7]

- Simple: Patients who are successfully extubated following a first attempt (approximately 60% of ICU patients). [8]
- Difficult: Patients who fail initial weaning and require up to three SBTs or up to seven days for successful extubation (approximately 25% of ICU patients and associated with increased morbidity). [8]
- Prolonged: Patients who fail three or more weaning attempts or require seven or more days of MV (approximately 15% of ICU patients and associated with increased hospital mortality). [8]

Weaning Readiness

In any mechanically ventilated patient, daily assessment for weaning readiness should be immediately initiated once the inciting respiratory insult has begun to improve. [1] The effects of any neuromuscular blocking agents must be reversed and sedatives that suppress the respiratory drive should be sufficiently weaned or held. [9]

Other prerequisites for weaning readiness include: [7]

- Stable hemodynamics (the patient should be on little to no vasoactive support, or at a minimum, this requirement should be decreasing or stable)
- Sufficient respiratory muscle strength and pulmonary function (the patient should be able to sustain spontaneous breathing and maintain acceptable gas exchange with vital capacity > 10 ml/kg, respiratory rate < 35 breaths/min., negative inspiratory force < -20 cm H_2O, tidal volume > 5ml/kg)
- Acceptable oxygenation (SpO_2 >90% on FiO_2 < 0.4 PEEP < 8 cmH_2O, or PaO_2:FiO_2 ratio > 150)
- Optimized volume status (euvolemia or net negative fluid balance)
- Acceptable electrolyte profile (potassium, calcium, and phosphate are important for muscle function)
- Adequate mentation (mental status must at least be sufficient to cooperate with the weaning process, however a low Glasgow Coma Score is not necessarily, in and of itself, a contraindication to weaning or extubation)

Evidence Based Weaning Strategies

The efficacy of different weaning modes has been evaluated in prospective randomized studies.

Out of 456 mechanically ventilated patients, Brochard et al. randomized 109 patients who had initially failed a breathing trial to one of three weaning strategies: 1) gradual reduction in pressure support (PS); 2) synchronized intermittent mandatory ventilation (SIMV) with gradual reduction in backup rate; or 3) intermittent T-piece trials of
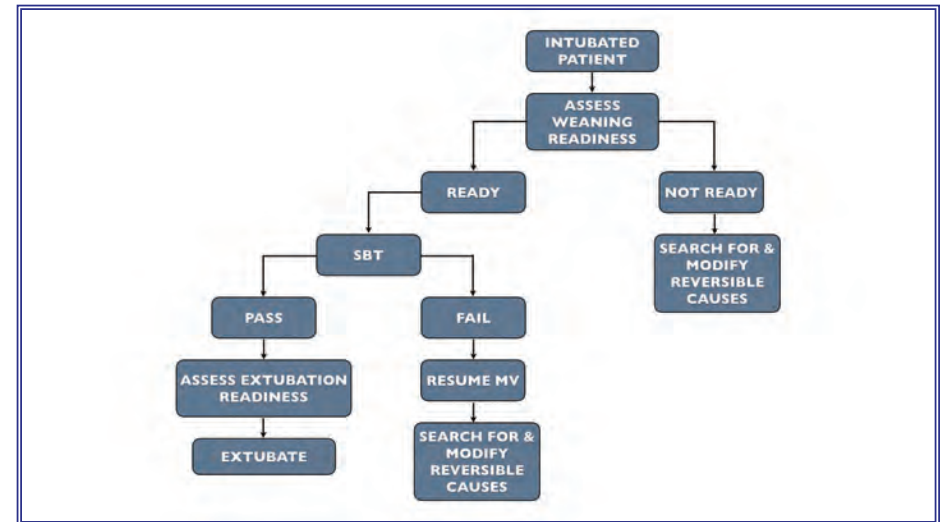
Figure 17.1 Algorithm for Weaning from Mechanical Ventilation
SBT: spontaneous breathing trial; MV: mechanical ventilation.
Adapted from Figure 1 in McConville and Kress[1].

progressively longer durations. PS was found to significantly reduce the duration of weaning. [5]

Esteban et al. enrolled patients who had initially failed a breathing trial into one of four weaning strategies: 1) SIMV with gradual reduction in backup rate; 2) PS ventilation in which the pressure support was gradually decreased; 3) multiple daily T-piece trials; or 4) once per day T-piece trials. These authors found that the once daily versus multiple daily T-piece trials were equivalent, and that both approaches were superior to either SIMV or PS. [6]

Based on evidence from these and other studies, expert consensus is that 1) intermittent trials of spontaneous breathing via T-piece or PS are likely equivalent, and 2) evidence clearly does not favor the use of SIMV for weaning. [7]

Attempts have been made to wean patients from MV using alternative (or newer) modes of ventilation with limited success. A noteworthy example is automatic tube compensation (ATC). This mode, which has a unique ability to compensate for the nonlinear pressure drop across the endotracheal tube (ETT) during spontaneous breathing, was found to be equally as efficacious as a T-piece or PS for weaning in at least one study. [10] Although consideration should be given to ATC for patients who fail a SBT because of a small diameter ETT, there is a lack of evidence to make definite statements about the use of ATC for difficult to wean patients. [7]

The Weaning Process / Spontaneous Breathing Trial

Neither clinical experience alone nor complex algorithms have been shown to accurately predict whether mechanically ventilated patients can breath spontaneously. Rather, the definitive test or "gold standard" to gauge a patient's readiness for spontaneous

breathing is the spontaneous breathing trial (SBT).[1] A SBT is performed with little to no ventilatory support; it is accomplished by switching from a mode that provides full support such as AC to either PS or continuous positive airway pressure (CPAP). Alternatively the patient can be placed on T-piece. Ideally, sedative infusions that suppress respiratory drive and level of consciousness should be held.[1]

Esteban conducted a multicenter prospective randomized controlled trial in 526 medical-surgical ICU patients to determine the effect of SBT duration on outcome. They found after a first SBT, whether targeted to 30 minutes or 120 minutes in duration, were equally efficacious at achieving successful extubation.[11] Most practioners today believe a SBT lasting 30 minutes is generally sufficient.

The SBT is a binary test in which failure can be defined by objective and subjective parameters such as the following:[1]

1) Respiratory rate > 35 breaths per minute for more than 5 minutes
2) Oxygen saturation of < 90%
3) Heart rate > 140 beats per minute or sustained change in HR of > 20%
4) Systolic blood pressure of > 180 mm Hg or < 90 mm Hg
5) Anxiety
6) Diaphoresis

Aside from the SBT, other methods to predict readiness for spontaneous breathing and extubation have been proposed and evaluated. Yang and Tobin found the ratio of respiratory rate (in breaths per minute) to tidal volume (in liters), termed rapid shallow breathing index (RSBI), to be a useful adjunct to the SBT. Specifically, a RSBI > 105 was found to accurately predict extubation failure, however a RSBI < 105 was not as accurate at predicting patients who could be successfully extubated. These findings have been subsequently corroborated by a systematic review of multiple RSBI studies.[12]

Many studies have demonstrated that developing and instituting a protocol driven approach to weaning is beneficial. Benefits include a decreased time to extubation[3], possible decrease in the incidence of reintubation, and in at least one study, a decrease in the incidence of ventilator associated pneumonia and mortality.[13] Additionally, pairing SBTs with a sedation "holiday" may improve extubation success and mortality.[14] A protocolized approach to weaning should ideally be developed in a multidisciplinary fashion, and once implemented, these protocols can often be performed by nurses or respiratory therapists.[1]

Final considerations following a successful SBT and prior to extubation are to ensure the patient can maintain a patent airway. There should be an assessment of the quantity and consistency of secretions, presence of a strong enough cough, an adequate gag reflex and/or swallow, and, if appropriate, verification of an adequate endotracheal tube cuff leak.[7] Mental status is also a key component regarding the patient's ability to "protect" his/her airway.

Prolonged Weaning and Weaning Failure

Weaning failure occurs when a SBT is not successful or a patient requires reintubation within 48 hours of extubation.[7] In assessing reasons for weaning failure, it may be helpful to take a systems based approach:

1) Fatigue (weaning to exhaustion)
2) Respiratory [The primary issue is an imbalance between the respiratory load and

respiratory capacity. Considerations include an unresolved primary insult, excessive work of breathing due to other disease processes, air trapping (autopeep), etc.]

3) Cardiovascular (myocardial ischemia, left or right ventricular failure; weaning can increase myocardial wall stress, increase myocardial demand and unmask myocardial dysfunction)

4) Neurologic or Neuromuscular (cerebral hemorrhage or ischemia, critical illness myopathy or neuropathy)

5) Nutrition (malnutrition or overfeeding)

6) Electrolytes (hypomagnesemia, hypophosphatemia)

7) Acid Base (metabolic alkalosis, acidosis)

8) Infection

Rates of extubation failure vary widely among ICUs. On average, approximately 15% of patients in whom mechanical ventilation is discontinued require reintubation within 48 hours.[7] The average rate of failed extubations in surgical ICUs is 5-8% while in medical and neurologic ICUs it is as high as 17%. Non-invasive ventilation to prevent re-intubation may be beneficial when ventilation, but not oxygenation, is the cause of failure. Reintubation is associated with prolonged hospital stay and increased mortality.[1]

Tracheotomy may be considered for patients who require prolonged weaning. Rationale for early tracheotomy includes easier airway suctioning, improved patient comfort with less sedation and enhanced ability to communicate (decreased requirement for sedatives). However, the timing of tracheotomy remains controversial.[1] A recent meta analysis concluded that there is insufficient evidence of improved outcomes to warrant a recommendation for early tracheotomy.[15]

Failure to wean from mechanical ventilation should promptly initiate a thorough and systematic search for the underlying etiology, as often times, the patient's condition can be further optimized and/or the underlying cause for failure is potentially reversible.

Summary

Mechanically ventilated patients should be assessed at least daily for weaning readiness. Patients who meet criteria should be promptly placed on a SBT. In general, a SBT should be targeted to 30 minutes duration and should be performed by placing the patient on low-level PS or a T-piece. Patients passing a SBT should immediately be assessed for extubation and liberated from the ventilator, if appropriate. Failure to wean at any stage should prompt a search for an etiology, and reversible causes of failure should be corrected or at least further optimized. In the interim, a non-fatiguing form of MV should be utilized. See Figure 17.1 for an algorithm summarizing the weaning process.

A proactive, standardized, and evidence-based approach to weaning reduces the duration of MV and improves outcomes. "Best practice" in the ICU should incorporate a structured and evidence-based approach to weaning from MV.

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Questions

17.1 In reference to the case description at the beginning of this chapter, what is the next best step in his management?
- A. Proceed directly to extubation
- B. Place the patient back on AC for 24 hours, then attempt another SBT
- C. Switch to synchronized intermittent mandatory ventilation (SIMV) with pressure support and gradually decrease pressure support as tolerated.

17.2 In reference to the case description at the beginning of this chapter, which of the following should be further optimized prior to extubation?
- A. Low Glasgow Coma Score
- B. Malnutrition
- C. Chest radiograph demonstrating large right sided pleural effusion

17.3 Which of the following is not an evidence-based indication for the use of non-invasive ventilation?
- A. Preventing reintubation of a patient with a $PaCO_2$ of 70 mmHg and SpO2 93% on 2L nasal cannula shortly after extubation.
- B. Preventing reintubation of a patient with a $PaCO_2$ of 40 mmHg and SpO2 88% on FiO_2 0.9 shortly after extubation
- C. Preventing reintubation of a patient with a COPD exacerbation

Section 5: Shock and Cardiac Management

18. Management of Shock

David P Ciceri MD

Key Points

- Hypovolemic, cardiogenic, obstructive and distributive are the four classic categories of shock.

- Patients in shock commonly have a combination of types of shock.

- Dynamic parameters, rather than static parameters, have been demonstrated to be highly predictive of fluid responsiveness in hypotensive patients.

- Trauma patients in hemorrhagic shock should be resuscitated with PRBC and FFP in a 1:1 ratio and consideration to including platelets also in a 1:1:1 ratio.

- Hydroxyethyl starch solutions should not be given to critically ill patients including those with sepsis, and those admitted to the ICU.

A 65 year old female initially is admitted to the hospital with abdominal pain and fever. A CT scan showed right lower quadrant mass and she is found to have an abscess at laparotomy. She has a very slow recovery on the hospital ward. 9 days after surgery she developed a deep venous thrombosis of her left upper extremity secondary to a PICC line and was therapeutically anticoagulated with heparin. Two days later she developed a depressed level of consciousness, heart rate of 115 beats per minute and a systolic blood pressure of 84 mm Hg, and was transferred to the ICU. Immediately upon arrival in the ICU, the patient had a large melanic stool, heart rate increased to 135 and systolic blood pressure fell to 65 mm Hg.

Overview

Shock is a clinical syndrome characterized by inadequate perfusion to meet organ and/or cellular needs. The adequacy of perfusion is commonly described in terms of oxygen delivery, which is the product of cardiac output and arterial oxygen content. The principal components of arterial oxygen content are the hemoglobin and arterial oxygen saturation. Shock may be caused by a significant decrease in oxygen delivery or less commonly a relative inability of oxygen delivery to meet increased oxygen or perfusion demands. Shock may also be caused by the loss of the microcirculation to appropriately direct perfusion to areas of cellular need as is commonly seen in distributive shock states. Lastly, there may be impaired utilization of oxygen at the cellular level. Some investigators hypothesize this occurs with mitochondrial dysfunction in septic shock. Also, more than one physiological abnormality can be contributing to shock in a given patient.

Types of shock

A common approach to categorizing different types of shock states is into four separate shock syndromes:

A. Hypovolemic
B. Cardiogenic
  1. Left ventricular systolic dysfunction – most common in adults
  2. Dysrhythmmias
  3. Valvular disease
  4. Right ventricular failure

5. Hypertrophic cardiomyopathy
C. Obstructive shock
1. Massive pulmonary embolism
2. Cardiac tamponade
3. Tension pneumothorax
D. Distributive or vasodilated shock
1. Septic shock
2. Neurogenic shock secondary to spinal cord injury
3. Acute adrenal insufficiency
4. Hepatic failure
5. Anaphylactic shock

This classic description is useful but also a significant over simplification, which may lead to improper management on occasion. First, complicated patients may have more than one etiology of shock and the clinician must rapidly search for additional diagnoses especially if the patient is responding poorly to efforts at resuscitation. Second, all severe hypoperfusion/ shock states, if uncorrected, will ultimately lead to systemic inflammation and the superimposition of a distributive or vasodilated shock state. Lastly, this classification system may lead to an under appreciation of the complex changes which are commonly present in patients with severe septic shock. There will be significant vasodilation of both the venous capacitance vessels, as well as the arteriolar resistance vessels, leading to significant relative hypovolemia until volume resuscitation restores an adequate intravascular volume. There is increased movement of all acellular fluids into the interstitium so that the patient will need continued volume therapy until inflammation begins to abate. In addition, in adults with septic shock there is invariably bi-ventricular systolic and diastolic dysfunction. The myocardial dysfunction may be mild and the patient may have an elevated cardiac output after volume resuscitation because of tachycardia and a decreased afterload because of vasodilation. But in a significant number of patients (> 1/3) the myocardial depression will be more severe and the patient will have a low normal or even low cardiac output despite optimal resuscitation.

Assuming good cardiac function in an adult with septic shock is a common potentially lethal mistake.

Common clinical manifestations:
Neurological:
A. Anxiety, Delirium, Altered level of consciousness – ranging from somnolent to unresponsive
B. Inability to protect airway
Pulmonary:
A. Tachypnea
B. Hypoxemia – mild hypoxemia with a clear CXR to severe ARDS
Cardiovascular:
A. Hypotension (SBP < 90 mm Hg or more than 40 mm Hg less than baseline)
B. Tachycardia
C. Extremities may be cool and mottled or warm with brisk capillary refill (after volume resuscitation) depending upon the etiology of shock

Renal:
A. Decreased urine output

Common laboratory findings:
A. Hypoxemia
B. Metabolic acidosis
C. Increased serum lactate
D. Elevated troponin with myocardial ischemia but mild to moderate elevations can also be seen secondary to myocardial dysfunction in septic shock
E. Coagulation abnormalities and thrombocytopenia
F. ECG findings suggestive of myocardial ischemia or infarction in cardiogenic shock. Non-specific abnormalities common in other shock states.
G. CXR
1. Cardiogenic pulmonary edema
2. ARDS

Monitoring in patients with shock

To borrow a phrase from Stephen King, the world of monitoring has moved on in most intensive care settings. Pulmonary artery catheterization (PAC) is rarely performed in any setting outside of cardiac surgery in most institutions. There are probably specific clinical scenarios (i.e. patient with pulmonary hypertension and severe right ventricular dysfunction) in which the information obtained from a pulmonary artery catheter can be essential to guide therapy. One result of the dramatic decline in the use of pulmonary artery catheters is the loss of physician and nursing expertise in the use of this monitoring device in complicated patients outside of the Cardiac Surgery Intensive Care Unit. The reduced expertise and the decreased data quality may increase complications.

A second major shift has been the realization that static "filling" pressures such as the central venous pressure (CVP) and the pulmonary capillary wedge pressure (PCWP) have questionable value in assessing volume status, preload or predicting fluid responsiveness in any ICU patient population. Dynamic parameters, however, have been demonstrated in multiple studies to be highly predictive of fluid responsiveness in hypotensive patients. One of the simplest dynamic challenges that is useful in a spontaneously breathing patient is to assess the change in cardiac index (CI) or stroke volume index (SVI) caused by passive leg raising. A baseline measurement is obtained with the patient sitting 30 degrees upright. The patient is quickly lowered to the supine position and the legs are manually raised to 30 to 45 degrees. This causes a central redistribution of about 500 mls of blood in the average adult. An increase in CI or SVI of > 10% is a powerful predictor that the patient will respond to a subsequent fluid bolus.

There are a host of other dynamic parameters that can be employed in more critically ill patients who are being supported with mechanical ventilation. Positive pressure ventilation increases intrathoracic pressure, which impairs right ventricular filling and may cause over distension of the lung in some patients. This in turn could increase right ventricular afterload. These effects are greater in hypovolemic patients and result in a fall in right ventricular stroke volume with inspiration. The reduced right ventricular stroke volume leads to a reduced left ventricular stroke volume in the cardiac cycle. The variation in stroke volume is seen as changes in systolic blood pressure and pulse pressure, pulse oximeter pulse variability index or stroke volume variation. All of these

can be used to predict whether a patient is likely to respond to the next fluid bolus.

There are several conditions that need to be present to use dynamic parameters to predict fluid responsiveness. The patient should not be over breathing the ventilator and should be receiving a tidal volume of ≥ 8 ml/kg predicted body weight. The patient is likely to respond to a subsequent fluid bolus if significant variation is present in the dynamic parameter (Δ Systolic Blood Pressure, Δ Pulse Pressure, Pleth Variability Index, Stoke Volume Variation, Velocity Time Integral variation with esophageal Doppler monitoring, etc.). The patient should be in a regular cardiac rhythm otherwise each stroke volume is different because of different R – R intervals and diastolic filling time. Dynamic parameters may also not be useful in patients with an open thorax, abdominal compartment syndrome or severe right ventricular failure.

During volume resuscitation it is imperative that close attention be paid to the patient's pulmonary status so that any subtle worsening such as decreased oxygenation or pulmonary complicance.is detected before and even during each fluid bolus. Pulmonary deterioration during volume resuscitation should lead the clinician to carefully reassess the patient's condition before proceeding with successive volume administration.

The concept of oxygen transport has been attempted to be used for decades to help guide resuscitation. Both the logic and the mathematics are very appealing but despite numerous investigations there has been only one study in over 40 years, which has demonstrated an improvement in outcome using this approach in patients with shock. This study randomized patient with severe sepsis or septic shock in the Emergency Department to standard therapy or early goal directed therapy (EGDT), which targeted a central venous oxygen saturation ($SCVO_2$) of > 70 % during the first 6 hours of care. The patients who received EGDT had a lower mortality and fewer complications. This study forms the basis for the first two recommendations of the Surviving Sepsis Campaign. Unfortunately, this study's findings have not yet been replicated although there are several ongoing studies at the current time. To complicate matters, numerous other studies have not found any cost or outcome benefit with monitoring mixed venous oxygen saturation (SVO_2). There is also no consistent relationship between changes in the $SCVO_2$ or SVO_2 and the cardiac index even in cardiac or cardiac surgery patients. However, a low and falling SVO_2 (or $SCVO_2$) in an unstable patient may be an ominous sign and an indication to measure the key components of oxygen delivery and reassess oxygen demand.

Echocardiography, both transesophageal and transthoracic, has become an essential tool to help determine the etiology of shock and help guide therapy. One can rapidly determine global left and right ventricular function, evaluate for the presence of pericardial fluid, and assess inferior vena cava size and collapsibility as an indicator of fluid responsiveness. More advanced echocardiographers can assess for valvular function, evidence of outflow tract obstruction, and superior vena cava collapsibility. Echocardiography can be rapidly performed in every patient who is not responding well to resuscitation efforts and perhaps in most if not all patients in shock in an intensive care setting. Combining the findings on one or more echocardiographic examinations with continuous assessment of cardiac index, stroke volume index or another dynamic predictor of fluid responsiveness is an excellent contemporary way to guide shock resuscitation. (Please see chapter 9, Ultrasound in the ICU).

Goals of Resuscitation

A. Rapidly restore tissue perfusion by obtaining:

1. Adequate or normal oxygen delivery (DO_2)
   a. $DO_2 = (1.34 \times Hgb \times SaO_2) + (0.003 \times PaO_2)$
2. Normal cardiac index (CI) and in many cases normal or optimal stroke volume index (SVI). Supranormal CI or DO_2 has not been proven to be beneficial once shock has ensued.
3. $SCVO_2 > 70\%$
4. Clearance of lactic acidosis

B. Maintain an adequate blood pressure. MAP ≥ 65 mm Hg is the most commonly recommended goal although there is likely significant patient-to-patient variation for an optimal target. Available monitoring technologies do not allow for identification of patient specific optimal blood pressure targets.

C. Avoid hydrostatic pulmonary edema.

D. Avoid myocardial injury.

E. Avoid precipitating abdominal compartment syndrome by avoiding excessive crystalloid resuscitation.

Therapeutic Recommendations

Airway and breathing:

The first consideration in any unstable patient is whether or not the patient is able to protect their airway and maintain appropriate levels of oxygenation and minute ventilation. This assessment and decision is particularly crucial for the patient in shock. There is no role for noninvasive ventilation in a patient who is in shock. Patients in shock may not show a progressive rise in their $PaCO_2$ as an indicator of respiratory deterioration. Instead they may have ongoing vasopressor requirements and many times a worsening metabolic acidosis before they abruptly suffer a respiratory arrest with dire consequences.

Fluid therapy:

There is now reasonable data to assist in making rational fluid choices in shock resuscitation. There is repeated observational data that in trauma patients, who require massive transfusions (2 -3 % of all civilian trauma cases), resuscitation with packed red blood cells (PRBCs) and fresh frozen plasma in a 1:1 ratio may improve outcomes. There may also be benefit to the 1:1:1 administration of platelets with PRBCS and FFP.

The administration of 0.9% normal saline results in the same clinical outcomes as 4% albumin in a wide range of critically ill patients. Hydroxyethyl starch (HES) preparations of all kinds are associated with worse outcomes in patients with septic shock and the FDA has released a statement that HES solutions should not be given to critically ill patients including those with sepsis, and those admitted to the ICU.

Fluids for resuscitation should be given as patient and disease appropriate boluses over 5 – 10 minutes, looking for an effect on blood pressure, heart rate, cardiac output, perfusion and most specifically the stroke volume index (SVI). The primary hemodynamic purpose of administering a fluid bolus is to increase preload to augment the SVI. If the SVI is low and not increasing with appropriate fluid boluses, then the problem is likely not hypovolemia and an alternative diagnosis needs to be pursued. An echocardiogram at this point may be helpful. Close attention should be given to the patient's pulmonary status during volume resuscitation.

Vasoactive medications

Vasopressors

There are now large well conducted randomized controlled trials to help guide the choice of vasopressors in different shock states. Norepinephrine is superior to dopamine in multiple different categories of shock. The use of norepinephrine is associated with ½ the rate of atrial fibrillation (11% vs. 22%) compared with dopamine in cardiogenic, septic and hypovolemic shock. Several systematic reviews suggest that the use of dopamine may be associated with higher mortality in septic shock. Vasopressin use is associated with significant reductions in other vasopressor use in septic shock and in patients with vasodilated shock following cardiac surgery.

Inotropes

Dobutamine, epinephrine and the phoshodiesterase inhibitors are inotropes used in different clinical situations based upon pharmacological activities and historical practice. There are no comparative outcome trials. Phosphodiesterase inhibitors, such as milrinone, cause pulmonary vasodilation and can be a good choice in a patient with pulmonary hypertension or right heart failure.

Mechanical Cardiac Support

There are a variety of different options for supporting a patient in shock including intra-aortic balloon pumps (IABP), ventricular assist devices (VAD) and veno-arterial extra-corporeal membrane oxygenation (ECMO). (Please see chapter 23, ECLS and VAD)

Recommendations for selected shock states:

Hypovolemic:

  A. Patient who is NOT bleeding
    1. Isotonic crystalloids
    2. Albumin
    3. No HES

  B. Hemorrhagic shock
    1. Obtain excellent intravenous access
    2. Avoid excessive use of crystalloids and albumin
    3. Anticipate effects of next round of fluids/ blood products (i.e. Patient with Hgb 7.3 gm/ dl and giving 4 units of FFP; must also give PRBCs if pulmonary status allows)
    4. Check coagulation status (conventional tests and viscoelastic tests) and correct abnormalities aggressively

  C. Severe trauma with hemorrhagic shock requiring massive transfusion
    1. PRBC:FFP ratio of 1:1
    2. Early administration of platelets may be helpful
    3. Tranexamic acid (TA); if less than 3 hours after injury; 1 gram IV over 10 minutes followed by 1 gram IV over 8hr

Cardiogenic shock - Medical patient:

  A. Echocardiography to assess for ventricular and valvular function and to look for complications – ventricular septal defect, ruptured chordae tendinae
  B. Historical practice has been to use dopamine and dobutamine and reserve norepinephrine for severe hypotension (SBP < 70 mm Hg) although data from a recent prospective trial suggests norepinephrine may be a superior agent.
  C. Consider mechanical support with IABP, which may not be beneficial, or VAD.
  D. Urgent revascularization (thrombolytic, PCI or surgery) if ischemic heart disease is the cause.
  E. Fluid administration may not be helpful. Only a small percentage of patients will be hypovolemic because of excessive diuresis or other processes.

Cardiogenic shock - post-cardiac surgery:

  A. Fluid resuscitation may be necessary because of vasodilation and ongoing losses.
  B. Correct coagulopathy.
  C. Optimize pacing.
  D. Transesophageal echocardiography can be useful
  E. Dobutamine and epinephrine are commonly used as inotropic agents. Limited data suggests epinephrine may succeed when dobutamine has been ineffective.
  F. Phosphodiesterase inhibitors can be employed as inotropic agents and as a pulmonary vasodilator. They will also cause significant systemic vasodilation which may have to be corrected with a vasopressor such as norepinephrine. The combination of a beta adrenergic agonist, like epinephrine, with a phosophodiesterase inhibitor is a potent inotropic combination.
  G. Norepinephrine may be used to treat significant vasodilation if optimal intravascular volume and inotropic support are ensured.
  H. Vasopressin in physiological replacement doses (0.03 – 0.04 mcg/kg-min) may allow significant decreases in the dose and duration of administration of other vasopressor agents.
  I. Mechanical circulatory assistance, VAD or V-A ECMO, may be required. An IABP is still employed in this setting at times but any increase in CO would be expected to be modest at best.

Obstructive shock - Pulmonary embolism:

  A. Acute right ventricular failure is usual cause of demise.
  B. Ensure adequate systemic anticoagulation unless contraindicated.
  C. Add inotropic agent to support right ventricular function with consideration for phosphodiesterase inhibitor.
  D. Consider systemic thrombolytic therapy in appropriate candidates.
  E. Consider surgical embolectomy if patient is not a candidate for thrombolytic therapy.
  F. Consider inhaled pulmonary vasodilators: inhaled prostacyclin PGI_2 and nitric oxide.
  G. Consider V-A ECMO

Obstructive Shock - Cardiac tamponade:

  A. May have modest initial improvement with fluid bolus.
  B. Echocardiography for diagnosis
  C. Norepinephrine to support blood pressure
  D. Urgent drainage of pericardial fluid by pericardiocentesis, pericardial window or sternotomy depending upon the setting.

Vasodilated or distributive shock - Septic shock:

A. Volume resuscitation guided by dynamic parameters and clinical response.

B. Isotonic crystalloid or albumin (HES products are contraindicated)

C. Norepinephrine is first choice for vasopressor to maintain MAP $\geq$ 65 mm Hg.

D. $\geq 1/3$ of adult patients with septic shock will have significant myocardial depression. Echocardiography should be performed in many patients with septic shock.

E. Some patients will require inotropic support with dobutamine or epinephrine to achieve a normal CI and SVI.

F. Hydrocortisone 200 mg/day may be considered in patients requiring more than one vasopressor. This can be given in divided doses (50mg q6h) or as an infusion of 9mg/h.

G. Aggressive resuscitation must be combined with successful treatment of the infectious or inflammatory cause of septic shock.

Summary

The care of the patient with shock is challenging and requires aggressive efforts to restore and maintain tissue perfusion while avoiding harm. Newer approaches such as the use of dynamic parameters to predict fluid responsiveness and bedside echocardiography performed by Intensivists has radically changed the approach to monitoring and guiding therapy.

Questions:

18.1 Which statement regarding fluid therapy is correct?
A. Transfusion to Hgb > 12 gm/dl improves tissue oxygen delivery and outcomes in patients with shock.
B. Hydroxyethyl starch preparations are proven to be safe and effective agents in critically ill patients at risk for renal failure.
C. The use of 4% albumin or 0.9% Normal Saline has been shown to result in similar clinical outcomes in a wide variety of critically ill patients.
D. Crystalloid resuscitation has been demonstrated to result in better outcomes than 4 % albumin in patients with septic shock.

18.2 Which of the following predicts fluid responsiveness in a critically ill patient?
A. Stroke volume variation
B. Central venous pressure
C. Cardiac output
D. Pulmonary artery wedge pressure

18.3 Which of the following statements are true regarding the use of vasopressors in shock?
A. Dopamine use causes a much higher rate of atrial fibrillation than norepinephrine in patients with shock.
B. Norepinephrine may be associated with a higher survival rate than dopamine in patients with septic shock.
C. The addition of vasopressin to norepinephrine has not been shown to improve clinical outcomes in patients with septic shock.
D. All of the above

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19. Diagnosis and Treatment of Dysrhythmias

Ryan Laterza MD and Adam S Evans MD

Key Points

• Dysrhythmias are common in the intensive care unit

• When evaluating a patient with a dysrhythmia, first determine if the patient is hemodynamically stable, then obtain a 12 lead ECG to answer: Is the rhythm slow or fast? Regular or irregular? Are QRS complexes narrow or wide (>120 ms)? Does every P have a QRS?

• Ventricular fibrillation (VF) is incompatible with life. Only immediate defibrillation will convert VF into a life-sustaining rhythm.

A 71 year-old woman with a history of COPD, HTN, and DM type 2 has been in the ICU for 2 days following a 3 vessel CABG. The nurse calls you because the patient has a marginal BP, low urine output, and this ECG (figure 19.1) for 2 hours, and now she seems more lethargic...

Figure 19.1 Rhythm Strip

INTRODUCTION

Dysrhythmias are common in the intensive care unit (ICU) and complicate the management of patients with sepsis, renal failure, pulmonary disease, coronary ischemia and heart failure. Surgery is a major risk factor in the development of post-operative dysrhythmias due to pain, inflammation, electrolyte abnormalities, and anemia.

This chapter is not meant to serve as an exhaustive description of the morphology, pathophysiology, and treatment of all known and unknown arrhythmias! It is intended to help house staff quickly review and understand the current treatment options in managing the most common arrhythmias encountered in the ICU.

PATHOPHYSIOLOGY

Atrial Bradyarrhythmias

1. Sinus Bradycardia (SB) is often caused by decreased automaticity within the sinoatrial (SA) node. This can be secondary to increased vagal tone, absent sympathetic tone (e.g., high spinal), hypothyroidism, intracranial hypertension, hypothermia, drug toxicity, electrolytes, coronary ischemia, or primary SA node dysfunction.

2. Sinoatrial disease or sick sinus syndrome (SSS) is a degenerative disease of the conduction system including the SA and atrioventricular (AV) nodes. It is characterized by symptomatic bradycardia, frequent

sinus pauses, sinus arrest, junctional escape rhythms, and sinus bradycardia with paroxysmal atrial fibrillation.

3. AV nodal blockade (AVB) may be incomplete (1st and 2nd degree) or complete (3rd degree). The block may be temporary or permanent, and is caused by a variety of drugs and diseases. Common pharmacologic offenders are adenosine, calcium channel blockers, beta blockers, amiodarone, and digoxin. Inflammatory and infiltrative disorders (e.g., sarcoidosis), coronary ischemia, myocarditis, thyroid disorders, and malignancy can also lead to AVB. This rhythm is also a known complication following aortic or mitral valve surgery.

4. First degree AVB is defined as a PR interval > 200 ms. It is caused by a slow conduction through the AV node and rarely requires intervention. Second degree AVB usually reflects disease at the AV node (Mobitz I) or the His- Purkinje system (Mobitz II). Mobitz Type I (Wenckebach) is an irregular pattern of progressive PR interval lengthening until a QRS complex is dropped. It is usually transient and typically does not need treatment. Mobitz Type II is an irregular pattern of complete conduction blockade, resulting in randomly dropped QRS complexes without changes in the PR interval. The ventricular rate depends on the frequency of dropped beats. This type of AVB can proceed to complete third degree heart block. Third degree AVB is complete atrioventricular dissociation caused by atrial impulses not conducting through the AV node. The ECG will show independent atrial and ventricular rates with an escape rhythm from an ectopic focus distal to the block. The escape rhythm can have a narrow or wide QRS complex, with a HR of 40-60 bpm.

5. Pulseless electrical activity (PEA) is organized electrical cardiac activity without mechanical activity. Asystole refers to the complete absence of electrical and mechanical activity of the heart.

Atrial Tachydysrhythmias

1. Any rapid heart rate (> 100 bpm) that originates from the atria is referred to as a supraventricular tachycardia (SVT). They are categorized by their rhythm (regular vs. irregularly irregular) and generally have a narrow QRS complex.

2. Sinus tachycardia (ST) is defined as a heart rate > 100 bpm with 1:1 AV conduction and a regular rhythm. It can be differentiated by other types of SVT by its gradual onset and resolution. Common causes include pain, alcohol withdrawal, hyperthyroidism, and pulmonary embolism.

3. Reentry SVT can be caused by AV nodal reentry tachycardia (AVNRT) and AV reentry tachycardia (AVRT). Reentry SVT is characterized by a self-perpetuating reentry circuit between the atria and ventricle. The rhythm is regular and the morphology often shows a narrow QRS complex. Wolff-Parkinson-White (WPW) is the most common form of AVNRT and involves an AV bypass tract (i.e., bundle of Kent). WPW patients often complain of paroxysmal symptoms of palpitations and dyspnea. Their ECG findings show a decreased PR interval and the characteristic "delta sign" caused by early ventricular depolarization leading to a widen QRS. AV nodal blocking agents should be avoided in WPW patients with atrial fibrillation because they can paradoxically increase their HR.

4. Premature atrial contractions (PACs) arise from areas of ectopic foci in the atria. Most patients are asymptomatic with palpitations being the most common complaint. PACs are often caused by excessive caffeine, ethanol, stress or hyperthyroidism. They are differentiated from a PVC by their narrow QRS complex, presence of a P wave, and a short compensatory pause.

5. Atrial flutter is characterized by an atrial rate that is generally 300 +/- 20 bpm, with variable conduction through the AV node (usually 2:1). The typical "sawtooth" pattern is most prominent in lead II on ECG.

6. Atrial fibrillation is characterized by an irregularly irregular rhythm. The atrial rate is often around 300-400 bpm with variable conduction and loss of AV synchrony. The ventricular rate is usually 100-180 but can be higher in the presence of an accessory tract. High ventricular rates, known as rapid ventricular response (RVR), can lead to fatigue, heart failure, angina, and cardiovascular collapse.

Ventricular Dysrhythmias

1. Ventricular dysrhythmias are characterized by the absence of an associated P wave and often have a wide QRS complex (> 120 ms). Ventricular bradyarrhythmias are commonly ventricular escape rhythms caused by pacemaker sites distal to the AV node (e.g., 3rd degree AVB).

2. Premature ventricular contractions (PVCs) arise from one or more ectopic foci distal to the AV node. They are distinguished by their wide QRS complex, lack of a P wave, and long compensatory pause. The premature contraction leads to a decrease in stroke volume which is balanced by an increase in stroke volume after the compensatory pause on the following beat. PVCs may occur in normal hearts, but increasing PVC frequency may indicate coronary ischemia, valvular disease, cardiomyopathy, electrolyte disturbance, or a prolonged QT interval. They may also occur as a result of direct irritation from central catheters and guidewires.

3. Ventricular tachycardia (VT) can be defined by morphology (monomorphic vs. polymorphic), duration (sustained vs. non-sustained), and physical exam findings (pulse vs. pulseless). VT is generally caused by conditions which predispose the myocardium to reentry or make it more susceptible to develop abnormal automaticity such as ischemia, long QT interval, and heart failure.

   a. Monomorphic VT is characterized as a wide complex, fixed morphology, regular rhythm tachycardia. It can be well tolerated by some patients, but often is associated with symptoms of cardiac failure such as dyspnea, syncope, hypotension, and oliguria.
   b. Polymorphic VT has an irregular QRS pattern and is often an irregular rhythm. It can quickly deteriorate into ventricular fibrillation.

5. Torsades de Pointes (TdP) is a polymorphic VT associated with a long QT interval. It appears as a sine wave rotating on its own axis. It typically occurs when the QTc interval has been excessively prolonged (> 500 ms) and is often iatrogenic from antiarrhythmic agents (e.g., sotalol, procainamide), antipsychotic medications (e.g., haloperidol and droperidol), and methadone.

6. Ventricular fibrillation (VF) is incompatible with life. There is no associated pulse as the ventricle does not contract in an organized manner. It is associated with ischemic cardiac disease and is thought to be caused by reentry circuits and abnormal automaticity. Only immediate defibrillation will convert VF into a life-sustaining rhythm.

MANAGEMENT

When evaluating a patient with a dysrhythmia, obtain a 12 lead ECG, and answer the questions below. Knowing the answers to these questions will help guide pharmacologic and electrophysiologic treatment, and suggest underlying causes to treat.

1. Is the rhythm slow or fast?
2. Is it regular or irregular?
3. Are the QRS complexes narrow or wide (>120 ms)?
4. Does every P have a QRS and does every QRS have a P?
5. Is the patient hemodynamically stable?

Bradycardia

Treatment for bradycardia should be reserved for symptomatic patients and is often well tolerated until the HR is < 40 bpm. The mainstay of therapy is treating the underlying cause or removing the offending agent.

1. Atropine (0.5 mg IV per dose, every 3 to 5 min) is a vagolytic that can be used to temporarily treat bradycardia until definitive treatment is available. Atropine is ineffective after cardiac transplant and in symptomatic bradycardia secondary to Mobitz Type II and Third degree AVB.

2. Epinephrine (2-10 mcg/min IV) is a potent β_1 agonist which increases HR and contractility, as well as systemic vascular resistance (via α_1 receptor activity). Epinephrine administration can lead to tachydysrhythmias. Electrical pacing via a transcutaneous or transvenous route is recommended in cases of Mobitz II and 3rd degree AVB.

Tachycardia

Treatment of tachydysrhythmias should be focused on correcting underlying causes. Treatment is aimed at suppressing automaticity, prolonging the effective refractory time, and facilitating normal impulse conduction.

1. Adenosine (1st dose: 6 mg and 2nd dose: 12 mg rapid IV bolus) blocks the AV node, slows conduction time, and blocks reentry circuits. It is indicated for patients with a reentry SVT. Side effects are coronary vasodilatation, bronchoconstriction, and flushing.

2. Calcium channel blockers (CCB) have negative chronotropic (reduce SA firing) and dromotropic (slow conduction through the SA node) properties. This allows them to be very effective at rate control for most SVTs. Side effects are bradycardia, hypotension, and AVB.

3. Beta-blockers also have negative chronotropic and inotropic effects on the heart. This class of medication is contraindicated in patients with decompensated heart failure and high-degree AVB.

4. Amiodarone (150 mg IV bolus over 10 minutes followed by infusion) acts on Na+, K+, and Ca++ channels, as well as alpha and beta receptors. This causes prolongation of the myocardial action potential and refractory period, as well as decreasing the effect of circulating stress hormones (decreasing intracellular calcium). Amiodarone is effective in controlling the rate of all SVTs, including atrial fibrillation, and is indicated for refractory/recurrent VT and VF as well. Amiodarone has a very long half-life (approximately 60 days), and patients must be loaded to reach meaningful levels quickly. The amiodarone load can cause hypotension, bradycardia, and sinus arrest acutely. Long term side effects include pulmonary toxicity, ventricular dysrhythmias, rare hepatic toxicity, CNS symptoms, and thyroid dysfunction.

5. Digoxin inhibits the Na+/K+-ATPase membrane pump and through this mechanism indirectly increases the intracellular calcium concentration. It is a positive inotrope and prolongs the refractory period of action potentials reducing the maximum frequency of conduction through the AV node. It has a delayed peak effect (up to 6 hours), and a narrow therapeutic index (especially in the setting of hypokalemia).

Other Treatment Modalities

1. For SVT and ventricular dysrhythmias alternative options include lidocaine, procainamide, sotalol, flecainide, and dipyridamole. Optimizing the patient's electrolytes by maintaining the magnesium greater than 2 mg/dL and the potassium greater than 4 mEq/L is also helpful in preventing reoccurrence of the arrhythmia.

2. Synchronized cardioversion refers to the delivery of an electrical current to the myocardium synchronized to the R wave. This allows the delivered shock to safely depolarize all excitable tissue simultaneously, resetting all myocardial tissue to the same refractory period. This is thought to allow the dominant pacemaker cells to resume function and thereby suppress areas of ectopy and reentry. Complications of cardioversion include embolic events (particularly in atrial fibrillation), skin burns, myocardial dysfunction, dysrhythmias, and transient hypotension from myocardial stunning.

3. Defibrillation refers to the non-synchronized delivery of massive amounts of energy with the intent of depolarizing all of the myocardium simultaneously. If the energy is insufficient to completely affect all cardiac tissue, areas of fibrillation will remain and the heart will revert back after the refractory period. In addition, it seems that with time, ventricular fibrillation is more difficult to convert. Therefore, in pulseless VT/VF, it is recommended that high energy shocks (360J monophasic or 150-200J biphasic) be delivered as soon as possible.

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Questions

19.1 The ICU resident is called by a nurse to evaluate a 22 year-old man complaining of palpitations and dyspnea. He is post-operative day two from an appendectomy. His HR is 155 and his BP is 88/58. His ECG shows an irregularly irregular wide complex rhythm. The intern gives metoprolol 5 mg IV push and the patient's mental status deteriorates. Vitals are now HR 205 and BP 71/37. Which of the following in this patient's history is most consistent with the condition that resulted in this paradoxical response?

    A.   History of chest pain exacerbated by exertion alleviated by rest.
    B.   History of dyspnea when lying flat.
    C.   History of paroxysmal palpitations, shortness of breath, and dizziness.
    D.   History of sharp chest pain radiating towards the back.

19.2 A 61 year-old man is post-operative day number two following a mitral valve repair. His ECG shows an irregularly irregular narrow complex tachycardia with a HR of 145. His vitals are HR 151, BP 120/52, SpO2 96% on room air. His preoperative TTE showed an LVEF of 55%. Which of the following is the most appropriate initial therapy?

    A.   Amiodarone
    B.   Metoprolol
    C.   Digoxin
    D.   Cardioversion

19.3 A 74 year-old woman is status post a three-vessel CABG. On post-operative day one, she is found to have an altered mental status and is having difficulty breathing while lying flat. Her vitals are HR 32 and BP 72/32. ECG shows what appears to be complete disassociation between the P wave and the QRS complex. Which of the following would be the best initial step in management?

    A.   Atropine
    B.   Chest Compressions
    C.   Cardioversion
    D.   Cardiac Pacing

20. Diagnosis and Treatment of Myocardial Ischemia

Katie Menzel MD and Dawn Nye DO

Key Points

• **The risk of PMI peaks within the first three postoperative days.**

• **Arrhythmias, acute heart failure, acute mitral regurgitation are all acute complications of PMI.**

• **Therapy is aimed at improving oxygen supply versus demand ratio and various forms of anticoagulants.**

A 70-year-old male is admitted to the ICU immediately post-operatively following a radical cystoprostatectomy with ileal conduit creation. Blood loss was 2L and 4 units PRBC were transfused. He arrives intubated with stable vital signs. His past medical history includes obesity, hyperlipidemia, diabetes mellitus, and a 50 pack-year smoking history. On postoperative day 0, he develops new hypotension and EKG changes.

Background

Anesthesiologists routinely care for and manage critically ill post-operative patients, whose unique characteristics increase their risk of myocardial ischemia and infarction. Early recognition and therapeutic intervention of acute myocardial ischemia is critical to reducing morbidity and mortality.

Physiology

Myocardial ischemia or infarction can occur any time myocardial oxygen demand exceeds supply. In the post-operative patient, this can be due to either the disruption of an atheromatous plaque resulting in intracoronary thrombus or to an imbalance between the supply and demand of oxygen from other causes. The latter mechanism is likely the most common scenario leading to post-operative MI (PMI) in the ICU and is sometimes called "demand ischemia."

Myocardial oxygen supply

The myocardium is perfused by the coronary arteries, which arise from the aortic root (Figure 20.1). The difference between aortic and ventricular pressures determines the coronary perfusion pressure. In the left ventricle, due to high systolic, transmural pressures, perfusion of the subendocardium occurs exclusively during diastole. Because of its lower ventricular pressure, the right ventricle is perfused throughout the cardiac cycle. If the aortic diastolic pressure is low, or if the ventricular end-diastolic pressure is sufficiently high to

impede forward flow, myocardial ischemia may occur. Additionally, as the heart rate increases, less time is spent in diastole, thereby decreasing coronary perfusion.

Smaller arteries have increased resistance to flow as governed by Poiseuille's law; as their radius decreases, flow decreases exponentially. Thus, even without plaque rupture, patients with atheromatous or small coronary arteries are at increased risk for MI.

Finally, blood that reaches the myocardium must be adequately oxygenated in order to fuel metabolism and prevent ischemia. Increased hemoglobin and oxygen saturation (and to a lesser extent PaO_2) will all increase the oxygen content of blood. Oxygen content = $1.36*SaO_2*Hgb + 0.003*PaO_2$

Myocardial oxygen demand
As the number or force of cardiac myocyte contractions increase, the oxygen demand increases. Therefore, oxygen demand is proportional to heart rate, wall tension, and contractility.

Postoperative Myocardial Infarction (PMI) Mechanisms
The risk of PMI peaks within the first three postoperative days. Several physiologic changes contribute to this risk:
- Extravascular fluid mobilization increases preload and myocardial wall stress
- Prothrombotic state from coagulation cascade activation and inflammation
- Catecholamine surges (including related to post-operative pain) increase heart rate and blood pressure

In addition to altering the balance of myocardial oxygen supply and demand directly, these changes predispose individuals with atherosclerosis to plaque rupture.

Diagnosis
The signs of PMI may be as nonspecific as altered mental status, arrhythmia, or shock. Chest pain may be masked by analgesics, and intubated patients often cannot communicate symptoms. Furthermore, symptoms can often be attributed to many other causes in a post-operative patient.

Electrocardiography (ECG) may show a number of changes. Elevation or depression of the ST segments in a regional distribution of leads suggests ischemia arising from a
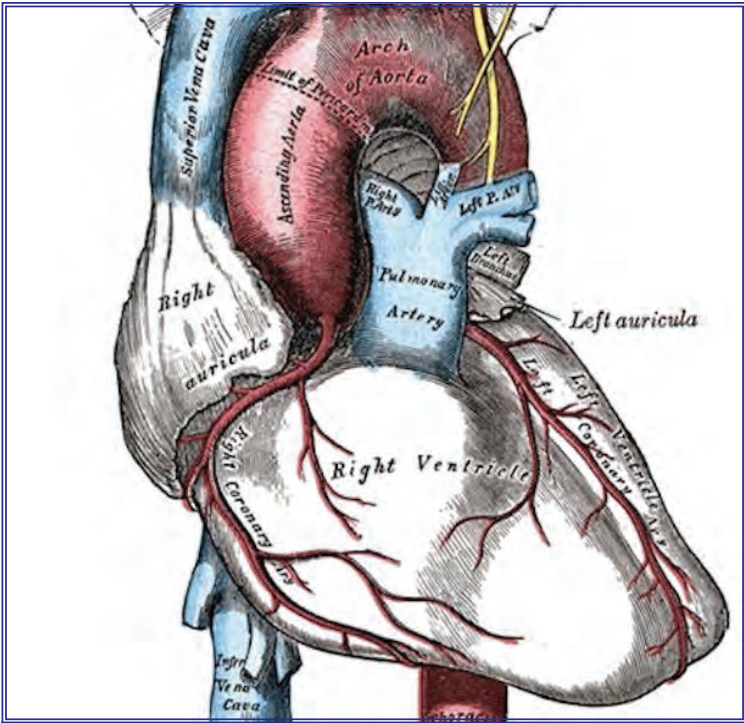
Figure 20.1 The surface anatomy of the heart, viewed anteriorly.

specific coronary artery. Other nonspecific ST or T wave changes can also occur in MI.

Injured myocardial cells release enzymes that can be measured as biomarkers of MI. While cardiac troponins T and I are currently the most sensitive and specific biomarkers, they may also be elevated in heart failure and renal insufficiency and are not sufficient to "rule in" MI.

Echocardiography can also be useful in the assessment of regional wall motion, valve function and overall cardiac function. Regional wall motion abnormalities are especially helpful if there is a prior study available for comparison. Echocardiography also allows noninvasive measurements of some hemodynamic parameters, including right and left sided pressures and cardiac output.

Once a diagnosis of myocardial ischemia is made, cardiac catheterization and angiography is used to identify the anatomic location of the culprit atherosclerotic lesion (Figure 20.2).

Table 20.1 Differential diagnosis based on common EKG changes, Echo changes and symptoms					
	Tako-tsubo cardiomyopathy	Pericarditis	Pulmonary Embolus	Pneumothorax	Hypovolemia
EKG changes	+	+	+*		
Echo changes	+		+*		
Symptoms	+	+	+	+	+
*may see pattern of right heart strain on EKG and/or right heart failure on echo					

Classification

Several classification schemes exist to describe MI:

Anatomic:
- Transmural versus nontransmural
- Involved segments of myocardium (inferior, anterior, septal, etc.)

EKG:
- Q wave MI versus non Q wave MI
- ST elevation MI (STEMI) versus non-ST elevation MI (NSTEMI)

Clinical: Based on 3rd universal definition of MI from the 3rd Global MI Task Force
- Type 1: due to a primary coronary event (plaque rupture, dissection)
- Type 2: due to imbalance in supply and demand
- Type 3: sudden unexpected cardiac death
- Type 4a: associated with percutaneous coronary intervention (PCI)
- Type 4b: in stent stenosis
- Type 5: associated with CABG

Complications:

There are several serious complications of MI to be aware of when treating critically ill post-operative patients.

Electrical

Bradyarrhythmias: occur when the conduction system becomes ischemic.
- Sinus bradycardia, junctional bradycardia with or without ventricular escape, and complete heart block.
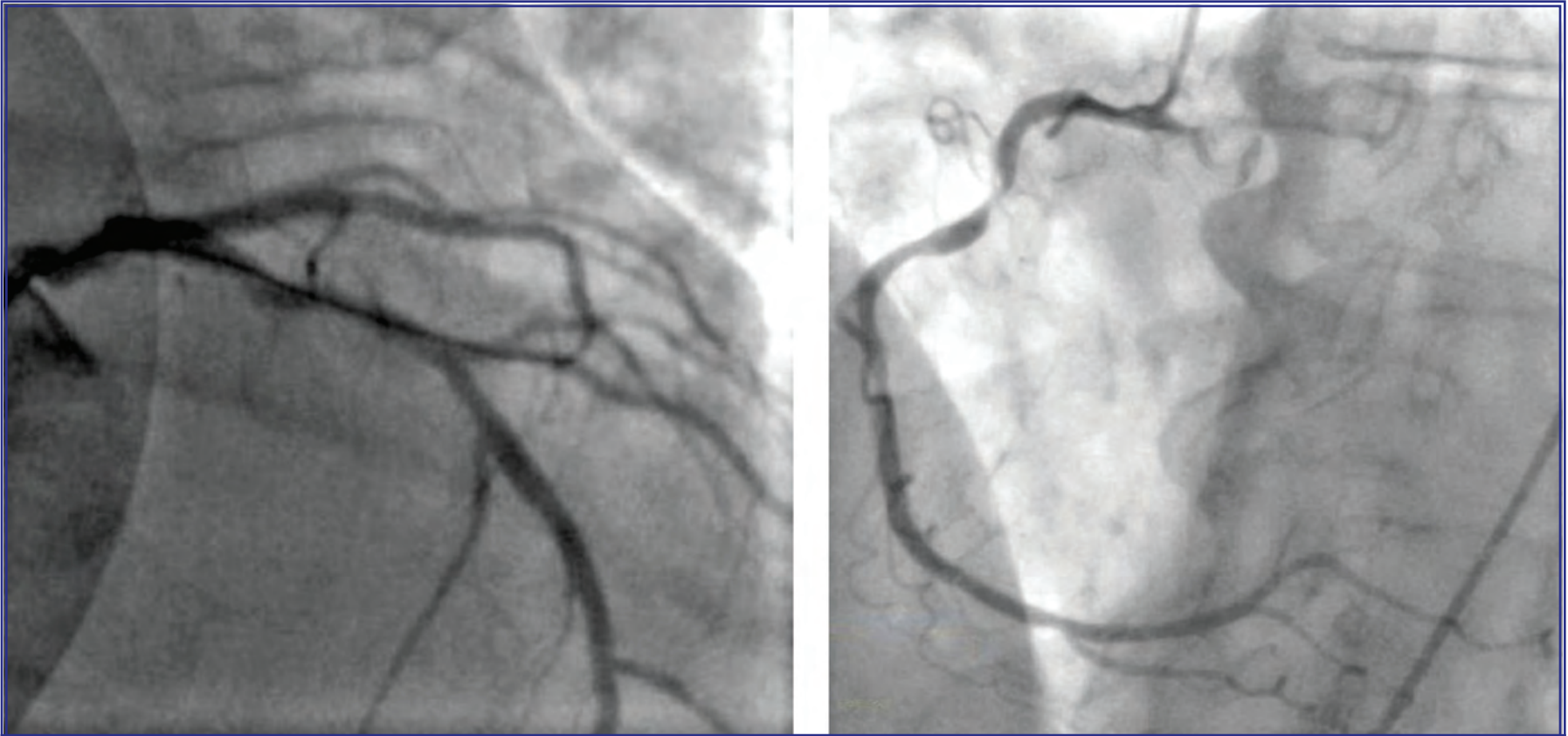
Figure 20.2 Cardiac Catheterization: The image on the left demonstrates stenosis of the left main artery (LMA). The image on the right demonstrates stenosis of the right coronary artery (RCA)

Tachyarrhythmias: occur when ischemia leads to irritability of the myocardium and disorganized transmission of electrical impulses.
 • Atrial: sinus tachycardia, supraventricular tachycardias (SVTs) and atrial fibrillation or flutter with or without rapid ventricular response
 • Ventricular: ventricular tachycardia (VT) and ventricular fibrillation (VF)

Mechanical
Acute heart failure: occurs when impaired myocardial function reduces cardiac output.
 • Left heart failure symptoms include: pulmonary edema, pulmonary hypertension, and cardiogenic shock.
 • Right heart failure symptoms include: peripheral edema, increased JVD, hepatomegaly, and cardiogenic shock.

Wall rupture: occurs when infarcted tissue weakens and tears.
 • Usually occurs 2-7 days after completed infarct.
 • Can occur in the septum (ASD or VSD) or as free wall rupture.
 • Classic presentation is of cardiogenic shock and a new murmur.

Acute mitral regurgitation: may occur when rupture of ischemic papillary muscle causes flail leaflet and acute, severe MR.
 • Has a poor prognosis.
 • Usually occurs with inferior infarcts.
 • Classic presentation is of shock, pulmonary edema and a new murmur.

LV aneurysm: is caused by dyskinetic, scarred apical tissue leading to ballooning.
 • LV thrombus may form due to stasis and turbulent flow in LV aneurysm.
 • Embolisms may occur to organs supplied by the LV, including brain, kidneys, extremities, and gut.
 • Persistent ST elevations are common in the apical territories, despite lack of active ischemia.

Therapy
Pharmacologic therapies
 • Antiplatelet agents: prevent platelet aggregation, adhesion and cohesion.
 • Aspirin (cyclooxygenase inhibitor) reduces mortality and is used as immediate therapy.
 • Thienopyridines (clopidogrel, ticlopidine) maintain stent patency after PCI.
 • Oxygen: improves PaO_2, SaO_2 and remains standard of care despite lack of evidence for reduced morbidity or mortality.
 • Nitrates: dilate coronaries, improving subendocardial perfusion. Systemic vasodilation reduces preload and afterload.
   • Effective in first 48hrs of MI
   • Avoid in acute inferior wall MI as it can cause profound hypotension.
 • Beta-blockers: decrease myocardial oxygen demand (decreased heart rate and contractility), increase myocardial oxygen supply (increased diastolic time), and
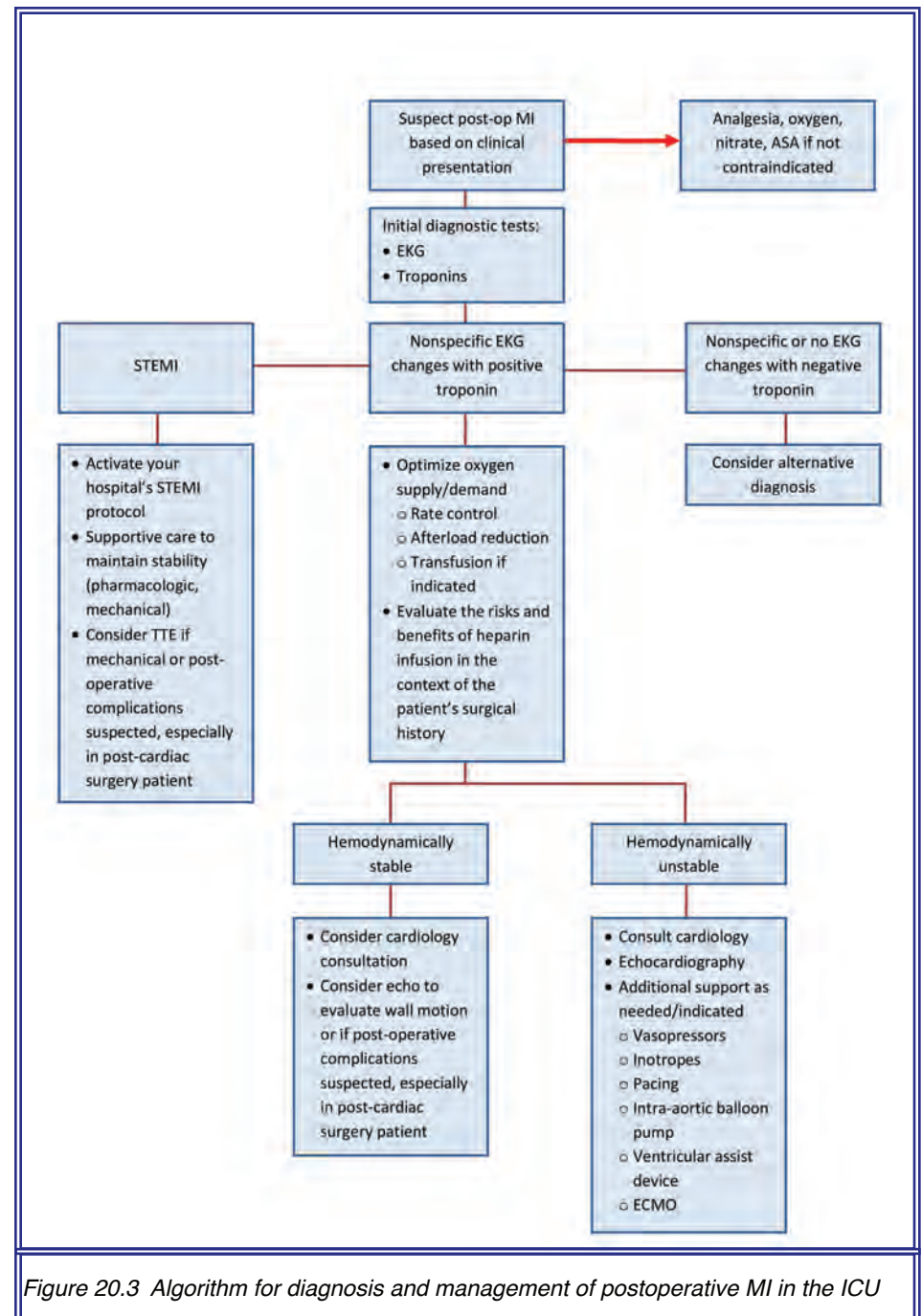
Figure 20.3 Algorithm for diagnosis and management of postoperative MI in the ICU

reduce mortality in the first week post-MI. They are also anti-arrhythmogenic.

• Unfractionated heparin: inhibits thrombus propagation by activating anti-thrombin III.

  • Administered as infusion acutely until long-term anticoagulation is established

• G2b3a inhibitors (abciximab, eptifibatide, tirofiban): antagonize platelet G2b3a-receptors, inhibiting fibrin binding to platelets and platelet aggregation.

  • Use during PCI reduces mortality, reinfarction, and need for further revascularization.

• ACE inhibitors: reduce afterload through vasodilation and are recommended within 24 hours of AMI as tolerated by blood pressure.

  • Use caution in patients with renal injury.

• Statins: reduce inflammation, improve endothelial function, reverse prothrombotic states, and reduce atherosclerotic plaque volume.

  • High intensity statin therapy (atorvastatin 80mg) reduces early recurrent ischemic events compared to moderate therapy (40mg) or placebo.

• Fibrinolytics (tPA): early use restores coronary blood flow in 50 – 80% of cases of STEMI or new bundle branch block; however, significant bleeding risk often prevents their use in the post-operative population.

Hemodynamic support:

• Inotropes (milrinone, dobutamine, epinephrine): increase myocardial contractility if cardiac output is inadequate.

• Vasopressors (norepinephrine, phenylephrine, vasopressin): increase peripheral vascular resistance to increase mean arterial pressure.

• Vasodilators (nitroglycerin, nitroprusside, nicardipine): reduce afterload to allow forward flow.

Invasive therapies

Percutaneous coronary intervention: restores coronary flow in 90 – 95% of MI patients with a "door to balloon" time of less than 90 minutes.

  • Preferable to fibrinolysis for PMI after noncardiac surgery given lower bleeding risk.

Surgical Revascularization (CABG):
• Must have appropriate anatomy
• Urgent if PCI has failed (left main disease, unable to restore flow)
• Urgent if patient is unstable due to anatomical complications of MI

Support measures

Patients may require invasive hemodynamic support, in addition to medical management, following PMI.

• Transvenous pacemaker: Emergency transvenous leads may be placed to facilitate temporary external pacemaking for unstable bradyarrhythmia. A permanent pacemaker may be indicated if bradyarrhythmia does not resolve.

• Left ventricular (LVAD), right ventricular (RVAD) or biventricular (BIVAD) assist devices may be implanted to support cardiac output of a severely impaired ventricle.

  • Cannulation may occur emergently at the bedside or in the operating room.

  • The device is temporary but may be replaced with a permanent device as destination therapy or a bridge to transplant.

• Extracorporeal membrane oxygenation (ECMO):

  • Blood is circulated and oxygenated through an external heart-lung machine.

  • High risk for complications including bleeding, infection, ischemia, compartment syndrome.

  • Temporary

• Intra-aortic balloon pump

  • provides intra-aortic counterpulsation.

  • Inflates during diastole, increasing myocardial perfusion

  • Deflates during systole, creating negative aortic pressure and drawing blood forward

  • Temporary

  • Contraindicated in patients with aortic regurgitation.

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Questions:

20.1 Which of the following pharmacologic therapies is not indicated for the acute treatment of myocardial ischemia?
   A. Nonselective cyclooxygenase inhibitor
   B. Selective cyclooxygenase inhibitor
   C. Angiotensin converting enzyme inhibitor
   D. HMG-CoA reductase inhibitor

20.2 Which of the following will most improve the balance of myocardial oxygen supply and demand?
   A. Decrease in diastolic time
   B. Decrease in heart rate
   C. Increase in left ventricular end diastolic pressure
   D. Increase in partial pressure of dissolved oxygen in blood

20.3 How does the treatment of myocardial infarction differ in post-operative patients as compared to the general population?
   A. Post-operative patients are at higher risk for infection from indwelling devices such as transvenous pacemakers or ventricular assist devices
   B. Post-operative patients are not candidates for coronary artery bypass grafting
   C. Inotropes have been shown to impair anastomotic healing and should not be administered to post-operative patients
   D. Many pharmacologic therapies may be contraindicated due to an increased risk of surgical bleeding

21. Valvular Heart Disease

Sean Kiley MD

Key Points

• Valvular heart disease may occur as a result of several processes including: infective endocarditis, inflammatory diseases, congenital diseases, acute ischemia and chronic degeneration.

• Physiologic goals for aortic stenosis (AS) are to keep HR low and the ventricle full with adequate diastolic pressure to avoid ischemia.

• Physiologic goals for aortic regurgitation (AR) are to maximize forward flow with afterload reduction and increased heart rate. Intra-aortic balloon pump (IABP) is contraindicated.

• Mitral stenosis (MS) leads to left atrial enlargement and subsequent atrial fibrillation with increased PA pressures.

• Mitral regurgitation (MR) also results in an enlarged left atrium with increased pulmonary artery (PA) pressures, which is treated with afterload reduction. Unlike AR, IABP may be useful in cases of acute decompensation.

A 70 year old female, with no previous past medical history, presents to the ER with an acute abdomen. Preoperative physical examination demonstrated a 4/6 systolic ejection murmur, but the emergent nature of the case dictated immediate operative intervention without cardiac work up. Intraoperatively, a 30 cm segment of small bowel was removed due to ischemia. The patient was extubated in the operating room but experienced some shortness of breath in the PACU, initiating a transfer to the ICU. Upon admission to the ICU the patient's heart rate was 110 with ST segment depression in the anterior and lateral leads. Transthoracic echo demonstrated aortic valve gradient of 55 mmHg and valve surface area of 0.7 cm^2 in addition to a severely hypertrophied left ventricle, which demonstrated difficulty filling. Fluid resuscitation was initiated along with alpha 1-agonist therapy.

Introduction

Valvular heart disease can affect patients of all ages. It is most common in elderly patients, and, because the elderly population in the US is rising, it is likely that the incidence of valvular heart disease will rise as well. The most common valvular lesion is degenerative aortic stenosis followed by mitral regurgitation.

Most valvular disorders are progressive without medical management. Even with the benefit of medical management, many times these disorders require surgery for ultimate alleviation of symptoms. Recent progression in surgical technique has allowed many, who were previously considered inoperable, the opportunity for surgical repair.

Each valvular disorder presents unique management challenges, and it is common for multiple disorders to coexist, making management even more challenging. Patients with an existing valvular heart lesion who present with an acute insult (systemic inflammatory response syndrome (SIRS), sepsis, hemorrhage, etc.) are at high risk for acute cardiovascular collapse, depending upon the severity of the lesion. The following discussion aims at providing basic understanding of the causes of valvular heart disorders that are frequently encountered in critically ill patients, as well as diagnostic and therapeutic interventions.

Aortic Stenosis (AS)

A. Pathophysiology

  1. In the elderly, degenerative calcification causes thickening and or fusion of the valve leaflets, which then inhibits opening surface area. This can also be a congenital condition in which the patient is born with a bicuspid valve and the stenosis progresses as the person ages.

  2. Persistent contraction against a fixed resistance stimulates hypertrophy of the left ventricular wall. This results in a stiffened left ventricle and diastolic dysfunction.

  3. Severe stenosis reduces cardiac output. Severe left ventricular hypertrophy (LVH) puts a high demand on diastolic perfusion pressure of the left ventricle. This combination can cause acute ischemia.

  4. Severe stenosis causes progression to congestive heart failure. When this occurs, the aortic valve pressure gradient is not reflective of the severity of AS due to the low cardiac output.

B. Diagnosis

  1. Symptoms include: angina, exertional dyspnea, syncope.

  2. Physical exam findings include: soft ejection murmur, diminished aortic component of S2, pulsus parvus et tardus, and brachio-radial delay.

  3. ECG findings include: LV hypertrophy, strain pattern T wave inversion and ST depression.

  4. Doppler echocardiography can be used to assess the severity by measuring maximum jet velocity and mean transvalvular gradient, which allows calculation of aortic valve area. Direct measurement by planimetry can also be used to assess degree of stenosis.

  5. Left heart catheterization can be used to calculate transvalvular gradient and valve area.

C. Management

  1. Invasive monitoring is often required for tight management of blood pressure and fluids. An arterial line should be utilized for second-to-second blood pressure measurements. A central venous line (CVL) may be utilized for infusion of vasoactive drugs in acutely ill patients. Bedside ultrasonography is often helpful for evaluation of fluid status.

  2. Perioperative hemodynamic goals for patients with AS:

    a. Maintain sinus rhythm and avoid tachycardia (60-70 beats per minute). Patients with concomitant aortic regurgitation may tolerate higher heart rates (80 -90 beats per minute). Atrial contraction maximizes left ventricle preload. Thus immediate cardioversion should be used in the setting of supraventricular arrhythmias causing hemodynamic instability. Appropriate post-operative analgesia is important to prevent tachycardia.

    b. Avoid hypovolemia. It is difficult to assess an appropriate volume status with pulmonary artery catheter because the wedge pressure underestimates preload secondary to decreased ventricular compliance. Bedside ultrasonographic assessment of ventricular volume and inferior vena cava (IVC) diameter variability may provide better assessment tools.

    c. Avoid acute arterial hypotension. It might precipitate ischemia and cardiac arrest. An alpha agonist (phenylephrine) is the agent of choice in the setting of arterial hypotension since it maintains diastolic filling time with a reflexively lower heart rate. If a patient has underlying decreased cardiac output (EF< 40%), norepinephrine might be advantageous. Norepinephrine causes a mild to moderate increase in contractility via beta-1 activity as well as preservation of systemic vascular resistance via alpha-1 activity. Patients receiving mechanical ventilation need careful titration of sedatives and analgesic agents since these agents can cause arterial hypotension. It is mandatory to treat pain first and then reassess patient for requirement of hypnotics to facilitate mechanical ventilator support and comfort.

D. Treatment

  1. The medical goal is to maintain cardiac output while preventing volume overload and pulmonary edema. This serves as a bridge to surgical or percutaneous intervention.

  2. There are several surgical procedures that may be utilized for corrective therapy, depending on the patient and severity of the lesion. Percutaneous balloon valvuloplasty, used for palliation, can cause severe aortic insufficiency (AI). Transcatheter aortic valve implantation for critical aortic stenosis is currently being used in patients not deemed surgical candidates; however, successes in this procedure may lead to a broader application. Despite this, traditional open-heart surgery is still used for most cases.

Aortic Regurgitation (AR)

A. Pathophysiology

  1. Regurgitant flow across the aortic valve can be caused by a number of different processes including: abnormalities of aortic valve leaflets (calcific degeneration, bicuspid valves, destruction from endocarditis), aortic root dilation (aneurysm of ascending aorta, aortic dissection), and endocarditis.

  2. Acute AR (acute dissection or acute endocarditis) can result in acute cardiovascular decompensation.

  3. Chronic AR results in chronic pressure and volume overload, and causes progressive ventricular dilation.

B. Diagnosis

  1. Physical findings include a diastolic murmur, narrow pulse pressure, and marfanoid features.

  2. Echocardiography provides a definitive diagnosis. It may demonstrate thickened valve leaflets, flail leaflets, a prolapsed valve, vegetations, and/or aortic root dilation. A regurgitant jet will be apparent across the aortic valve on color flow Doppler. Transesophageal echo is useful for suspected thoracic aortic dissection.

C. Management

  1. Perioperative goals are to decrease the regurgitant volume and maximize forward systemic flow. Thus, relatively fast heart rate (90-100 beats per minute) is preferred to decrease the time in diastole and subsequent regurgitant volume. After load reduction may also be utilized.

  2. It is important to keep in mind that the use of an intra-aortic balloon pump (IABP) is contraindicated. This is because inflation of the balloon during diastole will cause massive overload to the left ventricle and aggravate cardiac decompensation.

D. Treatment

  1. Symptomatic patients with severe AR should undergo surgery irrespective of LV size and function. Patients with severe, chronic AR need medical optimization.

  2. Endocarditis with hemodynamic compromise should prompt urgent surgery.

  3. Asymptomatic patients should be followed closely. Surgery is indicated with

earliest signs of decompensation. Chronic mild AR in the perioperative period is well tolerated.

Mitral Stenosis (MS)

A. Pathophysiology

  1. Rheumatic heart disease is, by far, the most common cause of mitral stenosis. Modern early treatment of streptococcus infections has reduced rheumatic disease significantly, thereby reducing the incidence of mitral stenosis. Rarely, calcium deposits, malignant carcinoid, lupus or amyloidosis can cause mitral stenosis in adults. It is also a rare congenital defect.

  2. Progressive disease causes an enlarged left atrium and atrial fibrillation. Pulmonary hypertension develops and will become more severe as disease progresses. The disease progresses slowly, but acute decompensation can occur with increased hemodynamic demands.

B. Diagnosis

  1. Physical findings include a diastolic rumble with an opening snap. Echocardiography is used for definitive diagnosis and quantification of severity.

C. Management

  1. Perioperative hemodynamic goals for patients with MS:

    a. Maintain sinus rhythm. Supraventricular tachyarrhythmias may precipitate pulmonary edema and cardiovascular collapse. Up to 50% of patients with chronic MS develop atrial fibrillation.

    b. Maintain normal cardiac contractility and systemic vascular resistance since these patients have a fixed cardiac output. The agent of choice in case of arterial hypotension is phenylephrine, because perfusion pressure must be assured and relative bradycardia secondary to baroreceptor reflex might be beneficial.

    c. Identify patients with pulmonary hypertension as a consequence of MS. This subgroup of patients need better management of all factors that worsen pulmonary hypertension (hypoxemia, hypercapnia, acidemia, and hypothermia). Some of these patients may present with right ventricular dysfunction. Inotropic support (epinephrine, milrinone or dobutamine) and judicious fluid management are important in this setting. The use of a pulmonary artery catheter is potentially helpful to guide the effect of interventions on pulmonary hypertension.

    d. Fluid management in patients with MS mandates careful monitoring. Suboptimal fluid resuscitation decreases cardiac output dramatically and excessive administration of fluids will precipitate pulmonary edema and acute right ventricular failure.

  2. Anticoagulation needs to be resumed after risk of postoperative bleeding has decreased (usually > 48-72h) in patients who preoperatively had an increased risk for intracavitary thrombus, i.e. intermittent atrial fibrillation, large left atrium.

D. Treatment

  1. Procedural intervention is necessary for definitive treatment. Mitral balloon valvuloplasty may be used in specific cases with favorable morphology. Otherwise, the valve must be replaced surgically.

Mitral Regurgitation (MR)

A. Pathophysiology

  1. MR can result from abnormalities of the annulus (dilatation), valve leaflets (myxomatous change, leaflet damage from endocarditis, shrinkage from rheumatic disease), chordae tendinae (rupture or elongation), or papillary muscle (rupture or elongation).

  2. Acute MR from ischemia or infarction causes acute LV overload and cardiogenic shock (> 50% of patients with MI present some degree of MR).

  3. Chronic MR results in progressive increase in LV compliance followed by increase in LVEDV as LV dilates.

B. Diagnosis

  1. Physical exam findings include: holosystolic murmur at the apex radiating to the axilla, lung rales, and peripheral edema.

  2. TEE is the best technique to determine the degree and nature of MR. Echocardiography also assesses the status of LV function & provides an estimate of PA pressures.

C. Management

  1. Treat underlying causes such as fluid overload, anemia or infection and optimize preload with diuretics and vasodilators.

  2. Coronary revascularization is indicated for regional wall motion abnormalities causing mitral valve apparatus dysfunction.

  3. For acute decompensation, the pharmacological agents of choice are similar to AR (milrinone or dobutamine). In contrast to AR, IABP is an appropriate therapy in MR. Diuretics may be considered for treatment of pulmonary edema.

  4. Perioperative hemodynamic goals for patients with MR are similar to AR patients. However the left ventricle has lower afterload in comparison. Thus left atrial dilation and pulmonary hypertension occurs progressively. Mitral regurgitation deteriorates with afterload increase.

D. Treatment

  1. Mitral valve repair may be indicated for a prolapsed leaflet. Replacement may be indicated if annular morphology does not allow for ring repair.

  2. Valve resection and replacement is performed for endocarditis with heart failure to avoid further structural damage.

  3. Concomitant MAZE may be indicated for paroxysmal AF.

Tricuspid Regurgitation (TR)

A. Pathophysiology

  1. Tricuspid regurgitation is most commonly functional in nature as a consequence of advanced mitral valve disease leading to pulmonary hypertension, RV dilatation and tricuspid annular dilatation. Thus, normal pulmonary arterial pressures are suggestive of structural tricuspid valve disease or primary right ventricular dysfunction.

B. Diagnosis

  1. Clinical findings include systolic murmur that increases with inspiration, prominent jugular pulsation, and, occasionally, pulsatile liver.

C. Management

  1. Perioperative hemodynamic goals for patients with TR and right ventricular dysfunction:

    a. Maintain appropriate preload. A reasonable goal can be to closely trend the CVP and maintain it around 15 mmHg. Fluid overload can aggravate TR and RV dysfunction.

    b. Maintain adequate RV myocardial perfusion pressure. The RV receives

perfusion both in systole and diastole. It is important to avoid hypotension so myocardial ischemia is prevented.

c. Decrease RV afterload. Manipulation of all variables that affect pulmonary vascular resistance is helpful to assure better right ventricular performance (PaO_2, PCO_2, pH, hypothermia, and unnecessary use of vasopressors).

d. Maintain normal to high heart rates (> 80's-90's beats per minute). Treat brady-arrythmias aggressively. Low heart rates are inappropriate for state of shock and regurgitation tends to be worse in patients with lower heart rates.

e. Increase RV contractility. Epinephrine or milrinone in combination with norepinephrine are adequate choices for inotropic/vasopressor support in severe RV dysfunction.

D. Treatment

1. Repair is indicated for severe TR with mitral valve disease that requires mitral surgery. Replacement may be considered for cases not amenable for repair.

This chapter is a revision of the original chapter authored by Sriharsha D Subramanya, M.D. and Jose Diaz-Gomez, M.D.

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Questions

21.1 Which of the following is a perioperative hemodynamic goal for aortic stenosis?
   A. Decrease afterload
   B. Limit intravascular volume replacement
   C. Avoid tachycardia
   D. Avoid bradycardia

21.2 Which of the following is contraindicated in aortic regurgitation?
   A. Tachycardia
   B. Afterload reduction
   C. Intra-aortic balloon pump therapy
   D. Surgical correction

21.3 Is the use of a PA catheter sometimes indicated in the management of mitral stenosis?
   A. No, because it is old technology that has no place in modern ICU practices.
   B. No, because the risks outweigh the benefits.
   C. Yes, because a PA catheter is integral in the management of heart failure that results from mitral stenosis.
   D. Yes, because a PA catheter can assist in the management of pulmonary hypertension, which may result from mitral stenosis

22. Adult Congenital Heart Disease

Anila Balakrishnan MD and Dawn Nye DO

Key Points

- More children born with CHD are reaching adulthood

- The clinician should know the primary lesion, whether the lesion was surgically corrected or intervened upon, and if there are any residual hemodynamic lesions present

- Cardiology consultation is warranted for all ACHD beyond a hemodynamically insignificant simple shunt

A 30-year-old man presents to the ED with progressive shortness of breath and lower extremity edema. His past medical history is significant only for a heart murmur as a child and seasonal allergies. On exam, he is noted to have a loud holosystolic murmur heard best at the left lower sternal border, cyanosis of the skin, clubbing of the fingers, and 2+ pitting edema. Echocardiography reveals a large ventricular septal defect (VSD) with right ventricular hypertrophy and right ventricular systolic pressure (RVSP) estimated to be approximately 121 mmHg.

Introduction

Adult congenital heart disease (ACHD) is becoming more prevalent in the clinical setting as children born with congenital heart defects are surviving into adulthood. Approximately 0.4-1% of babies are born with congenital heart disease, and greater than 85% survive into adulthood.[1-3] In 2000, the prevalence of adult congenital heart disease was estimated to be about 2800 adults per 1 million. This is a sign of advancement in the medical field over the years, but it also poses a unique new challenge to those providers who may not be prepared to care for such complex patients in the clinical setting. Although a vast topic, we will present some basics of managing patients with adult congenital heart disease.

Overview of common ACHD

Various types of classification of ACHD include the following: cyanotic vs. acyanotic; simple, moderate, severe complexity; and simple shunts, obstructive lesions, regurgitant lesions, complex lesions (this group is discussed in more detail below).

Simple shunts include unrepaired, hemodynamically significant shunts. Examples include atrial septal defects (ASD), ventricular septal defects (VSD, see Figure 22.1), atrioventricular septal defects, patent ductus arteriosus, and patent foramen ovale (PFOs). Ventricular shunts may require expert consultation and close hemodynamic monitoring, especially if the patient is undergoing the physiologic changes of a critical care illness. However, after successful repair, most of these patients do not require specialist care.

A. Management:
   1. Air filters for IVs. IV lines should be completely free from air bubbles. Watch for paradoxical air embolism.
   2. Avoid nitrous oxide
   3. Close vigilance for arrhythmias. Septal defects are associated with conduction defects.

Obstructive lesions

A. Coarctation of the aorta involves stenosis of the proximal thoracic aorta. There

Figure 22.1 Ventricular Septal Defect (VSD), a type of shunt lesion
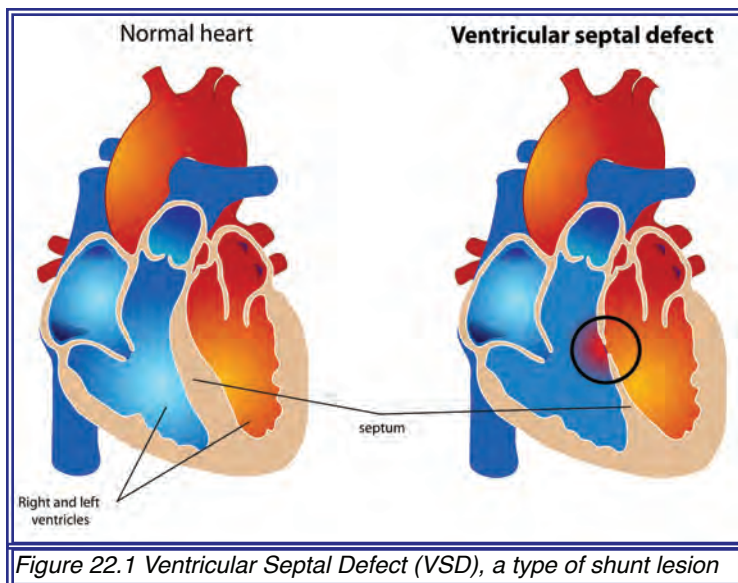
are many variants of this lesion, but the most frequently encountered lesion is at the point of insertion of the ductus arteriosus.[4] Severe coarctation presents in the neonatal period and is repaired within the first few days of life. Less severe coarctation can present later in childhood or even in adulthood. Once repaired, with no evidence of recoarctation, these patients can be treated like normal adults during times of critical illness. It is important to measure blood pressure in all four limbs to evaluate for recoarctation; differences should be < 20 mmHg. This will also allow the clinician to assess if the left subclavian artery was sacrificed during the procedure. These patients have an increased propensity for hypertension as adults.

B. Left Ventricular/Right Ventricular Outflow Obstruction (LVOTO/RVOTO) encompasses several stenotic lesions beginning at the anatomic LVOT or RVOT and stretching to the descending portion of the aortic arch or pulmonary artery, respectively. These obstructions can be supravalvular, valvular or subvalvular.
   1. Lead to ventricular hypertrophy and subsequently, heart failure
   2. Evaluate for heart failure and outflow obstruction

C. Congenital mitral stenosis: These patients are at increased risk in unrepaired or incomplete repair for the following:
   1. Atrial arrhythmias

   2. Pulmonary hypertension
   3. Right heart failure

Regurgitant lesions

A. Ebstein's anomaly is a defect where the tricuspid valve is abnormal and sits low in the right ventricle, with an "atrialized" right ventricle above the valve. The valve's leaflets are restricted which leads to severe regurgitation and right heart failure. If surgically repaired, these patients are at risk for arrhythmias from scar tissue near the conduction system.

B. Marfan's syndrome is a genetic disorder of connective tissue, which can lead to severe dilation of the aorta. It can also be associated with mitral and aortic regurgitation.

C. Tetralogy of Fallot (TOF, Figure 22.2) is a collection of four defects that usually requires repair in the first two years of life. However, even if repaired, these patients can present in the future with right heart failure secondary to pulmonary insufficiency from pulmonic valve repair. The four defects include the following:
   1. Ventricular septal defect (VSD)

Figure 22.2 Tetralogy of Fallot, a type of regurgitant lesion
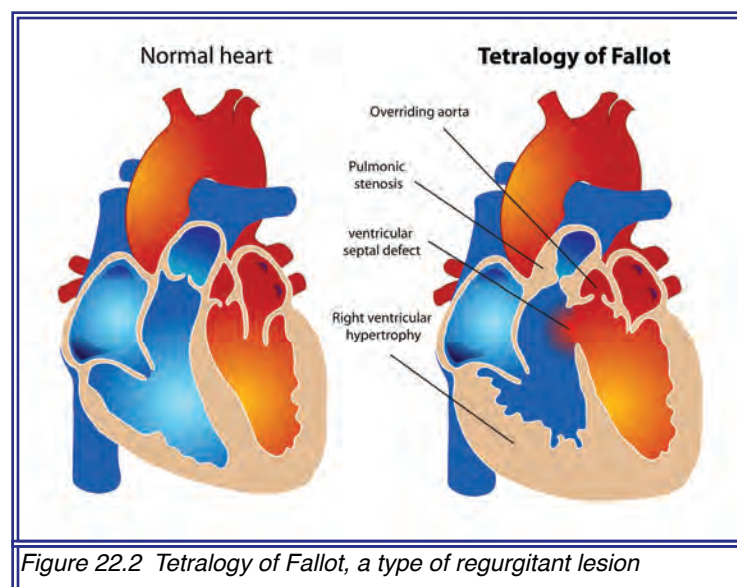
   2. Overriding aorta
   3. Pulmonary stenosis and RVOTO
   4. Right ventricular hypertrophy

Complex lesions

A. Transposition of great arteries (TGA) involves malposition of the pulmonary artery and aorta and may also involve abnormal arrangement of any great vessel, which is referred to as transposition of the great vessels. The standard surgical TGA repair until the late 1980s was the Mustard or Senning repair, which consisted of a two-way baffle placed between the right and left atria to redirect blood flow to the appropriate ventricle. The Mustard procedure utilizes a synthetic material to create the baffle, whereas the Senning procedure utilizes the patient's own tissue. Currently, repairs are by arterial switch. Long-term complications of the Mustard/Senning repairs are as follows:

  1. Atrial dilation and heart failure from thinner right ventricle being used as the systemic pump

  2. Increased incidence of arrhythmias from scar tissue

  3. Baffle complications, notably stenosis and leaking

B. Congenitally corrected transposition of great arteries occurs when the heart rotates abnormally during development leading to the ventricles being reversed. If not repaired, these patients have a systemic right ventricle, which increases the risk of arrhythmias and early onset heart failure. If repaired by a double switch procedure there is less risk of arrhythmias. However, regardless of repair, these patients may have abnormal coronary artery anatomy and are prone to ischemia at younger ages.

C. Univentricular heart (left or right single ventricle) is a group of disease processes whose classification has been a controversial subject. Most commonly, it refers to a functional single ventricle with a second rudimentary or hypoplastic accessory ventricle. The AV connection is associated with one ventricular chamber (Figure 22.3).[3] The Fontan procedure is used to palliate the following lesions: tricuspid atresia, pulmonary atresia, and hypoplastic left heart syndrome. The procedure entails a two-stage process where venous return is directly connected to pulmonary arteries without going through the ventricle. Note, in this surgically altered circuit, cardiac output (CO) is no longer determined by the heart, but rather by transpulmonary flow.
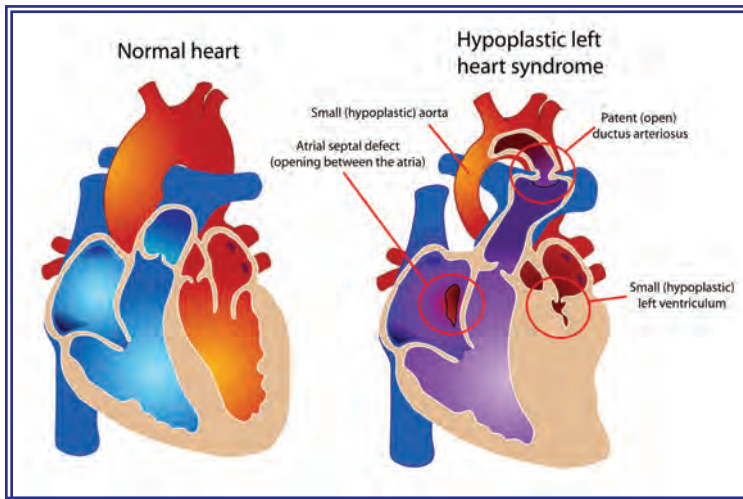
Figure 22.3 Hypoplastic Left Heart

  1. Advantages

    a. Near normal arterial saturation

    b. Decreased chronic volume overload state

  2. Disadvantages

    a. Chronic venous hypertension

    b. Arrhythmias

    c. Decreased CO at rest and with exercise

D. Modified Blalock-Taussig shunt (BT shunt) is temporarily used to direct blood flow to the lungs and improve cyanosis and can be used in the first stage of the Fontan procedure. The original surgery involved a branch of subclavian artery or carotid artery, which was separated and attached to the pulmonary artery. Now, an artificial conduit is used to connect subclavian or carotid artery to pulmonary artery.

Management in the clinical setting:

Management in the clinical setting requires a thorough understanding of the specific cardiopulmonary anatomy of ACHD patients and imposes an intellectual challenge for the clinician who cares for this patient population. Specifically, the clinician should know the primary lesion, whether the lesion was surgically corrected or intervened upon, and if there are any residual hemodynamic lesions present. It is imperative to consider how interventions that were undertaken affect the patient's current circulation. Furthermore, it is important to understand the patient's "normals," such as their baseline hemoglobin, baseline oxygen saturation, systemic blood pressure, pulmonary blood pressure, and baseline ECG.

Table 22.1 Acyanotic vs Cyanotic Lesions

Acynotic	Cyanotic (the 5Ts)
Ventricular Septal Defect (VSD)	Transposition of the Great Arteries (TGA)
Patent ductus arteriosus (PDA)	Tetralogy of Fallot
Atrial septal defect (ASD)	Truncus arteriosus
AV canal	Tricuspid valve abnormalities
	Total anomalous pulmonary venous connection
	Other: pulmonary atresia, hypoplastic left heart, coarctation of the aorta, Eisenmenger syndrome

Management depends on presence of the following:

A. Shunt, balance between the systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) is very important

  1. Left-to-right shunt (i.e. ASD, VSD, PDA, BT shunt). Patients are acyanotic, but are more prone to pulmonary congestion. AVOID high PaO_2 and low $PaCO_2$ as they cause pulmonary vasodilation and can worsen pulmonary congestion. In general, the shunt decreases with decreased SVR and increases with decreased

PVR. There are minimal onset time effects on IV medications during procedural sedation. Examples include:

a. PDA: Patients are more prone to coronary ischemia due to ongoing pulmonary runoff during diastole; a mildly low diastolic BP can lead to coronary ischemia.

b. BT shunt: shunt between subclavian artery and pulmonary artery

i. Flow is proportional to SVR; in systemic hypotension, pulmonary blood flow will decrease

ii. Blood pressure in ipsilateral arm will be decreased, so BP monitoring should be contralateral to repair

2. Right-to-left (i.e. TOF). Results in drop in SaO_2 that is refractory to increasing oxygen concentration. It also increases dead space ventilation due to decreased pulmonary blood flow. IV medications will have a faster onset than usual. Management:

a. Volume

b. Alpha agonists (i.e. phenylephrine) will increase SVR and reduce shunting

c. Beta blockers, will decrease RVOTO

B. Pulmonary HTN

1. Early pulmonary hypertension. Increase in PVR in response to hypothermia, stress, pain, acidosis, hypercarbia, hypoxia and elevated intrathoracic pressure.

2. Chronic pulmonary hypertension, fixed. PVR is greater than SVR causing right to-left shunt. Example:

a. Eisenmenger syndrome = most common reason for cyanosis. These patients have hypoxemia, myocardial dysfunction and arrhythmias. Management:

i. Phlebotomy, if hyperviscosity syndrome present

ii. IV fluid to avoid hypotension/dehydration

iii. Main goal is to prevent further increase in shunting by increasing SVR and decreasing PVR.

C. Hypoxemia.
Caused by two main mechanisms in this patient population. Of note, these patients tend to be polycythemic, therefore it is important to ensure adequate hydration.

1. Inadequate pulmonary blood flow. Management:

a. Maintain systemic blood pressure

b. Minimize factors that will increase PVR

c. Avoid sudden increases in oxygen demand

2. Mixing of deoxygenated and oxygenated blood. Management:

a. Avoid pulmonary vasodilation, which increases cardiac work and decreases systemic blood pressure.

b. Balance systemic flow and pulmonary flow. Do not expect normal SaO_2.

D. Ventricular dysfunction

1. Causes: Volume overload (large shunts, valve insufficiency), obstructive lesions, cardiac muscle disease, and ischemia

2. Presentation is variable: examples are weight gain, nausea, bloating, decreased appetite, fatigue, tachycardia, tachypnea, pulmonary congestion, hepatomegaly, lower extremity edema, and narrow pulse pressure

3. Management:

a. Maintain cardiovascular stability as much as possible. IV drugs take longer to reach target areas from prolonged circulatory time.

b. Afterload reduction with vasodilators may be necessary to decrease cardiac workload and improve cardiac output.

E. Arrhythmias are very common. They are often secondary to scarring from previous cardiac surgery or due to distention of the atria/ventricles. Supraventricular arrhythmias are more common and may not respond to traditional medical management.

Specific considerations in the ICU

A. Renal protection. This is especially important in patients with cyanotic lesions due to compensatory mechanisms; they have hyperviscosity and arteriolar vasoconstriction.

1. Minimize nephrotoxic agents, including caution with IV contrast

2. Maintain renal perfusion pressure (RPP)

a. RPP = MAP-CVP

b. Extra vigilance in patients with elevated CVP due to baseline cardiac physiology: TOF, Ebstein's anomaly, single-ventricle with Fontan circulation.

c. Watch for increased intraabdominal pressures as a mechanism for decreased renal perfusion (i.e. ascites, right heart failure).

B. Hepatic dysfunction. Result of chronic elevations in CVP, usually from long-standing heart failure or elevated right heart pressures leading to centrilobular necrosis and fibrosis. Acute or chronic hepatic dysfunction can develop if the patient has a low CO or hypoxia. Patients with Fontan circulation are at increased risk and, over time, these patients can develop varices and life threatening gastrointestinal bleeds.

C. Hematology and coagulation

1. Cyanotic patients are polycythemic with associated iron deficiency, thrombocytopenia and platelet dysfunction.

2. Right heart failure leading to liver dysfunction and prolonged PT and increased bleeding risk.

3. Fontan circulation leading to increased risk for thrombosis due to stasis within the repaired pathway and increased factor VIII levels.

4. Key management issues

a. Early mobilization

b. DVT prophylaxis

c. Careful monitoring of coagulation status

D. Pulmonary considerations

1. Etiology of pulmonary compromise

a. Hypoplasia of one lung

b. Restrictive lung disease

c. Scoliosis

d. Diaphragmatic paralysis due to prior phrenic nerve injury

2. Left heart failure: Patients may benefit from positive pressure ventilation (PPV) by increasing cardiac output.

3. Right heart failure: PPV can lead to decrease in right ventricular output due to decreased pressure gradient between great veins and right atrium. In patients with poor right ventricular function, this can compromise systemic cardiac output.

4. Fontan without communication between common atrium:

a. Avoid high PEEP

b. Early extubation when possible

c. Can consider high frequency jet ventilation and negative pressure ventilation as alternatives.

E. Cardiac Considerations

1. Heart failure: Medical management is mostly supportive with treatment for symptoms. Follow AHA guidelines for CHF management.

2. Arrhythmias are the most common cause of admissions in this population accounting for 31%. Onset may be a sign of hemodynamic decompensation. Catheter ablation results are generally worse in this population. Anti-arrhythmics are generally poorly tolerated due to negative inotropic properties and side effects.

3. Sudden cardiac death. Unexplained syncope may be a warning sign.

a. 5 defects are known to have the greatest risk: TOF, TGA, congenitally corrected TGA, aortic stenosis, and univentricular heart

b. Prevention

i. Internal cardiac defibrillator (ICD) implantation is indicated in ACHD survivors of cardiac arrest after excluding reversible causes (secondary prevention)

ii. Patients with sustained ventricular tachycardia (VT)

a) Invasive hemodynamic monitoring

b) Aggressive replacement of electrolytes (particularly K+, Mg++)

c) Electrophysiology (EP) evaluation

1) First line treatment is catheter ablation versus surgical resection, if feasible

2) ICD placement if ablation/surgical resection unsuccessful or not possible

3) EP testing should be considered in patients with non-sustained VT to determine risk of sustained VT

4) Note: prophylactic anti-arrhythmics are not indicated for asymptomatic patients with isolated premature ventricular contractions (PVCs)

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Case Discussion
This patient is showing evidence of Eisenmenger syndrome. VSDs cause left-to-right shunting, which results in higher blood flow and pressure directed towards the lung, leading to pulmonary hypertension. Over time, this pulmonary hypertension will cause scarring of the lung parenchyma and hypertrophy of the myocardium, eventually leading to a reversal of the shunt (right to left).[7] If this patient had presented prior to the development of severe pulmonary hypertension with Eisenmenger syndrome, his VSD could have been amenable to repair. With the current presentation, his main options would be for symptomatic treatment and/or heart-lung transplantation.

Questions

22.1 Which of the following is the most common reason for admission in the ACHD patient population?
A. Congestive heart failure
B. Infection
C. Arrhythmia
D. Myocardial infarction

22.2 Which of the following is true?
A. Repaired simple shunts (ASD, VSD, PDA) require specialist care
B. In a patient with a modified Blalock-Taussig shunt, blood pressure should be measured in the arm contralateral to the repair
C. In Ebstein's anomaly, patients tend to have tricuspid stenosis
D. Positive pressure ventilation is beneficial in right heart failure and improves cardiac output

22.3 All of the following are cyanotic congenital heart lesions, except?
A. Tetralogy of Fallot
B. Patent ductus arteriosus
C. Truncus arteriosus
D. Transposition of the great arteries

23. Extra-Corporeal Life Support and Ventricular Assist Devices

Mariya Geube MD and Edward A Bittner MD PhD

Key Points

• **Extracorporeal life support (ECLS) is a comprehensive term that describes all manner of extracorporeal support including oxygenation, carbon dioxide removal and hemodynamic support.**

• **Veno-venous cannulation is used for isolated respiratory failure (tissue hypoxia secondary to hypoxemia), whereas veno-arterial cannulation is used for cardiac failure (tissue hypoxia secondary to hypoperfusion) with or without respiratory failure.**

• **Ventricular Assist Devices (VADs) can be used as a bridge to recovery, bridge to heart transplantation or as a permanent support – destination therapy. Conditions that need to be corrected before VAD placement include patent foramen ovale or atrial septal defect, aortic insufficiency, mitral stenosis, ventricular septal defect and ventricular thrombus.**

A 32 year-old woman is admitted to the ICU with respiratory failure after aspiration of gastric contents, which occurred during induction of anesthesia. Her ICU course is complicated by progressively worsening hypoxemia. Chest radiograph reveals bilateral infiltrates consistent with ARDS. ARDS-Net ventilation is initiated, diuretics are administered to decrease pulmonary edema, nitric oxide is administered to improve her oxygenation. Despite this support, the patient's oxygenation further deteriorates. Given the failure of conventional management the decision is made to initiate venovenous ECLS. Eight days later the patient's cardiopulmonary function improves to the point that she is successfully liberated from ECLS. On ICU day 14, the patient is extubated and a day later transferred out of the ICU.

EXTRA-CORPOREAL LIFE SUPPORT

Extracorporeal life support (ECLS) is the use of a mechanical device to temporarily support heart and/or lung function during cardiopulmonary failure, which is potentially reversible, until organ recovery or replacement occurs. In the current literature, ECLS has replaced the older term Extra Corporeal Membrane Oxygenation (ECMO), which omits reference to inherent additional supporting measures such as hemodynamic support or carbon dioxide removal.

Indications
- Refractory cardiogenic shock
- Post cardiac arrest cardiopulmonary support
- Failure to wean from cardiopulmonary bypass (CPB) after cardiac surgery
- As a bridge to recovery, to heart transplantation or to placement of a long term supportive device
- Severe hypoxemic respiratory failure in patients with ARDS despite the optimization of ventilatory support
- Bridge to lung transplantation or severe primary graft dysfunction after lung transplantation
- Hypercarbic respiratory failure with intractable respiratory acidosis

Modes of ECLS
- Venoarterial (VA ECLS) – Venous-arterial cannulation is used for cardiac failure (tissue hypoxia secondary

to hypoperfusion) with or without respiratory failure

• Venovenous (VV ECLS) – Supports respiratory function only and requires native heart function to deliver oxygenated blood to the tissues (it does not provide hemodynamic support)

ECLS device circuit

The ECLS circuit consists of intravascular cannulas, a blood pump, a membrane oxygenator, conduit tubing, a heat exchanger and alarms. Access may use a vein and artery (VA) or two veins (VV).

• Vascular access for cannulation,

  - VA ECLS:

    1. Peripheral ECLS – a venous cannula is placed in the femoral vein and an arterial cannula in the femoral artery – appropriate for emergent situations. (Figure 23.1A)

    2. Central ECLS – a venous cannula in the right atrium and an arterial cannula in the ascending aorta – appropriate in case of failure to wean from CPB during open heart surgery. Requires sternotomy. (Figure 23.1B)

    3. Cervical ECLS – a venous cannula is placed in the internal jugular vein and arterial cannula is placed in the axillary artery (carotid artery in infants). (Figure 23.1C)

  - VV ECLS: a double lumen cannula is placed in the superior vena cava (SVC) or two separate venous cannulas are inserted (femoral vein for drainage and SVC for infusion). (Figure 23.1D)

• Oxygenator – works as an artificial lung where the blood is saturated with oxygen and CO_2 is removed. Currently used membranes are composed of silicone or hollow-fiber. It is very important to monitor the oxygenation of pre-oxygenator and post-oxygenator blood gas samples to assess the adequacy of the membrane function.

• Tubing system – length and diameter determine the blood flow resistance (Poiseuille's law).

• Sweep gas – fresh gas is delivered to the membrane oxygenator to allow for gas exchange. The composition is determined by a blender that mixes air with oxygen in desired proportions. The gas flow rate determines the CO_2 clearance, and the pump blood flow determines the oxygenation.

• Blood pump

  - Roller pumps – require a reservoir between the venous drainage cannula and the pump and utilize gravity for drainage into the reservoir.

  - Centrifugal pumps – most commonly used in ECLS and CPB machines. They create high negative pressures in the circuit eliminating the need for drainage by gravity. Adequate venous return to the heart is required.

Physiology of VA ECLS

Venous blood is drained from the right side of the heart, circulates through the device pump where gas exchange occurs and is reinfused into the aorta. An important consideration is the size of the venous cannula, which should enable a blood flow of at least 50-60 ml/kg/min in adults. Central cannulation allows better venous drainage and higher flows and is suitable for patients with higher metabolic requirements such as patients in septic shock. The adequacy of blood flow is assessed by monitoring mean ar-

Figure 23.1.ECLS Cannulation Options: A: femoral vein, femoral artery; B: right atrium, aorta; C: internal jugular, axillary (carotid) artery; D: femoral vein, superior vena cava
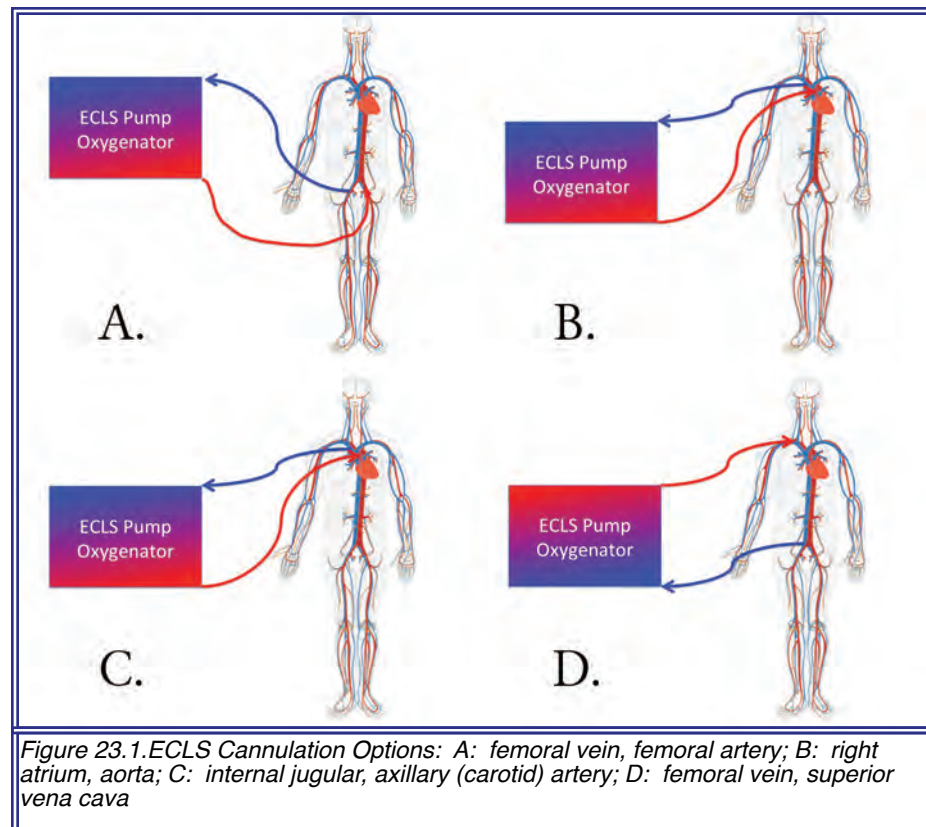
terial pressure, mixed venous oxygen saturation (SvO_2), lactate levels, and base excess. The degree of hemodynamic support is controlled by changing the pump flow. Dialing up the pump flow increases the amount of blood diverted from the heart to the ECLS circuit and is an appropriate maneuver in case of tissue hypoperfusion or inadequate oxygenation.

ECLS increases left ventricular afterload, because the left ventricle ejects against the retrograde flow coming from the arterial cannula. With poor left ventricular function, this may cause a complete failure of the left heart with increased left atrial and pulmonary venous pressures, and result in pulmonary edema or hemorrhage. In this situation, inotropic support and afterload reduction may be beneficial.

Oxygenation of the upper body in peripheral VA ECLS depends on the mixture of the retrograde flow from the arterial cannula and the cardiac output of the left ventricle. When there is preserved cardiac function (e.g. VA ECLS placed for respiratory support), deoxygenated blood coming from the non-functioning lungs into the left ventricle is ejected into the proximal aortic vessels (arteries perfusing heart and brain) causing significant tissue hypoxia of these organs. Hypoxemia in this situation can be corrected by maximizing the ECLS flow, by changing the placement of the arterial cannula to the axillary or subclavian artery or by inserting an additional venous cannula into the SVC

to return some of the oxygenated blood to the right atrium.

Oxygenated blood returns from the ECLS circuit to the circulation with a saturation of 100%, whereas the blood passing through the failing lungs has a saturation of approximately 75%. Mixing of oxygenated blood returning from the ECLS oxygenator together with the poorly oxygenated blood ejected from the left ventricle results in an arterial saturation that is a proportional average of the two sources of blood. Usually a SaO_2 of 90% is achieved, as measured from an upper extremity arterial line. An increase in arterial SaO_2 may indicate (1) improvement in native lung function, (2) decreased cardiac output (since most of the blood comes back from the extracorporeal pump) or (3) increased ECLS flow (if cardiac output is constant). [2]

Weaning of ECLS – Inotropic support is initiated 12 hours before a weaning trial. ECLS blood flow is then gradually decreased, while monitoring the pulsatility of the arterial waveform. Systolic function during the weaning process can be assessed by echocardiography.

Physiology of VV ECLS

Blood is drained from the venous system into the ECLS machine where gas exchange occurs and then is reinfused back into the venous system. Widely accepted criteria for initiation of VV ECLS include severe refractory hypoxemia with PaO_2/FiO_2 ratio below 50-80 for at least 6 hours, uncompensated hypercapnea with a pH < 7.15 or excessively high inspiratory pressures above $35-40 cmH_2O$.[3]

The primary determinants of arterial oxygenation (PaO_2) during VV ECLS are the pump flow rate, the patient's native lung function and the degree of recirculation (see below). While on ECLS, the goal is to provide "rest" for the native lungs (achieved by reducing ventilatory parameters: FiO_2 30%, respiratory rate 5/min, plateau pressures below $20-25cm\ H_2O$).

Recirculation occurs when the drainage and return cannulas are positioned within the same vessel (e.g. SVC) or when a double lumen venous cannula is used. A portion of oxygenated blood returning from the ECLS circuit into the major vein is drained back into the ECLS circuit together with deoxygenated venous blood. Recirculation may result in significant arterial hypoxemia. It can be recognized when PO_2 of the gas sample taken before the oxygenator is higher than the PaO_2 of the arterial blood. Placing the drainage cannula in the SVC and the return cannula in the IVC reduces the problem.

Utility of ECLS in ARDS – Early studies (1970's-80's) on the use of ECLS in adult patients with severe ARDS showed very low survival rates (10%). More recent studies have shown survival rates of 40-60% among selected patients with ARDS managed with ECLS.[4] This improvement has likely resulted from improvements in ventilator techniques, ECLS circuits, clinical experience, and supportive care. In current practice, extracorporeal life support is warranted in patients with severe respiratory failure with an expected mortality risk exceeding 70-80%.

Weaning of ECLS - Signs of improvement in lung function are a reduction in the circulatory flow required to achieve the same PaO_2 and an increase in the arterial oxygen saturation compared with the mixed venous saturation. When the patient is considered ready for a weaning trial, the pump flow is gradually decreased, while ventilatory support is optimized and the circuit gas flow is then stopped. Recovery of the lung function generally takes longer than recovery of the heart function – usually 1 to 3 weeks.

Complications

- Clot formation – especially important in VA ECLS, because large and mobile clots in the circuit can result in systemic thrombembolism.
- Oxygenator failure – detected by worsening of gas exchange in pre and post membrane blood samples and an increase of the pressure gradient across the membrane.
- Air embolism – may occur if any component of the venous circuit is open to the atmosphere or if there is a tear in the membrane oxygenator.
- Bleeding – full heparinization during ECLS support is required. Potential sites of bleeding include the gastrointestinal tract, surgical sites (eg: tracheostomy) or intracranially. ECLS also results in a consumptive thrombocytopenia secondary to platelet sequestration in the circuit, which may also contribute to bleeding.
- Cannulation related – bleeding, arterial dissection or pseudoaneurysm, limb ischemia resulting from arterial cannula malposition or venous congestion of the limb resulting from the venous cannula.
- Infection

VENTRICULAR ASSIST DEVICES

Ventricular Assist Devices (VADs) are used for mechanical cardiac support in patients facing imminent death due to acute or decompensated chronic heart failure on maximal inotropic support. They can be used as a bridge to recovery, a bridge to heart transplantation or as a permanent support – destination therapy. A device that provides support to the left ventricle is referred to as an LVAD, to the right ventricle as an RVAD and to the left ventricle as an LVAD, to the right ventricle as an RVAD and to
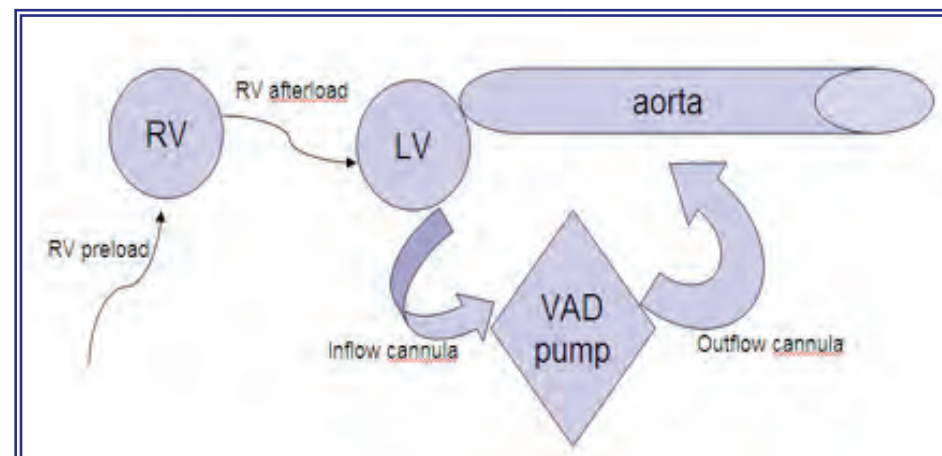

Figure 23.2 Schematic Depiction of LVAD Circuit

both ventricles as a BiVAD.

Indications:
 • Cardiogenic shock following acute myocardial infarction
 • Cardiogenic shock following cardiac surgery
 • Acute heart failure secondary to myocarditis or acute cardiomyopathy
 • Decompensation or progression of chronic heart failure
 • Primary graft dysfunction after heart transplantation
 • Selection criteria: Cardiac index (CI) < 2.0 L/min/m²; Pulmonary capillary wedge pressure (PCWP) > 20mmHg; systolic blood pressure (SBP) < 80mmHg with impaired end organ perfusion while receiving maximal conservative therapy including intravenous inotropes and intra-aortic balloon pump (IABP).

Technical considerations
 • Cannulation sites
  - Flow is defined relative to the position of the device: inflow cannula – directs blood from the heart to the device; outflow cannula – directs blood from the device to the aorta (Figure 23.2).
  - LVAD – inflow cannula is placed in left atrium or left ventricular apex; outflow cannula is placed in the ascending aorta
  - RVAD – inflow cannula is placed in the right atrium; outflow cannula is placed in pulmonary artery
 • VAD types based on flow pattern
  - Pulsatile flow devices – eject the blood in a pulsatile fashion into the aorta. These devices are extracorporeal, require the presence of valves, and valve malfunction is common long term.
  - Non-pulsatile flow devices – these devices are implantable, do not require valves, and use axial or centrifugal pumps creating non-pulsatile (continuous) flow.
 • Position of the device relative to the body
  - Extracorporeal – consist of a bulky machine situated outside the body
  - Intracorporeal – small and light devices, associated with decreased bleeding and infection rate compared with extracorporeal devices.

Cardiac conditions that require correction before VAD implantation
  1. Patent Foramen Ovale (PFO) or Atrial Septal Defect (ASD) –impose risk for right to left shunt and severe hypoxemia.
  2. Aortic insufficiency – results in regurgitant blood flow through the incompetent valve into the left ventricle and then back into the device. This regurgitant flow can lead to increased pump flow from recirculation, as well as further left ventricular overload and dysfunction, while there are signs of systemic hypoperfusion. The aortic valve should be replaced or oversewn prior to implantation
  3. Mitral stenosis – results in low flow through the inflow cannula
  4. Ventricular thrombus – is common in the left ventricular apex in patients with poor ventricular function
  5. Ventricular septal defect – imposes risk for right to left shunt and severe

hypoxemia.

Management of VADs in the Intensive Care Unit
Most often patients come to the ICU with VADs placed in an emergent fashion either after unsuccessful weaning from CPB or due to cardiogenic shock. These patients usually have acute end organ injury secondary to the associated low flow state. Despite improvement in organ function after mechanical support is initiated, mortality of these patients is high, 30-40% survival to discharge. Patients who have VADs placed in elective fashion have more favorable outcomes.

Approximately 30% of patients with left ventricular (LV) failure who undergo VAD insertion have concomitant right ventricular (RV) failure, but only a small proportion (~10%) of them require RVAD placement. Unloading the left ventricle along with inotropic support usually improves RV function.

Vigilant monitoring of intravascular volume is important for optimal VAD function. Hypovolemia creates sucking effect on the left ventricle, which is potentially detrimental. Fluid overload may aggravate right ventricular dysfunction and thus lead to insufficient flow to the left ventricle. Monitoring fluid status is challenging and requires consideration of the mean arterial pressure, pump flow, and right and left ventricular filling pressures.

With non-pulsatile devices, pulse pressure is very narrow, often it is absent. Noninvasive blood pressure monitoring, using the oscillation method, as well as pulse oxymetry are inapplicable. Arterial line monitoring results in a tracing, which reflects the mean arterial pressure (MAP). Due to the lack of pulsatile flow, placement of arterial catheters can be challenging and requires ultrasound guidance.

Table 23.1 Etiology of systemic hypotension in patients with LVAD					
Etiology	Pump flow	CVP	PCWP	CO	MAP
Hypovolemia	↓	↓	↓	↓	↓
RV failure	↓	↑	↓	↓	↓
VAD failure	↓	↑	↑	↓	↓
Aortic Insufficiency	↑	↑	↑	↓	↓
Sepsis	↑	↓	↓	↑	↓
CVP: central venous pressure; PCWP: pulmonary capillary wedge pressure; CO: cardicac output; MAP: mean arterial pressure Adapted from Reference 6.					

Complications
 • Bleeding – Due to systemic anticoagulation
 • Inflow cannula malposition – May result in obstruction and inadequate drainage
 • Thromboembolic complications – Axial flow pumps are associated with a higher

thrombembolic rate. Systemic anticoagulation is of utmost importance.

• Infection – The risk for device infection increases with time, reaching approximately 25% at 3 months. Typical sites of infection are the driving line as it enters the skin or the device pocket. Sepsis is the most common cause of death in patients with intermediate and long term VADs.

• Device malfunction – With pulsatile devices the pump applies significant backpressure on the inflow valve, which typically becomes incompetent after about 6 months of use and requires replacement. Non-pulsatile devices have fewer components, thus are more durable.

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Questions

23.1 Which of the following conditions needs to be corrected before LVAD placement in a patient with cardiogenic shock?
    A. Mitral insufficiency
    B. Atrial fibrillation
    C. Aortic insufficiency
    D. Aortic stenosis

23.2 Blood oxygenation during ECLS is determined by:
    A. Sweep gas flow rate
    B. Site of the arterial cannulation – peripheral versus central
    C. Blood flow rate through the ECLS pump
    D. Hollow fiber versus silicone membrane oxygenator

23.3 For which of the following patients is initiation of ECLS most appropriate?
    A. 78 yr old male with lung cancer and an obstructive pneumonia with severe hypercapnea and acidemia despite optimized mechanical ventilation
    B. 43 yr old female with end stage lung disease due to interstitial lung disease awaiting bilateral lung transplantation
    C. 28 yr old male patient with idiopathic pulmonary hypertension intubated for severe hypoxemia, whose pulmonary artery pressures responded well to inhaled nitric oxide
    D. 56 yr old female admitted for large spontaneous intracranial bleeding who sustained cardiac arrest 72 hours after admission.

Section 6: Gastroenterology & Nutrition

Chapters

- **Gastrointestinal Hemorrhage**
- **Nutritional Support**
- **Acute Pancreatitis**
- **Liver Failure**
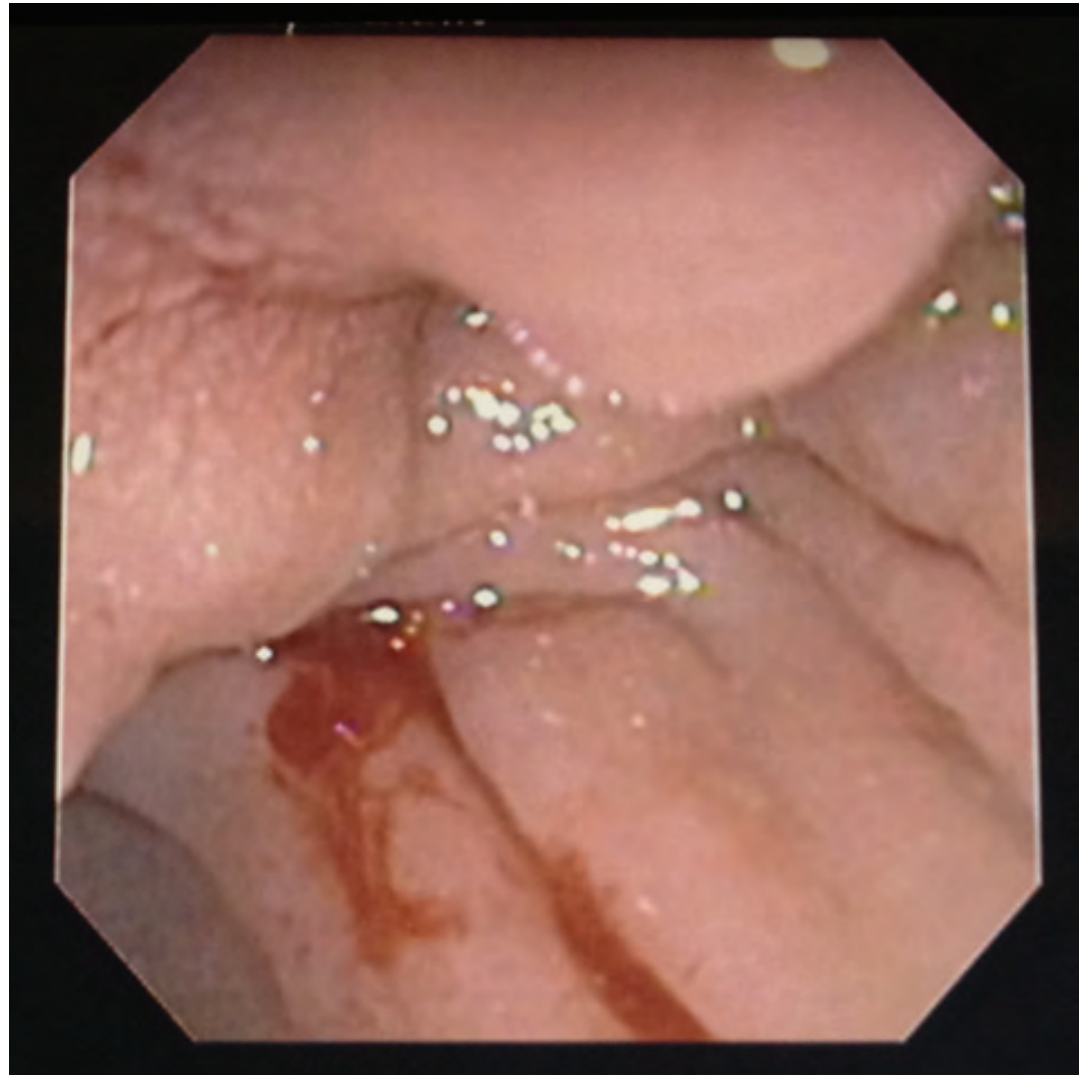
24. Gastrointestinal Hemorrhage

Evan Roller MD, Brian Wessman MD and Thomas J Graetz MD

Key Points

• Although decreasing in incidence secondary to prophylaxis, GI bleeding in the ICU can occur with significant associated mortality.

• For both upper and lower GI bleeds, endoscopy remains the initial diagnostic and therapeutic interventions of choice.

• H2RA and PPI are effective for prophylaxis, but injudicious use has been shown to increase nosocomial pneumonia and C.Diff infections.

• Surgery and/or interventional radiology should be consulted for refractory bleeding despite endoscopic therapies.

A 65 year-old man with a history of atrial fibrillation experienced a syncopal episode resulting in a subdural hemorrhage. He underwent a decompressive craniectomy and was extubated on POD #2. Now, on POD #3, he exhibits altered mental status, hematemesis, tachycardia, and hypotension. His most recent hemoglobin from this morning shows a drop of 5 g/dL

Introduction

Gastrointestinal hemorrhage (GIB) can be the etiology for admission to the intensive care unit (ICU) or may occur during the course of a hospital stay. Improvement in resuscitation strategies, enhanced endoscopic techniques, and prophylactic use of medications to prevent GIB have improved patient outcomes.

GIB can be divided into an upper GI source (pharynx to the ligament of Treitz) and lower GI source (distal to the ligament of Treitz). Upper GIB, which occurs more frequently than a lower GIB, can be further divided into variceal bleeding and non-variceal bleeding. Lower GIB can be divided into small bowel and colonic sources of bleeding.

Initial management of the patient with a significant GIB involves securing the airway (if needed) and maintaining hemodynamic stability. Endoscopy should be performed as soon as the patient is deemed to be stable in order to allow directed control of the hemorrhage, if the bleeding source can be identified. If ongoing hemorrhage persists, other medical treatments, imaging modalities, and surgical options should be explored.

Epidemiology:

A. General Population
  1. Incidence of 50-100 per 100,000 persons per year

2. Frequently leads to ED presentation/evaluation and ICU admission
B. Intensive Care population
1. Incidence of 1.5%; appears to be decreasing secondary to increasing use of GI prophylaxis, treatment of H. pylori, and early enteral feeding
2. Clinically overt bleeding occurs in 5%-25% of critically ill patients who did not receive prophylactic therapy[1]
C. Mortality rates for patients with massive GIB (bleeding resulting in hemodynamic instability with signs and symptoms consistent with hemorrhagic shock and evidence of either hematemesis or hematochezia) range from 20-39%[2]

Causes
A. Upper GIB:
(Important to exclude other sources of bleeding, such as pulmonary or intranasal)
1. Peptic ulcer disease (H.pylori, NSAID use)
2. Esophageal and gastric varices (secondary to liver failure)
3. Mallory-Weiss tears (increased abdominal pressure after vomiting)
4. Gastritis (NSAID use, Crohn's)
5. Esophagitis (gastroesophageal reflux)
6. Carcinomas (benign or malignant)
7. Stress related mucosal damage
8. Vascular malformations (gastric antral vascular ectasia)
9. Hemobilia (trauma, s/p ERCP, gallstone, inflammation)
10. Aortoenteric fistula
11. Pancreatic pseudocyst or pseudoaneurysm
12. Hemosuccus (bleeding into pancreatic ducts)
13. Dieulafoy lesion (gastric)
B. Lower Gastrointestinal bleed
1. Diverticular disease
2. Colitis (ischemic, infectious, Crohn's)
3. Hemorrhoids or fissures
4. Angiodysplasia/ vascular ectasias
5. Polyps/ neoplasm
6. Meckel's diverticulum
7. Colonic tuberculosis
8. Aortoenteric fistula
9. Infectious diarrhea (viral, bacterial, parasites)
10. Dieulafoy lesion (colonic)
11. Brisk UGIB source

Risk factors
A. Respiratory failure requiring mechanical ventilation for more than 48 hours
B. Coagulopathy (INR>1.5; platelet count <50 x 10⁹/L)
C. Acute renal insufficiency
D. Acute hepatic failure
E. Sepsis syndrome

F. Hypotension requiring use of vasopressors
G. Severe head or spinal cord injury (increased ICP increases cholinergic activity)
H. History of GI bleeding
I. Low intragastric pH
J. Thermal injury > 35% of body surface area
K. Major surgery (>4 hours)
L. High dose corticosteroids (>250mg/day hydrocortisone or equivalent)
M. Acute lung injury
N. Prolonged duration of enteral tube
O. Post transplantation
P. Smoking and alcohol abuse

Prophylaxis
A. Recommended for ICU patients with the following:
1. Coagulopathy (non-iatrogenic; i.e., not due to warfarin, etc.)
2. Mechanical ventilation > 48 hours
3. History of GI ulceration or bleeding within 1 year
4. At least two of the following risk factors: Sepsis, ICU stay longer than 1 week, occult bleeding lasting at least 6 days, use of more than 250 mg hydrocortisone or equivalent.
5. Significant burns
6. Neurotrauma (including intracranial bleeding from non-traumatic etiologies)
B. Stress ulcer prophylaxis
1. Optimize hemodynamic status, splanchnic perfusion and oxygen delivery
2. Enteral nutrition: buffers gastric acid; may provide energy for mucosa; increases secretion of cytoprotective prostaglandins and mucus; increases mucosal perfusion; and blunts vagal stimulation.
3. Avoidance of ulcerogenic medications: corticosteroids; slow release enteral potassium; and NSAIDS.
4. Pharmacologic agents[4]

a. Histamine type 2 receptor antagonists (H2RA): Inhibit H+:K+ ATPase exchange pump by binding to H2 receptor on parietal cell resulting in downstream decrease in acid secretion and potassium uptake. Can be administered enterally or intravenously. Issues include risk of tachyphylaxis when given intravenously, alterations in drug metabolism (interaction with cytochrome P450 for cimetidine, but not with famotidine or ranitidine), thrombocytopenia, impaired liver function, and interstitial nephritis. Elimination occurs via the kidneys, therefore, dose needs to be adjusted in patients with renal insufficiency. Less likely to be effective in patients with neurotrauma as they do not inhibit vagally-induced acid secretion.

b. Proton pump inhibitors (PPI): Inhibit gastric acid by forming irreversible disulfide bonds with H+:K+ ATPase exchange pump leading to inhibition of secretion of H+ by the parietal cell. PPIs can be administered enterally or intravenously. Issues include abdominal pain, nausea, diarrhea, and alterations in drug metabolism (interaction with cytochrome P450; i.e., reduction in clopidogrel efficacy in patients with CYP2C19 genotype).

c. Sucralfate: Basic aluminum salt coats gastric mucosa and forms protective

layer between gastric contents and mucosa without altering gastric pH. Only administered enterally. Issues include aluminum intoxication in patients with kidney injury, binding to drugs reducing absorption (digoxin, ciprofloxacin, and warfarin), and clotting of enteral feeding tubes.

    d. Antacids: Neutralize gastric acid and inactivate pepsin. Must be administered intragastric Q1-2hours (dose dependent on gastric pH)

    e. Prostanoids: Reduce ability of parietal cells to generate cyclic AMP in response to histamine, reducing gastric acid secretion while enhancing mucosal defense mechanisms.

C. Risks associated with prophylaxis treatment

  1. Increase in nosocomial pneumonia secondary to increased pH (less acid) of gastric contents resulting in increased bacterial growth

  2. Clostridium difficile enteritis shown to be increased in non-ICU patients receiving PPI or H2RA.

Diagnosis

A. History

  1. Hematemesis: Upper GI bleed

  2. Melena: Upper GI bleed or ascending colon

  3. Hematochezia: Brisk upper GI bleed (10%) or lower GI bleed (90%)

B. Gastric lavage: Negative if return is bilious AND non-bloody

C. Esophagogastroduodenoscopy (EGD), Colonoscopy, capsule endoscopy, double balloon enteroscopy

D. Tagged red cell scans, Meckel's scan

E. Mesenteric arteriography

F. Barium contrast upper GI series with small bowel follow through, enteroclysis

G. Laparotomy with intraoperative enteroscopy when all other diagnostic investigations have failed

Management and Treatment

A. Initial resuscitation

  1. Primary survey (Airway, Breathing, Circulation) followed by history and physical exam. Continuous monitoring of vital signs

  2. Endotracheal intubation for airway protection, if needed

  3. Resuscitation:

    a. 2 large-bore peripheral IVs (16G or larger), peripheral rapid infusion catheter (RIC), or 8.5 Fr (or larger) introducer central venous catheter.

    b. Initially administer isotonic crystalloid to maintain hemodynamic stability

    c. Administer blood components to maintain hgb 7-9g/dL, correct coagulopathy, and maintain platelets > 50,000/μL (ideally correcting coagulopathy should not delay endoscopy)

    d. In times of massive bleeding and exsanguination

      i. Activate massive transfusion protocol, if available

      ii. Consider tranexamic acid (evidence is conflicting)

      iii. Consider recombinant activated factor VII (evidence in literature conflicting)

  4. Place nasogastric tube and start gastric lavage. Obtain laboratory studies (CBC, coagulation studies, type and cross, comprehensive metabolic panel)

  5. Administer PPI bolus and follow by infusion to decrease risk of rebleeding. (pantoprazole 80 mg IV bolus then 8mg/hr for 24-72 hours)

  6. Mobilization of specialists: gastroenterology, general surgery, and interventional radiology (depending on underlying cause of bleeding and available resources)

B. Procedural Therapies

  1. EGD is recommended within 24 hours

    a. Establish diagnosis

    b. Provide definitive therapy with clips, banding, thermocoagulation, or sclerosant injection +/- epinephrine

    c. Provides information concerning risk of rebleeding

    d. May be difficult secondary to material in GI tract. Consider promotility agent

    e. Sedation required for procedure may result in inability to protect airway.

  2. Balloon Tamponade

    a. Sengstaken Blakemore, Minnesota tube, and Linton-Nachlas

    b. Requires secured airway

    c. Placement verification per institution protocol

  3. Surgical Management

    a. Indications

      i. Severe hemorrhage not responsive to resuscitation

      ii. Failed endoscopic hemostasis and medical management

      iii. Coexisting reason for surgery (perforation, obstruction neoplasm)

      iv. Consider splenectomy for gastric varices or colon resection for lower GI bleeding

  4. Portosystemic shunts (Transjugular intrahepatic portosystemic shunt)

    a. Primarily for recurrent bleeding secondary to upper GI varices

  5. Colonoscopy with laser or thermal coagulation

  6. Angiography with vasoconstrictor administration/embolization

C. Other considerations

  1. H. pylori screening

  2. Consider octreotide for variceal bleeding

  3. Empiric antibiotics for spontaneous bacterial peritonitis prophylaxis in patients with end-stage liver disease and ascites

Outcome

A. Rebleeding

  1. Occurs in 10-15% of patients usually in 48 hours

  2. Endoscopic findings that predict rebleed: active bleeding vessel = 55%; non-bleeding visible vessel = 43%

  3. Location of ulcer: Higher incidence on lesser curvature and posterior-inferior wall of duodenum

  4. Perform EGD again and attempt to achieve hemostasis. Consider interventional radiology if available.

B. Poor prognostic factors

1. Esophageal varices
2. Coagulopathy with INR >1.3
3. Chronic liver or renal disease
4. Thrombocytopenia (plt <150K), anemia (hgb <10 g/dL)
5. Initial systolic blood pressure <100 mmHg
6. Advanced age

C. Mortality: 5-10%

Future Therapies[7]

A. Vaccines for H. pylori and hepatitis C
B. Wireless endoscopy capsules
1. Evaluate bleeding in ED
2. With electrocautery to stop bleeding

Summary

GIB is a common disease process encountered in the critical care setting. Patients at risk include those on mechanical ventilation and those with traumatic brain injury. Its incidence has decreased due to early recognition of risks factors, early enteral nutrition, adequate prophylaxis, and improved ICU care. Different imaging modalities, as well as medical and invasive treatments are available, yet EGD remains the most commonly used diagnostic and therapeutic tool. Rational transfusion of blood products, correction of coagulopathy, and resuscitation with crystalloids are fundamental. The goal of management is to first restore hemodynamic stability and then proceed with diagnostic and/or more invasive procedures.

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Questions:

24.1 Factors resulting in a reduced incidence of stress gastritis in the ICU setting include:
A.   Greater awareness of the pathophysiology of the disease
B.   Increased use of prophylactic agents
C.   Early use of enteral feeds
D.   Improvement in resuscitation
E.   All of the above

24.2 A 65 year old woman, on mechanical ventilation in the ICU, had an episode of bright red blood output via her NGT 3 days ago. Endoscopy at the time was negative. She is currently having a recurrence of UGIB with hemodynamic instability. What would be the best next step:
A.   Repeat endoscopy
B.   Surgical treatment
C.   Angiography
D.   Initiate resuscitation
E.   Colonoscopy

24.3 An 86-year old woman is admitted to the ICU after presenting with hematochezia. An EGD is negative. Colonoscopy is unsuccessful due to the presence of large amounts of blood and stool in the colon. The patient remains hypotensive despite aggressive resuscitation. A mesenteric angiogram showed a bleeding vessel in her transverse colon. Embolization was attempted, but it was not successful. The next best step in management of this patient is:
A.   Subtotal colectomy
B.   Administration of DDAVP
C.   Initiation of vasopressin infusion
D.   Bolus 300 micrograms of octreotide followed by an infusion
E.   Administration of recombinant factor VIIa

24.4 A 49-year old alcoholic is admitted to the ICU after developing an UGIB following severe retching during a binge drinking episode. After resuscitation, an EGD is performed which shows linear tears on the gastric side of the gastroesophageal junction. The most important aspect of management is:
A.   Expectant observation
B.   Administration of antiemetics
C.   Raising the gastric PH
D.   Endoscopic thermal coagulation of the tear
E.   Esophageal resection

25. Nutritional Support

Jeffrey A Katz MD

Key Points

• **Malnutrition is associated with increased morbidity and mortality, prolonged hospital stay, poor immune function and impaired wound healing.**

• **The goal of critical care nutrition is to prevent the complications associated with malnutrition.**

• **Enteral nutrition is preferred to parenteral nutrition** *(If the gut works, use it!)*

• **Refeeding syndrome is a potentially life threatening complication from hypophosphatemia during the initiation of feeding. Phosphate levels must be monitored closely.**

A 27 year-old, 84 kg man with no significant past medical history is involved in an industrial fire. Upon arrival to the ED, he is found to have burns over 40% of his body surface area. Initial fluid resuscitation is carried out and he is intubated for potential airway compromise due to suspected inhalation injury. You come on service 3 days after his admission to the ICU and receive this patient from the outgoing resident. He has no enteral access at this point and has been NPO in the 3 days since his accident. What are your initial nutritional goals for this patient?

Nutrition during critical illness presents many challenges to the clinician and is often approached through a multi-specialty team that includes physicians, nurses, and nutritionists. The goal of critical care nutrition is to significantly improve the outcome of a patient's critical illness by preserving lean body mass and avoiding the negative consequences of malnourishment. Enteral nutrition is always preferred to parenteral nutrition, however this is mainly determined by the underlying disease process and the functionality of the GI tract. The goal of this chapter is to provide a basic framework for critical care nutrition and highlight the challenges that the clinician will face.

Malnutrition

  A. Definition
    1. Protein Calorie Malnutrition: weight loss of > 10-15% of total body weight or body weight < 90% ideal
  B. Identification of patients at risk
    1. No reliable laboratory method to determine which patients are or at risk of malnourishment
      a. Albumin and pre-albumin are unreliable during critical illness
    2. Patient history is best determination of nutritional status
      a. Unintentional weight loss
      b. Prolonged NPO status
      c. Prolonged critical illness

    i. Patients lose up to 2%/day of muscle mass
    ii. Nutrition supplementation to prevent muscle loss
    iii. Safe to assume that these patients are malnourished and require nutrition support

C. Consequences of malnutrition
  1. Increased morbidity and mortality
  2. Prolonged hospital stay
  3. Impaired tissue function and poor wound healing
  4. Immune suppression and increased risk for infection

Basic Metabolic Needs

There are three basic categories of macronutrients
  - Carbohydrates: 3.4kcal/g
  - Lipids: 9kcal/g
  - Protein: 4.1kcal/g

Determination of daily caloric need of critically ill patients.

A. Harris-Benedict Equation
  1. Primarily used for non-ventilated patients
  2. Men: $B.E.E = 66.5 + (13.75 \times kg) + (5.003 \times cm) - (6.775 \times age)$
  3. Women: $B.E.E. = 655.1 + (9.563 \times kg) + (1.850 \times cm) - (4.676 \times age)$
    a. B.E.E.= Basal Energy Expenditure
    b. kg=weight in kg, cm=height in cm, age=age in years

B. Ireton – Jones Equation
  1. Primarily used in mechanically ventilated patients
  2. Total calorie need=1784-11(A)+5(W)+244(S)+239(T)+804(B)
    a. A=age in years, W=weight in kg, S=sex (1=male 0=female)
    b. T=trauma (1=yes 0=no), B=burns (1=yes 0=no)

C. Mifflin-St. Jeor Equation
  1. Men: $(9.99 \times kg) + (6.25 \times cm) – (4.92 \times age) + 5$
  2. Women: $(9.99 \times kg) + (6.25 \times cm) – (4.92 \times age) -161$
    a. kg=weight in kg, cm=height in cm, age=age in years

D. These formulas may underestimate the metabolic needs of patients with certain underlying disease processes.
  1. 25% Increase: peritonitis, long bone fractures, mild/moderate trauma
  2. 50% increase: severe infections, multi-system organ dysfunction, severe trauma
  3. 100% increase: severe burn (>40% total body surface area)

E. Simplified daily caloric estimations can also be made based on a patient's weight and estimated stress level.
  1. Maintenance or minimal stress: 25-30 kcal/kg/day
  2. Moderate stress: 30-35 kcal/kg/day
  3. Severe stress (e.g. burns): 35-40 kcal/kg/day

Composition of Nutrition Supplementation

A. Step 1: Calculate protein-based calories
  1. Daily protein requirement is 1.2-2.0 g/kg/day
B. Step 2: 15-30% calories from lipid
C. Step 3: Remainder of calories from carbohydrates (30-70%)
D. Step 4: Evaluate nitrogen balance to assess adequacy of protein-based calories.
  1. Nitrogen balance = nitrogen intake – nitrogen losses
  2. If negative, then increase protein-based caloric intake
E. Step 5: Trace Elements, Vitamins, and Other Additives
  1. Selenium and vitamins are associated with lower mortality however remains controversial.
    a. Likely little harm and possible significant benefit to trace elements and vitamins, so often added
  2. Immune modulating additives have been an active area of nutrition research
    a. Fish oils and borage oils have been shown to be efficacious in ALI/ARDS patients (controversial)
      i. Positive studies: decreased incidence of infections and pneumonia
      ii. Negative studies: increase in overall mortality
    b. Most trials have been negative and there is insufficient data to recommend routine administration of glutamine, arginine, or ornithine ketoglutarate.
    c. Glutamine has been associated with increased mortality in multi-system organ failure patients.

You calculate his estimated caloric needs, and decide to begin nutritional therapy. After numerous attempts, you are only able to get the nasoduodenal feeding tube into the patient's stomach. Do you feed into the patient's stomach? Should you start TPN instead?

Enteral Nutrition

A. Enteral nutrition is always preferred to parenteral nutrition if no contra-indications exist.
B. Enteral nutrition has decreased complication rates
  1. No difference in mortality has been shown between enteral vs parenteral nutrition
  2. Decreased infection rate in patients on enteral nutrition
C. Advantages
  1. Maintenance of structural integrity of GI tract
  2. Release of endogenous GI substances such as cholecystokinin, gastrin, and bile salts
  3. Increases blood flow to intra-abdominal viscera
  4. Preserves gut derived immune system including gut associated lymphoid tissue

(GALT)

D. Contra-indications to enteral nutrition
   1. Hemodynamic instability
   2. High vasopressor requirement
   3. High-output enteric fistula

E. Access for Enteral Nutrition
   1. Naso-enteric tube most common
      a. No difference in complications whether gastric or post pyloric feeding tube
      b. Caution advised with gastric feedings in patients with gastric pathology (ie:Gastroparesis, gastric outlet obstruction, gastric fistula)
      c. Pancreatitis: Jejunal feeding tube is preferred
   2. Surgical Feeding Tubes
      a. Reserved for patients who require long term enteral access
      b. Percutaneous Gastrostomy Tubes (PEG, G-Tube)
      c. Jejunostomy Tubes (J-Tube)

F. Enteral Nutrition Formulas
   1. Numerous formulas available
   2. Disease specific formulas
   3. Typical ICU formula has 1-2 kcal/mL

> *You place a nasal feeding tube that ends in the patient's duodenum. How do you decide at what rate to start his tube feeds? How do you monitor his tolerance of feeding? Is there utility in monitoring gastric residual volumes?*

G. Initiation of enteral feeding
   1. Radiographic verification of the feeding tube is absolutely necessary.
   2. Enteral feedings should be started within 24-48 hours of ICU admission, if possible. If hemodynamically compromised, should hold enteral nutrition until fully resuscitated and stabilized
   3. In ICU, presence or absence of flatus or bowel sounds is not a requirement for initiation of enteral feeding
   4. Head-of-bed should be elevated to 30-45 degrees for aspiration precautions
   5. Can consider pro-motility agents if necessary
   6. EDEN Trial
      a. Compared low volume enteral feeds: 30% goal calories (10-20cc/hr) for six days then advanced to goal versus starting at 25cc/hr and advancing to goal as quickly as tolerated (q2h advances by 25cc/hr)
      b. No difference in mortality, ventilator free days, or infections
      c. Full feeding group had increased emesis, gastric residuals, use of prokinetic agents, higher glucose, and more constipation
   7. Common practice is to initiate enteral feeds at 30% calorie goal for 24 hours then increase by 10-15cc/hr every six hours as tolerated

H. Tolerance of Enteral Feeding
   1. Patient complaints of pain, gastric distention, flatus, radiographic evidence of ileus
   2. Monitoring gastric residual volume for tolerance of tube feeding is controversial
      a. JAMA 2013: Not monitoring residual gastric volumes during enteral feeding does not lead to more pneumonia
      b. JPEN Guidelines 2009: Should not hold tube feedings unless gastric residual volume is greater than 500cc
         i. Leads to inadequate nutritional support

Total Parenteral Nutrition

A. Advantages of TPN
   1. Ability to provide nutrients to patients who cannot tolerate enteral feeding
   2. If severe malnutrition and non-functional GI tract, TPN for 7 days prior to surgery may improve outcomes

B. Disadvantages
   1. Risk of systemic infection is much higher
   2. Liver complications include transaminitis, cholestasis, steatosis, steatohepatitis, fibrosis, and cirrhosis
   3. Hyperglycemia:May be the reason why TPN has higher infection risk
   4. Need for Central Access
      a. TPN is hypertonic and requires central access
      b. Peripheral parenteral nutrition does exist but requires high volume load
      c. Single lumen dedicated to TPN to help reduce infectious risk

C. Initiation
   1. The appropriate time frame to start parenteral nutrition remains controversial if a patient is not malnourished prior to ICU admission
   2. Late parenteral nutrition (8 days) has been shown to be associated with fewer complications than early initiation (48 hours). NEJM 2011
      a. Fewer infections, less cholestasis, more ventilator free days, and reduced duration of renal replacement therapy
      b. Late TPN group maintained on dextrose containing fluids
   3. If a patient is expected to be strict NPO for prolonged period of time, it is reasonable to start TPN early

D. Monitoring
   1. Electrolytes including calcium, magnesium, and phosphate
   2. Blood glucose
   3. LFTs
   4. Triglycerides
   5. Fluid Balance

After 10 days on the ventilator, he has been deemed medically stable such that he can be weaned from mechanical ventilation and potentially extubated. On numerous attempts at weaning, he becomes tachypneic and develops a mild respiratory acidosis necessitating continued mechanical ventilation. What nutritional factors may be playing into the difficulty weaning from the ventilator and how might you quantify them?

Nutrition Monitoring

A. Several nutrition scales used to calculate the nutritional status of patients. Parameters used in these scales include laboratory values (albumin, prealbumin, etc.), BMI, stress level, and amount of weight loss.

B. Metabolic cart
  1. Calculation of the patient's metabolic needs via indirect calorimetry
  2. Helps to ensure the patient is not being underfed or overfed.
  3. Metabolic carts are highly expensive and not shown to be beneficial; not recommended currently by JPEN guidelines

C. The Fick equation
  1. The amount of oxygen absorbed is equal to the amount of oxygen consumed
  2. Extrapolated to the amount of carbon dioxide produced.
  3. Patient must be metabolically stable
     a. Dynamic conditions such as sepsis, trauma, and burns give inaccurate results.
     b. End-tidal carbon dioxide per a given time is measured
     c. Using the Fick equation, the amount of oxygen consumed per minute is calculated.
     d. Respiratory quotient is calculated
        i. $RQ = CO_2$ expired $/ O_2$ inspired
        ii. 0.6-0.7 = starvation/underfeeding
        iii. 0.84-0.86 = desired range/mixed fuel utilization
        iv. 0.9-1.0 = primarily carbohydrate
        v. >1.0 = overfeeding/lipogenesis
  4. Overfeeding leads to difficulty weaning from the ventilator due to increased carbon dioxide production

Refeeding Syndrome

A. This potential complication may happen in chronically malnourished patients

B. These patients often have baseline hypophosphatemia

C. As feeds are initiated, there is an increase in serum insulin levels which shifts phosphate intracellularly and leads to a precipitous decline in serum phosphate

D. Hypophosphatemia with serum levels < 1mg/dL
  1. Respiratory failure secondary to diaphragmatic weakness
  2. Muscle weakness
  3. Rhabdomyolysis
  4. Hemolysis
  5. Altered mental status including gait disturbances and paresthesias
  6. Cardiomyopathy

E. Monitor serum phosphate levels with repletion often necessary

This chapter is a revision of the previous versions by R. Dean Nava, JR, MD and Gustavo Anagaramo, M.D.

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QUESTIONS

25.1 A patient has been on enteral tube feeds for 24 hours at 30% predicted caloric needs and the tube feed rate has been increased. A gastric residual of 200cc has been aspirated. What is your next step?
  A. Check an abdominal x-ray for evidence of an ileus
  B. Hold tube feeds and re-check gastric residual in six hours
  C. Continue current feeding schedule
  D. Initiate total parenteral nutrition

25.2 A metabolic cart (indirect calorimetry) is obtained on a patient and the respiratory quotient is calculated to be 1.1. What nutritional maneuver should generally be undertaken first in this situation?
  A. Nothing; keep nutritional support as it is
  B. Increase overall caloric intake
  C. Decrease overall caloric intake
  D. Increase carbohydrate fraction of nutritional support

25.3 Advantages of enteral feeding include all of the following EXCEPT:
  A. Maintenance of GI structural integrity
  B. Decrease in GI visceral blood flow
  C. Preservation of GI immune function
  D. Decrease in infectious risk

25.4 After beginning to provide nutritional support to a chronically malnourished patient, they develop confusion and dyspnea. The electrolyte disturbance most likely to be involved is:
  A. Hyperkalemia
  B. Hypokalemia
  C. Hypophosphatemia
  D. Hyperphosphatemia
  E. Hypermagnesemia

26. Acute Pancreatitis

Mariya Geube MD and Edward A Bittner MD PhD

Key Points

• The majority of patients who present with acute pancreatitis have a mild self-limiting disease with a benign clinical course, but 20% have severe acute pancreatitis (SAP) with local and extra-pancreatic complications. SAP requires ICU admission and is associated with high morbidity and mortality.

• Infection of necrotic (peri)pancreatic tissue is present when: (1) gas in the necrotic tissue is identified on contrast enhanced CT; (2) a positive gram stain or culture is obtained with Fine Needle Aspiration (FNA); or (3) a positive culture is obtained from the initial necrosectomy/drainage.

• Indications for surgical intervention in acute pancreatitis are infected (peri)pancreatic necrosis and/or intraabdominal complications, including hemorrhage, bowel obstruction, perforated viscus and abdominal compartment syndrome.

A 54 year old man with a history of alcohol abuse presents to the emergency department with severe epigastric pain radiating to his back, along with nausea and vomiting for the past 2-3 days. On exam, he is tachycardic and hypotensive. Laboratory data is notable for elevated amylase and lipase values. A non-contrast abdominal CT scan shows an enlarged pancreas with a peripancreatic fluid collection. After initial aggressive fluid resuscitation, the patient remains hypotensive, tachycardic, oliguric, and has an altered mental status. His ABG shows a pH 7.33, PaCO$_2$ 25, PaO$_2$ 64 on 6L/min oxygen supplementation, with a BE of -6.8 and Lactate 3.7.   Chest radiograph shows bilateral diffuse opacifications. The patient is intubated and admitted to the ICU.

Etiology

The most common causes of severe acute pancreatitis (SAP) are heavy chronic alcohol consumption and gall-stone disease. Other etiologies include trauma, hypercalcemia, hypertriglyceridemia, medications, infections, and post-ERCP.   In 20% of patients, the etiology of SAP is unknown.

Pathogenesis

The release of activated pancreatic enzymes leads to auto-digestion of the pancreatic parenchyma resulting in inflamation, microvascular injury, and necrosis. Activated enzymes may also enter the systemic circulation causing endothelial injury and activation of the inflammatory and coagulation cascades resulting in distant organ damage. Common associated organ dysfunction include shock, acute lung injury and acute respiratory distress syndrome (ALI/ARDS), and acute renal failure.

The morbidity and mortality in SAP are highest in the first two weeks of the disease and are determined by early and progressive development of multi-organ failure.

Classification

1. Severity
    a. Mild acute pancreatitis
        i. No local complications
        ii. No systemic organ dysfunction
        iii. Resolves within one week
    b. Moderately severe acute pancreatitis
        i. Presence of local complications
        ii. Transient systemic organ dysfunction < 48 hours duration
        iii. Exacerbation of co-morbid disease
    c. Severe acute pancreatitis (SAP)
        i. Presence of local complications
        ii. Persistent systemic organ failure > 48 hours
2. Type
    a. Interstitial pancreatitis (edematous form) – 80% of the cases
    b. Necrotizing pancreatitis – 20% of the cases
3. Local complications
    a. An acute peripancreatic fluid collection (typically found in interstitial pancreatitis)
    b. An acute necrotic collection defined as an area of non-viable pancreatic or peripancreatic parenchyma in the early stage of the disease before demarcation. The mortality rate in patients with this complication is approximately 10% with sterile necrosis and 25% in cases of infected necrotic pancreatic tissue [3]
    c. A pancreatic pseudocyst is an organized fluid collection enclosed by granulation tissue located outside of the pancreas (homogeneous liquid on CT scan) as a result of persistent leak from the pancreatic duct, usually occurring 4 weeks after disease onset.
    d. A walled-off necrosis is a well-organized collection of heterogeneous liquid and non-liquid necrosis in a well defined capsule more than 4 weeks after disease onset.
    e. The term pancreatic abscess has been abandoned in the current classification, replaced by the more contemporary term infected (peri)pancreatic fluid collection [2].

Diagnosis

1. Clinico-laboratory diagnosis of acute pancreatitis is based on the classical presentation of abdominal pain, nausea, vomiting and markedly elevated pancreatic enzymes (amylase and lipase at least three times higher than the normal limits).
2. There is a lack of correlation between the degree of elevation of the amylase and lipase, and the clinical severity of the disease.
3. Organ specific scoring systems have been created to assess the clinical severity and prognosis of acute pancreatitis – Ranson criteria, Glasgow criteria. For extra-pancreatic organ injury assessment – Acute Physiology and Chronic Health Evaluation (APACHE II) - is commonly used.
4. The CT Severity Index for acute pancreatitis (Table 26.1) is the sum of 2 other scores derived from the initial unenhanced (CT) and contrast-enhanced (CECT) CT scans [4]
5. The initial assessment of the severity of acute pancreatitis is based on the clinical presentation and the presence or absence of systemic organ failure. A CECT scan or MRI does not need to be obtained immediately after admission because local complications are not often evident in the first 3-4 days. Local complications should be suspected when, in the course of the disease, there is a recurrence of the abdominal pain, secondary peak in the pancreatic enzymes, aggravation or development of new organ dysfunction, or systemic hypotension.   Any of these should prompt immediate assessment with repeat imaging study (Figure 26.1).
6. Infected necrotic pancreatic tissue is presumed when extraluminal gas is identified on CECT, a positive gram stain or culture is obtained from fine needle aspiration (FNA), or a positive culture is obtained from the initial necresectomy/drainage[5].
7. Although FNA is the gold standard for diagnosis of infected necrotic pancreatic tissue, it may miss the infection because it is based on obtaining a small piece of tissue. Repeat FNA from a different spot increases the sensitivity of the test.

Table 26.1 CT Severity Index for acute pancreatitis	
Imaging	**Points**
Unenhanced abdominal CT scan	
Normal Pancreas	0
Enlargement of the pancreas	1
Changes in pancreas and peripancreatic tissue	2
Single fluid collection	3
Two or more fluid collections	4
Contrast enhanced abdominal CT scan (proportion of necrosis)	
0%	0
<30%	2
30-50%	4
>50%	6
Total Score	0-10
Score > 7 predicts high morbidity and mortality	

Management of Severe Acute Pancreatitis

Guidelines for the management of severe acute pancreatitis (SAP) in the Intensive Care Unit have been established by a multidisciplinary international consensus conference [6].

1. The initial management of SAP is supportive and consists of aggressive fluid resuscitation, adequate pain relief, antiemetics, and prevention and treatment of organ failure.
2. Patients with SAP should be admitted to the ICU when they meet conventional criteria for intensive care unit admission.
3. Antibiotic prophylaxis
    a. Infection of necrotic pancreatic tissue is unusual in the first week of disease onset. It occurs in 40-70% of patients with SAP after 2 weeks and is the leading cause of morbidity and mortality.
    b. Confirmation of infection is very important, since there are significant differences in the prognosis and management of sterile versus infected necrotic tissue.

Distinguishing between the two can be challenging since the systemic inflammatory response syndrome (SIRS) commonly occurs with SAP whether or not infection is present.

c. Prophylactic antibiotics are not recommended for patients with SAP within the first week of disease onset, although there is some controversy surrounding this practice. A recent meta-analysis suggests that prophylactic antibiotic use is not associated with a significant reduction in infected necrotic tissue, requirement for surgery, or mortality. However, there was a significant reduction in the hospital length of stay in the group treated with prophylactic antibiotics.[7]

d. Routine prophylactic antibiotics in patients with SAP have been shown to result in a shift of bacterial flora from Gram-negative microorganisms to fungi and Gram-positive microorganisms with the development of multiple drug resistant strains.

e. Significant clinical deterioration with high suspicion for infection of necrotic tissue (usually after 10-14 days) should prompt initiation of broad spectrum antibiotic therapy. Rapid de-escalation should occur after return of culture data and antibiotics may even be discontinued if infection is not confirmed.

f. The initial antibiotic therapy should be directed towards Gram-negative bowel flora with good penetration into pancreatic tissue (ie, carbapenems, fluoroquinolones, cephalosporins).

g. There is insufficient data to support the use of selective decontamination of the digestive tract (SDD) with nonabsorbable antibiotics for patients with SAP. This therapy is currently not recommended.
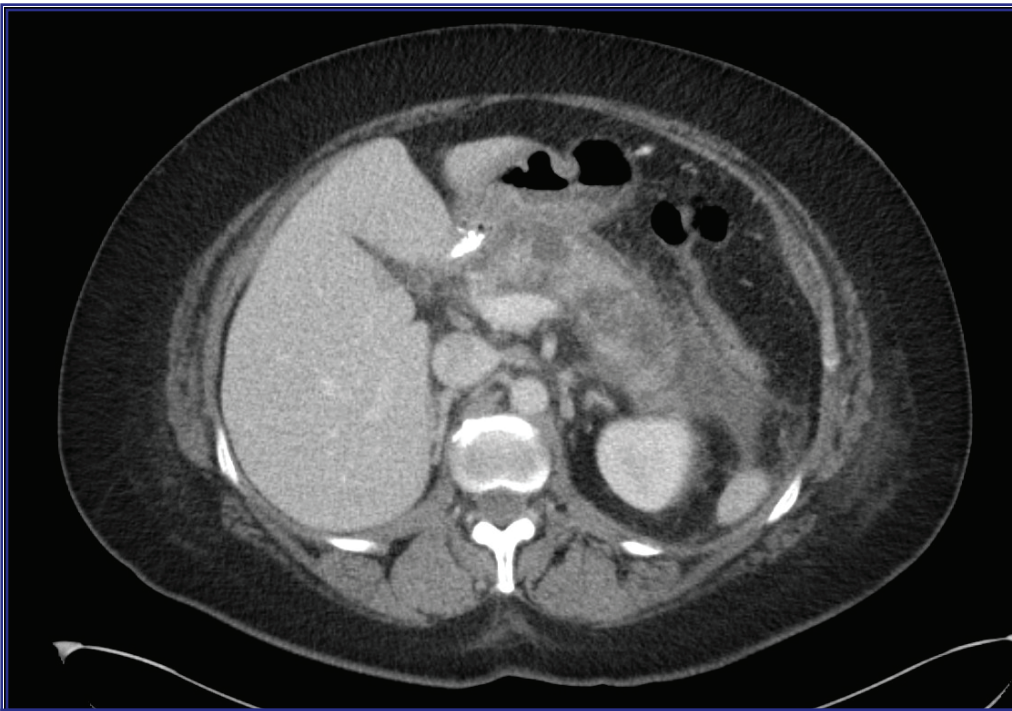
Figure 26.1 CT Scan abdomen, showing severe acute pancreatitis (SAP)

4. Surgical Intervention

a. The necessity and timing of surgical intervention in patients with SAP has been studied extensively. Clinical outcomes are improved by delaying surgery more than 4 weeks from disease onset. This delay allows a clear demarcation to develop between necrotic and non-necrotic tissue. Early intervention carries the risk of seeding the sterile necrotic tissue with microorganisms and incomplete debridement with the need for further surgery.

b. Indications for surgical intervention include: infected necrotic tissue and/or intra-abdominal complications including hemorrhage, bowel obstruction, perforated viscus, and abdominal compartment syndrome.

c. The standard surgical procedure is open transperitoneal or retroperitoneal necrosectomy (debridement) with placement of large bore drains. With this approach, viable pancreatic parenchyma may inadvertently be removed resulting in exocrine pancreatic insufficiency and diabetes mellitus.

d. For well-contained, well-defined collections, less invasive techniques including percutaneous drainage, endoscopic (transgastric) drainage, and minimally invasive retroperitoneal necrosectomy may be used. As compared to the standard surgical approach, these techniques offer control of the source of infection without complete removal of the gland tissue. A "step-up" technique[8] is currently used, in which percutaneous or endoscopic drainage of the pancreatic fluid collection is performed to mitigate sepsis. If there is no clinical improvement, this is followed by minimally invasive retroperitoneal video-assisted necrosectomy. The advantages of the "step-up" technique are a decrease in surgical trauma, less systemic inflammatory response (compared to an open technique), sparing of pancreatic gland tissue, and a decrease in the incidence of diabetes and postoperative hernias.

e. In acute pancreatitis resulting from obstruction of the common bile duct (acute biliary pancreatitis), current recommendations support urgent ERCP with sphincterotomy (within 72 hours of disease onset) for release of the obstruction. In patients without obstruction who have suspected or confirmed gallstone disease, cholecystectomy is indicated, but should be postponed until recovery from the episode.

5. Nutrition

a. The need and timing of nutritional therapy for patients with SAP should be based on the severity of the disease and the nutritional status of the patient.

b. SAP is a hypercatabolic state and early institution of nutrition is crucial to prevent severe malnutrition.

c. Classical thinking that bowel rest is needed in acute pancreatitis to decrease enzyme release from the pancreas has been abandoned due to a substantial body of literature showing that early institution of enteral nutrition is well tolerated with a resulting reduction in morbidity.

d. For patients with mild to moderate acute pancreatitis, guidelines recommend slow advancement of their diet within the first 3 to 4 days of disease onset as tolerated.

e. Enteral nutrition, compared with parenteral nutrition, has been shown to be associated with a decreased infection rate, length of hospital stay, lower number of required surgical interventions, and a trend toward decreased mortality.[9] Enteral feeding, compared to the parenteral route, is believed to reduce infectious complications from bacterial translocation by improving intestinal blood flow, resulting in the preservation of the integrity of the gut mucosa and gastrointestinal

associated lymphoid tissue (GALT). Enteral feeding also attenuates the systemic inflammatory response in patients with SAP.

f. Ideally, enteral nutrition should be instituted after the initial resuscitation and within 24 hours of admission in patients with SAP. Enteral nutrition may be administered in the presence of local pancreatic complications such as fistulas, pseudocyst and ascites.

g. Nasogastric tubes may be used for administration of enteral nutrition. Postpyloric placement is not necessarily required if gastric feeding is well tolerated. Continuous feeding is preferred over bolus or cyclic administration.

h. Parenteral nutrition should be considered only if attempts to feed the bowel have failed by day 6 or 7 in a normally nourished patient.

i. Immunomodulating formulas (IMF), balanced nutritional formulas supplemented with substances believed to modulate inflammation and improve immune function, have been studied in patients with pancreatitis. Some studies have suggested that arginine supplemented formulas can exacerbate pancreatitic inflammation, while formulas containing fish oil may have some benefit on the infection rate and reduce mortality.

j. Administration of probiotics has been associated with an increased incidence of multi-organ failure in patients with acute pancreatitis and therefore is not recommended.

k. Semi-elemental/elemental and polymeric formulas are well tolerated with a similar incidence of pain, ileus, and bloating. Semi-elemental formulas are associated with decreased weight loss and hospital stay compared to polymeric formulas [10].

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QUESTIONS

26.1 The recommended initial management of acute necrotizing pancreatitis includes all of the following except
 A. Aggressive fluid resuscitation
 B. Oxygen therapy
 C. Broad spectrum antibiotic therapy
 D. Analgesic medications
 E. Anti-nausea medications

26.2 An indication for surgical intervention in a patient with acute pancreatitis is:
 A. Moderate or severe acute pancreatitis
 B. Presence of (peri)pancreatic necrosis
 C. Documented infection of pancreatic tissue from FNA sample
 D. New organ failure in a patient with Severe Acute Pancreatitis
 E. New onset of fever and increase in WBC count

26.3 Which intervention in severe acute pancreatitis has a confirmed morbidity benefit
 A. Early surgical intervention
 B. Prophylactic antibiotics
 C. Probiotics supplements
 D. Early enteral nutrition
 E. Bowel rest and parenteral nutrition

27. Liver Failure

C Patrick Henson DO

Key Points

• Acute liver failure is rare in the developed world; is usually due to viral infection or drug toxicity; has the potential for recovery, but overall has a high morbidity and mortality.

• Chronic liver failure is more common and is usually associated with alcohol consumption and Hepatitis B or C.

• MELD is a score based on INR, bilirubin and creatinine, and predicts short term mortality without liver transplantation

• Liver failure has broad systemic effects, with derangements in the neurological, cardiac, pulmonary, renal, hematological and immunological systems.

A 60 year-old, morbidly obese female with a past history of type 2 diabetes, chronic lower extremity cellulitis, and non-alcoholic steatohepatitis (NASH) causing chronic cirrhosis presents to the ED with complaints of fever and fatigue.

On assessment, core temperature is elevated at 39.5 C, pulse is 120 bpm, BP is 92/43 mmHg, and oxygen saturation is 93% on 4L nasal cannula. On examination, she is alert and oriented. She has ascites, and her lower extremities are warm and erythematous, with 1+ pretibial edema. Her labs are notable for:

WBC 14.1 x 10^9/L
Venous lactate 6.5 mg/dL
AST 72 IU/L
ALT 21 IU/L
Total bilirubin 9.1 mg/dL
Albumin 2.1 gm/dL
Alkaline phosphatase 81 IU/L
BUN 53 mg/dL
Creatinine 2.84
INR 2.1.

Blood cultures reveal Gram-positive cocci in clusters, which eventually speciates MSSA. She was transferred to the Medical ICU for management of severe sepsis. Her respiratory status and mental status declined, and on hospital day two she was intubated for altered mental status and hypoxic respiratory failure. She progressed to septic shock, requiring norepinephrine and vasopressin infusions. Her lactate was persistently elevated for the duration of her hospital stay. Her WBC continued to rise to 50, and repeat blood cultures on day four grew out candida albicans. Her mental status failed to improve with maximal medical and nutritional support. She became anuric on day five, even with adequate intracardiac filling pressures and systemic blood pressure. She was considered for emergency orthotopic liver transplantation, but given her multi-organ system failure and in congruence with her wishes, care was withdrawn on day six.

Diseases of the liver are important causes of ICU admission and contribute greatly to morbidity and mortality. Chronic liver failure (CLF) is significantly more common than acute liver failure (ALF), but the latter typically involves a more rapid disease progression, and necessitates more aggressive treatment.

ALF is relatively rare, especially in the developed world. Occurring in the absence of preexisting liver disease, it is most commonly a result of viral infection or drug toxicity. Spontaneous recovery is possible, since cirrhosis and fibrosis are not present, but barring this, liver transplantation is the only treatment. A rapid disease progression from the onset of jaundice to encephalopathy and coagulopathy is characteristic, and the timing of this progression can affect outcome. Individuals with slower courses ('subacute') are less likely to recover spontaneously, whereas the more rapidly progressing cases ('hyperacute'), commonly the result of acetaminophen toxicity, have more potential for recovery without liver transplantation. Regardless, the prognosis is grim, with high mortality rates and diminished quality of life following transplantation.

CLF is more common, especially in the United States. It is typically associated with alcohol consumption and viral infection with Hepatitis B or C, but also with medications and fatty liver disease. The disease progression is slow, in contrast to ALF, and spontaneous recovery is rare. The only definitive treatment for this condition is liver transplantation, although patients can be effectively managed for long periods of time

Scoring systems have been developed to assist in outcome prediction and treatment of patients with ALF/CLF. While generalized scoring systems such as the APACHE and SOFA criteria are beneficial in establishing illness severity of patients with liver disease, the Kings College Hospital criteria uses markers of hepatic function such as INR and bilirubin to predict the likelihood that a patient with ALF will survive without transplantation. This is important, since earlier transplantation carries improved outcomes in patients who will require it. MELD is associated with CLF. The score is based on INR, bilirubin and creatinine, and aids in prediction of short term mortality without liver transplantation.

$$MELD = 9.57*Scr + 3.78*Tbil + 11.2*INR + 6.43$$

This model has been shown to help in prognosticating acute LF as well, but given the possibility of spontaneous recovery, it is less helpful and is used almost exclusively for chronic disease.

The clinical presentation of the patient with LF will vary, especially given the rapidity with which the ALF patient progresses. Multiple organ systems are usually affected. Patients may be altered or comatose, hypotensive from cardiovascular instability, have respiratory difficulty and/or acute kidney injury, all of which can develop within days to weeks of initial disease presentation. CLF may present with many of the same clinical problems, but typically these patients are aware of their disease, and have been maintained on chronic therapies designed to reduce the burden on their other organ systems. With that said, the cirrhosis that accompanies CLF creates problems that are not associated with ALF, such as:

1. Portal hypertension, predisposing to splanchnic varices and bleeding,
2. Pulmonary hypertension, leading to right ventricular dysfunction and pitting edema;

3. Electrolyte abnormalities, such as chronic hyponatremia.
4. Severe encephalopathy, however, is less likely, and this suggests severe disease progression.

The goal of much of the treatment of ALF/CLF in the ICU is protection of the non-hepatic organs. With therapies designed to prevent further deterioration of the other systems, the potential for spontaneous healing improves, and if transplantation is to be performed, the improved health status of the recipient positively affects the short and long-term success of the procedure.

Organ-specific therapies

Neurological
Hepatic encephalopathy (HE) in ALF/CLF is due to decreased metabolism of circulating neurotoxic compounds, such as ammonia, which leads to swelling of astrocytes and disruption of normal cognitive pathways. In ALF, the condition develops rapidly, and as such, normal volume regulating mechanisms are overwhelmed. This predisposes to cerebral edema and elevated intracranial pressure. CLF patients typically have a slower progression of HE, and cognitive dysfunction may exist without the mechanical changes seen in ALF. Also, the development or worsening of HE in patients with either form of LF may be facilitated by inflammation in another part of the body, often due to infection.

HE is often reversible with treatment, although in many instances it involves liver transplantation. If refractory to treatment and without a suitable organ match, intracranial hypertension can become severe enough that brainstem herniation may occur. The strategies for management of HE should focus on controlling the intracranial pressure (quiet environment, sedation if needed, minimizing stimulation, etc.) and monitoring of dural pressure may be required. Targeting a cerebral perfusion pressure of 50-80 is considered acceptable. Coagulopathy may prevent the placement of an intracranial pressure monitor. In these cases, clinical signs of increased intracranial pressure should followed closely. Therapies to reduce ICP such as mannitol and hypertonic saline can be considered, although care should be taken with these to avoid rapid shifts in serum osmolality.

In conjunction with proper nutritional support, elevations in serum ammonia concentrations may be managed with lactulose or rifaximin. Polyethylene glycol may be safer than lactulose, and this is being studied. Rifaximin may be cost-prohibitive; therefore, lactulose is the treatment of choice. Therapeutic hypothermia does not appear to confer significant benefit in the management of HE and elevated ICP; and, it may contribute to the worsening of coagulopathy.

Cardiac
Increased cardiac output is associated with cirrhosis and CLF. Circulating vasodilatory compounds contribute to increased venous capacitance, most notably in the splanchnic circulation; and, this promotes the high-output cardiac state seen in advanced disease. While the cardiac output is usually supranormal, the actual ventricular systolic function may be depressed. As the disease state progresses, myocardial thickening and diastolic dysfunction become apparent. In patients with ALF, hypotension may predominate, given the shock-like state associated with acute disease. Cardiac function in ALF may

be variable, but is less likely to be affected in the same way as the patient with compensated cirrhosis. Careful evaluation of the cardiovascular system is recommended in patients with LF admitted to the ICU. Vasopressor and/or inotropic therapy may be necessary in either group, depending on the relative complexity of coexisting processes. Monitoring of intracardiac filling pressures may be indicated, and qualitative assessment of ventricular function with echocardiography is useful. There are no specific standardized recommendations for the utility of these devices in LF, separate from traditional recommendations.

Pulmonary

Given the acute nature of ALF, the range of potential pulmonary complications is broad and includes:

1. Respiratory depression and aspiration secondary to HE,
2. Pulmonary edema due to aggressive fluid resuscitation or cardiac dysfunction,
3. Pneumonia and
4. ARDS.

As HE worsens, the need to control the ventilation of patients with either ALF or CLF becomes more of a priority. Similar standards apply to the management of increased ICP relative to arterial CO_2 tension; namely, mild-moderate hyperventilation may be beneficial in the short term to prevent cerebral herniation, but barring that, targeting a normal CO_2 is preferred. Care should be taken to minimize stimulation and manage patient comfort when intubating and performing procedures on patients with HE.

Patients with cirrhosis and CLF are at risk of similar complications once their disease progresses, but this group is also at risk for the development of pulmonary hypertension. The pathogenesis of portopulmonary syndrome is attributed to:

1. Development of the aforementioned cardiac diastolic dysfunction,
2. Hypertension within the portal system, and
3. An imbalance of native circulating pulmonary vasoregulatory compounds such as prostacylin and thromboxanes.

Significant pulmonary hypertension, with mPAP above 40-45mmHg, suggests a very high perioperative mortality, and as such, liver transplantation may not be offered to these individuals. Echocardiography is important in the evaluation of patients with suspected portopulmonary hypertension, and right heart catheterization may be useful as well in select cases

Renal

As with other organs, the kidneys are affected in LF. With ALF, the maintenance of systemic perfusion pressure as well as optimization of intravascular fluid status are of paramount importance. In CLF, renal function may remain stable over time, but can progress to hepatorenal syndrome, a state characterized by hepatic and renal failure combined with circulatory abnormalities such as portal hypertension. The alterations in arterial and venous pressures in the splanchnic and portal circulations promote renal vasoconstriction and reduced filtration. Common conditions associated with this phenomenon include drainage of ascites with large volume shifts, bacterial infection, and some medications. A cirrhotic patient who develops oliguria and has presumed worsening renal function should be considered to have hepatorenal syndrome once prerenal failure from

hypovolemia and other causes of ATN (nephrotoxins, complications of diabetes, etc.) have been ruled out, Liver transplantation often reverses this condition, and TIPS can help. Medical therapies (such as midodrine, octreotide, and vasopressin analogues) that reduce the gastrointestinal shunting of blood away from the renal circulation may have benefit. Hemodialysis may also be indicated, although may ultimately worsen outcomes.

Hematology

Coagulopathy is one of the hallmarks of decompensated liver disease, and is seen in both ALF/CLF. While hepatic synthesis of clotting factors is obviously disrupted, platelet number and function are also frequently suppressed, as consumptive processes and splenic sequestration affect the circulating count and function. It is acceptable to allow the INR to remain elevated and to avoid platelet transfusion. The INR is not a good indicator of overall coagulation in liver failure patients as endogenous anticoagulants, such as antithrombin, protein C, protein S and components of the fibrinolytic pathways, are also reduced. The thromboelastogram may be a better indicator of coagulation and bleeding risk. Transfusion should be limited except in ongoing bleeding. It is usually not necessary to reverse coagulopathy for invasive procedures such as central venous catheter placement, liver biopsy, and paracentesis; although, it may be necessary for intracranial pressure monitor placement.

Nutrition

Metabolic support is important in patients with ALF/CLF. Given the relative risks and benefits of enteral and parenteral feeding, it is reasonable to attempt enteral feeds in those patients who will tolerate it, although the data is mixed, and both methods provide some value.

Severely malnourished patients have significantly worse disease outcomes; thus, early assessment of nutritional status is important. Chronically ill patients may have neglected their food intake in the months prior to admission, while acutely ill patients often have increased metabolic requirements. At any rate, oral supplementation with calorie counts and replacement of vitamin deficiencies are minimal requirements. Parenteral feedings are recommended when oral intake is not adequate (<30-40kcal/kg/day).

Immunology

The presence of infection in patients with ALF/CLF can often trigger clinical decompensation, and as such, should be avoided and aggressively treated. While empiric antibiotics are not recommended for all patients, those with advanced encephalopathy, presence of SIRS or positive cultures should receive antibiotic therapy, ideally tailored to culture data. In addition, patients listed for transplantation may benefit from empiric antibiotic and antifungal therapy, as new infections may cause them to be delisted.

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QUESTIONS

27.1 Which of the following is true of MELD (model of end-stage liver disease) scoring?
    A.   Signifies the level of hepatocellular injury
    B.   Extrahepatic organ systems are not involved in the calculation
    C.   Predicts mortality following TIPS procedure
    D.   Is only useful when patients have decompensated illness
    E.   Etiology of disease is a factor in the calculation

27.2 What is the new MELD of the patient from the case presentation?
    A.   14
    B.   18
    C.   25
    D.   33
    E.   45

27.3 Which is a common etiology of altered mental status in chronic liver failure?
    A.   Medication reaction
    B.   Increased intracranial pressure
    C.   Hyperglycemia
    D.   Increased ammonia
    E.   Hypoxia

27.4 Which of the following is the most likely cause of the patient's acute renal failure?
    A.   Portopulmonary hypertension
    B.   Renal artery stenosis
    C.   Abdominal compartment syndrome
    D.   Acute tubular necrosis from vancomycin administration
    E.   Hepatorenal syndrome

27.5 Why are patients with cirrhosis at high risk for infection?
    A.   Decreased hepatic synthesis of complement factors
    B.   Splenic sequestration of leukocytes
    C.   Splanchnic shunting of blood away from the liver
    D.   Decreased phagocytic activity of antigen-presenting cells
    E.   All of the above

Section 7: Renal and Electrolytes

Chapters

• **Acute Renal Failure and Renal Protection**

• **Acid-Base Balance**

• **Electrolyte Abnormalities**

• **Fluid Replacement in the ICU**

• **Renal Replacement Therapy**

28. Acute Renal Failure and Renal Protection

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Key Points

• The kidney provides a way for the body to filter and excrete waste, maintain electrolyte concentrations, control blood acidity, and regulate blood pressure

• Maintenance of normal renal function is dependent on the delivery of an adequate volume of blood at an appropriate pressure.

• Critically ill patients are at-risk for the development of AKI

• Contrast-induced AKI can be attenuated by aggressive IV hydration and oral N-acetylcysteine

A 60 year-old man presents to the ICU following a respiratory arrest. He is postoperative day 4 from a transhiatal esophagectomy. He has had diarrhea for the previous three days. His past medical history is notable for colon cancer and prior nephrectomy for trauma. Upon arrival to the ICU, he is intubated and laboratory studies are sent. Results are shown:

WBC 30.2 x 10^9/L
Hemoglobin 19 mg/dL
INR 1.5
Na^+ 139 mmol/L
K^+ 5.2 mmol/L
BUN 75 mg/dL
Creatinine 2.4 mg/dL

The healthy kidney provides a way for the body to filter and excrete waste, maintain electrolyte concentrations, control blood acidity, and regulate blood pressure. Even when injured through chronic conditions such as diabetes mellitus or hypertension, the system is typically able to continue functioning well enough to avoid serious complications. Syndromes of critical illness place the renal system at extremely high risk of acute injury, however, and these insults can be substantially more complicated to assess and manage. The acuity of the changes and the increased mortality and morbidity associated with renal injury in critical illness mandates a thoughtful and expeditious approach to diagnosis and treatment.

Maintenance of normal renal function is dependent on one major physiologic principle with two components. The major principle is the delivery of an adequate volume of blood at an appropriate pressure. The mechanical nature of filtration mandates this perfusion pressure to actively filter the plasma, in addition to providing oxygen to the organ (2 components). Acute kidney injury (AKI) usually occurs as a result of derangements in these physiologic processes that can result in rapidly progressive deterioration of renal function leading to difficulties in regulation of intravascular volume and pH and electrolyte abnormalities.

Long-term renal complications in outpatients are typically due to chronic hypertension, but acute hypotension is more of a concern in AKI. At a certain low mean arterial pressure (MAP), intrinsic autoregulatory processes become overwhelmed by perfusion pressure dependency, and the intrarenal blood flow falls off dramatically. While MAP is a good indicator of organ perfusion in the euvolemic patient, hypovolemia and cardiac insufficiency can also worsen renal function through a direct decrease in renal blood flow. As catecholamine

output increases to maintain normal MAP, the compromised patient will shunt blood flow from the renal system, and AKI often follows. Systemic shock of any kind is the biggest single risk factor associated with the development of AKI.

The physiologic principle of perfusion is important enough to warrant the optimization of its components, pressure and flow, in the face of any renal insult. In addition to the shock states, however, other factors associated with critical illness significantly increase the risk of AKI, such as sepsis, use of vasopressors, vascular embolic events, mechanical ventilation, and nephrotoxic medications. As might be expected, exposure to surgery is strongly associated with AKI, but studies have demonstrated that as many as one-third of patients who develop AKI have some degree of renal dysfunction prior to admission. It is fairly easy to predict that the diabetic patient with known aortic atherosclerosis who presents to the ICU on high-dose vasopressors following laparotomy for colonic perforation will be at extremely high risk for development of AKI. As we will see, the current challenges involve discriminating between individuals in the intermediate risk category, and management of these cases, once risk has been established.

Diagnostic criteria have been validated to define the continuum of AKI. RIFLE, and its subsequent modification, AKIN, provide a quick bedside tool to assess for the presence and severity of AKI. (Figure 28.1) Both use absolute serum creatinine concentrations and urine output as implicit measurements of renal function. Hallmarks of diagnosis include a rapid time course, usually less than 48 hours, rise in serum creatinine concentration by at least 0.3 mg/dL, and oliguria (UOP < 0.5cc/kg/hour) of at least 6 hours duration. The early stages of AKI in both sets of criteria suggest less severe injury, but progression to the later stages is inevitable without resolution of the insult. Early recognition, therefore, is extremely important. Mortality is significantly increased among patients in all stages.

All currently accepted diagnostic criteria for AKI rely on measurements that have high variability in patients, especially those with critically illness: urine output and serum creatinine. Total body water, diuretic use, nutritional status and body mass all confound one or both of these values, causing inappropriate or delayed diagnosis of AKI. This is especially true of serum creatinine, which has long been considered the gold standard for evaluation of glomerular filtration rate (GFR) and renal function. A recent study suggested that increases in creatinine could be delayed by 24 hours or more in patients with increased fluid accumulation, confounding the diagnosis in patients receiving large quantities of intravenous fluids. Novel biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL), cystatin C and interleukin-18 may be useful as markers of injury, but their use is not yet widespread. In the majority of patients, however, when the appropriate clinical suspicion is combined with accurate data, patients at risk should

AKIN Criteria

Serum Creatinine	Urine Output
STAGE 1: ≥ 0.3 mg/dL or ≥ 150-200% from baseline	< 0.5 mL/kg/hr for more than 6 hours
STAGE 2: ≥ 200-300% from baseline	< 0.5 mL/kg/hr for more than 12 hours
STAGE 3: ≥300% from baseline or ≥ 4 mg/dL with an acute increase ≥ 0.5 mg/dL or on RRT	< 0.3 mL/kg/hr for more than 12 hours

RIFLE Criteria

Urine Output	Serum Creatinine or GFR
< 0.5 mL/kg/hr for more than 6 hours	RISK: ≥ 150% from baseline or GFR decrease by > 25%
< 0.5 mL/kg/hr for more than 12 hours	INJURY: ≥200% from baseline or GFR decrease by > 50%
< 0.3 mL/kg/hr for more than 12 hours	FAILURE: : ≥300% from baseline or ≥ 4 mg/dL with an acute increase ≥ 0.5 mg/dL or GFR decrease by > 75%
	LOSS: Complete loss of kidney function > 4 weeks
	END-STAGE KIDNEY DISEASE: Complete loss of kidney function > 3 months

Only creatinine OR urine output is needed for each stage/criteria (the worst of either)

Figure 28.1 AKIN vs RIFLE criteria for kidney injury

be identified with reasonable success.

AKI can be classified as prerenal, postrenal, or intrinsic; simplistic terms that allow us to contextually frame the mechanism of injury, which helps guide appropriate management. Fractional excretion of either sodium or urea (Figure 28.2) can be calculated after assessment of the urine and plasma with low values suggesting decreased circulating volume and kidneys that are effectively reclaiming sodium in an effort to maintain intravascular volume. Higher values occur with higher than expected sodium wasting and/or a reduced ability to appropriately concentrate the urine. Additional standard assessment of the AKI patient includes investigation of the urine for tubular casts and eosinophils, suggestive of glomerular injury and drug-induced nephritis, respectively.

Ruling out obstruction to urinary flow and elevated backpressure should be considered as this is easily correctable. Hydronephrosis by renal ultrasound may suggest obstruction in the ureter or more distally. In early obstruction, the presentation may be similar to a hypovolemic state, with oliguria and evaluation of the urine revealing low urine sodium and low fractional excretion of sodium. In cases of prolonged obstruction, however, damage to the kidney may cause a presentation similar to acute tubular necrosis (ATN). In the ICU setting, kinks or clots in the urinary catheter are common and easily resolvable causes of oliguria, and these should be ruled out first.

Medical management strategies should first address the cause of AKI. Assessment of volume status and replacement or support of circulation should be considered to address global hypoperfusion. Administration of intravenous fluids is typically indicated in the setting of prerenal AKI, although dysfunction of other organ systems should be ruled out, as cardiac and hepatic failure can appear prerenal, yet they require quite different treatments. In most cases, cost-effective choices such as balanced salt solutions may be preferable to human albumin, while most synthetic starches are no longer recommended. In cases of hemorrhage or anemia, the benefit of replacing blood products may outweigh the risks of transfusion, and this should be determined on a patient-specific basis.

In conjunction with replacement of circulating volume, vasopressor support may be indicated, especially in cases of vasodilatory shock. The long-held belief that 65 mmHg is an acceptable MAP for renal perfusion has been challenged recently, and a pressure greater than 75 mmHg may be necessary for prevention of AKI. Even though vasopressor use is a risk factor for the development and worsening of AKI, this association is likely multifactorial and, regardless, systemic hypotension necessitates aggressive treatment. Norepinephrine infusion is the gold standard, while vasopressin and epinephrine may have additional benefits. Phenylephrine may also help maintain renal perfusion pressure, but the increased intrarenal vasoconstriction without increase in cardiac output may be deleterious to the kidney-at-risk. In septic patients, a trend toward worsened renal function was seen with phenylephrine when compared to norepinephrine. However, maintaining appropriate perfusion pressure takes precedence, and phenylephrine may be used based on availability.

As discussed above, cardiac causes of poor perfusion, such as low-output states due to poor contractility or obstruction to forward flow, may initially present with normal blood pressure. Accurate assessment of cardiac function is critical in patients suspected of having cardiac dysfunction leading to AKI. Inotropic support with milrinone, epinephrine, or dobutamine is typically the mainstay of cardiac support, and initiation of

these would be expected to help improve blood flow to the kidneys. In volume overload states, diuretic therapy may reduce venous pressure with resultant increase in tissue blood flow. However, although these agents can augment urine output, they may also worsen prerenal AKI. Diuretic therapy should be initiated with caution in AKI states. Dopamine is a potent vasoactive agent with vasopressor and inotropic effects while at low doses, acting as a diuretic. The action of dopamine on the renal system is to promote diuresis through increased demand on the kidney, without necessarily increasing tissue blood supply. Studies have shown that low-dose, or "renal-dose" dopamine, is not protective to the kidney and may increase mortality.

Many well-known nephrotoxins are currently in use in ICUs around the world. There are several potential injury mechanisms, including disruption of intrarenal hemodynamics, crystal formation, and direct tubular injury, among others. Antibiotics such as aminoglycosides, fluoroquinolones and penicillins are likely the biggest offenders, but common drugs such as ACE inhibitors, NSAIDs, and statins are also implicated. Inflammatory causes of AKI are the most common and eosinophils will be seen in microscopic evaluation of the urine sediment. Stopping the offending agent early enough and providing hemodynamic support may allow the renal system time to heal.

The rise in contrast-induced AKI (CI-AKI) parallels the increase in dye-requiring angiographic studies, like cardiac catheterizations and CT scans. The risk of serious injury increases with the severity of illness and, therefore, patients with no risk factors for AKI are extremely unlikely to develop CI-AKI. However, the critically ill patient is more likely to require studies such as these and they are also more likely to have other risk factors for AKI, placing them at higher risk of injury. The mechanism is not fully understood, but intrarenal vasoconstriction, direct cellular toxicity, and decreased production of vasodilatory mediators are all implicated.

The goal in management for CI-AKI is twofold: maintain adequate circulating volume and minimize exposure. Consider alternative imaging studies in patients with AKI or with significant risk factors, and avoid repeating contrast doses. Use of iso-osmolar or

$$FE_{Na} = (Plasma_{Cr} \times Urine_{Na}) / (Plasma_{Na} \times Urine_{Cr})$$

$$FE_{Urea} = (Plasma_{Cr} \times Urine_{Urea}) / (Plasma_{Urea} \times Urine_{Cr})$$

	Pre-Renal	Intrinsic Renal	Post-Renal
FE_{Na}	< 1%	> 1%	> 4%
FE_{Urea}	< 35%	50 - 65%	

Figure 28.2 Fractional Excretion of Sodium and Urea (FENa and FEU)
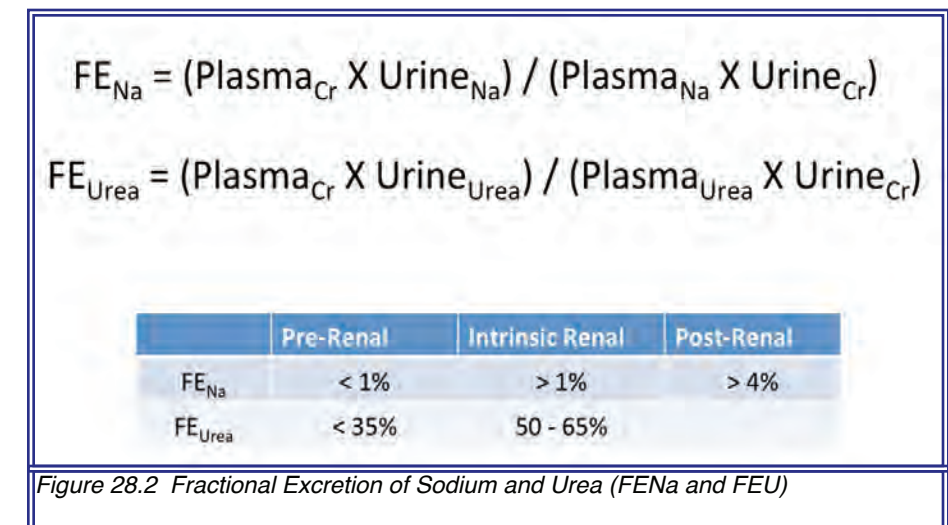
low-osmolar contrast media is associated with lower rates of CI-AKI in patients with renal dysfunction, so these should be used whenever possible. When contrast must be used in patients at risk for AKI, hydration should be initiated prior to the exposure and continued after the procedure, preferentially by the intravenous route. Balanced salt solutions are ideal, as well as sodium bicarbonate in D5W, which has been shown to have some benefit. The known free radical scavenger N-acetylcysteine has a relatively benign risk profile and has shown to be beneficial in emergent situations. It should be considered in all patients at high risk for CI-AKI in addition to aggressive hydration.

Ultimately, a percentage of patients will progress to require renal replacement therapy (dialysis), either in the short or long term. Critically ill patients are more likely to tolerate Continuous Renal Replacement Therapy (CRRT) over conventional intermittent hemodialysis (HD), although there seems to be no consensus on which improves mortality. More recent studies do support early initiation of renal replacement therapy with a reduction in length of mechanical ventilation. Early appreciation of worsening renal function remains critical.

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QUESTIONS

All of the following questions refer to the patient in the case summary.

28.1 Which of the following intravenous fluid is preferred for this patient?
    A. Packed red blood cells
    B. Hextend™
    C. Hespan™
    D. Lactated Ringer's
    E. Fresh frozen plasma

48 hours later, he is now in septic shock, requiring large doses of vasopressors to maintain MAP > 60 mmHg and increased ventilatory support to maintain oxygenation. He is oliguric, making < 10 cc/hour of urine.

28.2 Which of the following would be considered indications for urgent hemodialysis?
    A. ECG changes with K+ > 6.0 mmol/L following appropriate medical therapy
    B. PaO_2 of 50 mmHg (FIO_2 1.0) and chest x-ray with perihilar congestion and Kerley B lines
    C. pH < 7.1 and minute ventilation of 20 L/min
    D. All of the above

28.3 Which of the following complications is most likely to be related to AKI?
    A. Pericarditis
    B. Metabolic alkalosis
    C. Hypophosphatemia
    D. Hypercalcemia

His laboratory data eventually show a hyperkalemia and acidosis, with signs of volume overload. Vascular access is placed and continuous renal replacement therapy is initiated. Urine output is zero for the previous 6 hours. Serum creatinine is 3.1 mg/dL, up from a baseline of 1.4 mg/dL.

28.4 Which of the following parameters is suggestive of AKI by the AKIN criteria?
    A. Creatinine elevated 1.7 mg/dL above baseline
    B. Urine output of zero over 6 hours
    C. Absolute value of creatinine of 3
    D. A & B only

28.5 Which of the following is a true statement?
    A. AKI is rarely present in patients prior to ICU admission
    B. Patients requiring renal replacement therapy for AKI are more likely to require long-term dialysis
    C. Greater than 50% of patients with AKI require renal replacement therapy
    D. The occurrence of contrast-induced AKI is equally common in all ICU patients
    E. None of the above

29. Acid-Base Balance

Nahel Saied MBBCh

Key Points

• Acid-base homeostasis is critical to enzymatic function and metabolism. H+ concentration affects protein configuration leading to alterations in many critical metabolic pathways. It also alters the degree of ionization of many compounds thereby affecting their transport across cell membranes.

• The human body has a vast capacity to buffer H$^+$ in order to maintain a normal pH. Only when those reserves are depleted are significant acid-base disturbances observed.

• In general, most acid-base disturbances are mild and inconsequential. However, they provide an insight into disease processes that might otherwise be missed and could pose grave harm to the right patient.

• In critically ill patients, acid-base disturbances tend to be complex with more than one disorder present at any given moment. Distinguishing the primary disorder is crucial to its proper management.

A 27 year-old woman is admitted to the ICU for a salicylate overdose. While in the drugstore, she reported to the clerk that she had ingested 75 325-mg tablets of non-enteric coated aspirin. EMS was called and she was brought immediately to the hospital. In the ED, she received activated charcoal and polyethylene glycol. She was then transferred to the ICU for close monitoring. Upon her arrival into the ICU, laboratory studies are sent. Results are shown below.

ABG:
pH 7.53, PaCO$_2$ 23 mmHg, PaO$_2$ 111 mmHg, Base Deficit 3.0, Bicarbonate 19 mmol/L, Oxygen Saturation 99%
Chemistries:
Na$^+$ 141 mmol/L, K$^+$ 4.3 mmol/L, Cl$^-$ 106 mmol/L, CO$_2$ 17mmol/L, Mg$^+$ 2.6 mg/dL, Ca^{2+} 8.6 mg/dL, Phosphorus 3.0mg/dL, BUN 11mg/dL, Creatinine 1.25 mg/dL, Glucose 198 mg/dL, Salicylate 70 mg/dL

Overview:

The body's extracellular fluid (1/3 of total body water) contains 40 nanomol/L of hydrogen ion (H$^+$) and is regulated within a narrow range by metabolic, renal and respiratory buffering mechanisms. In general, those mechanisms are very effective in maintaining pH in the normal range (7.40 ±0.02) unless one or more of such mechanisms are impaired by disease process, e.g. renal or respiratory insufficiency. Most patients in intensive care units will have acid-base disorders related to their baseline medical conditions as well as the current disease process responsible for their admission to the ICU. One must not forget that many therapies required to treat critically ill patients will also result in acid-base disturbances. Treatment with diuretics, administration of a wide range of intravenous fluids and many others will directly impact acid-base balance and may need counter therapies until the normal compensatory mechanisms can restore the balance.

Acids, bases and buffering mechanisms

Acidosis or alkalosis is the process by which the pH changes from the normal neutral point (pH 7.40). One leads to the state of acidemia (pH < 7.35) while the other leads to alkalemia (pH > 7.45). Despite the clear difference of definition between "-osis" and "-emia", many clinicians use the 2 terms interchangeably. While acid-base disturbances occur in all body compartments, plasma, extracellular fluid as well as intracellularly, we will focus on the plasma component for the purpose of analysis and treatment.

Carbonic acid is a weak acid that is critical to understanding the basic acid-base balance. It rapidly and easily dissociates into its various states to stay in constant equilibrium. The ability of carbonic acid to generate hy-

drogen ion (H^+), bicarbonate ion (HCO_3^-) and carbon dioxide (CO_2) makes it a versatile compound. (Table 29.1) This allows both the lung (through CO_2 elimination) and the kidney (through HCO_3^- formation and reabsorption) to play a central role in maintaining acid-base balance and offer an essential and agile buffering capacity.

Table 29.1 Henderson and Modified Henderson Equations

$[H^+][HCO_3^-] = K1[H_2CO_3] = K2[CO_2][H_2O]$; K=dissociation constant
Since H_2CO_3 itself is of no clinical interest, we can use:
$[H^+][HCO_3^-] = K[CO_2][H_2O]$
Since H2O is constant in vivo:
$[H^+][HCO_3^-] = K[CO_2]$
Utilizing Henry's Law ($[CO_2]/PaCO_2 = 1/kH$; kH=Henry's constant):
$[H^+] = (24 \times PaCO_2)/[HCO_3^-]$ (which is the Modified Henderson equation)
Note: Hasselbach combined Henderson's equations with Sorensen's pH negative log transformation. This proved to be difficult to understand and provides no additional medical information to the analysis. Therefore, for the purpose of this chapter, we will ignore it and use the modified Henderson equation instead.

While the lung and kidney play a critical role in quick and effective buffering mechanisms through carbonic acid, there are other, less modifiable, intracellular buffering systems that contribute to the body's buffering capacity. Those include phosphate buffers, intracellular proteins, hemoglobin in erythrocytes, and more importantly bone (up to 40% of acute acid load buffering)

Acid-base analysis:

There are 2 major approaches to interpretation of the acid-base state: the traditional bicarbonate approach (HCO_3^-) and the strong ion difference (SID). While some believe SID may be more sensitive in detecting acid-base disturbances, in most cases, it offers little, if any, advantage over the traditional HCO_3^- centered approach. In this chapter, we will use the HCO_3^- centered analysis as it is simpler and, for all clinical purposes, is an accurate method of assessing and treating acid-base disturbances.

Typically, acid-base analysis is performed using a blood gas analyzer. The blood sample can be arterial or venous (ABG versus VBG). The analyzer directly measures pH, $PaCO_2$, PaO_2, and oxygen saturation while bicarbonate and base excess (BE) values are calculated. In addition, most blood gas laboratory equipment will also measure basic electrolytes (Na^+, K^+, Ca^{++}) and hemoglobin. Again, it is important to recognize that the HCO3- value provided by the ABG is a calculated value and not directly measured. Hence, for better accuracy, HCO_3^- values provided by direct electrolyte analysis technique using serum and not whole blood should be used for interpretation and analysis

when available.

When performing an ABG analysis, one should answer the following questions:
• What type of disorder exists? acidosis/acidemia or alkalosis/alkalemia?
• What is the primary disorder? Metabolic or respiratory?
• Is the primary disorder acute or chronic?
• Are there compensatory mechanisms in play and, if so, are they appropriate?
• Are there other independent disorders?

The following 6-step approach was proposed in the early 1980s and was refined in the 1990s. it remains easy to follow and answers the above questions systematically.
• Step 1: Is the pH acidemic or alkalemic?
• Step 2: Is the primary disturbance respiratory or metabolic?
• Step 3: For a respiratory disturbance, is it acute or chronic?
• Step 4: If a metabolic acidosis exists, determine whether an anion gap is present.
• Step 5: Determine if a secondary metabolic disturbance co-exists with an anion gap acidosis.
• Step 6: Assess the degree of compensation by the respiratory system for the primary
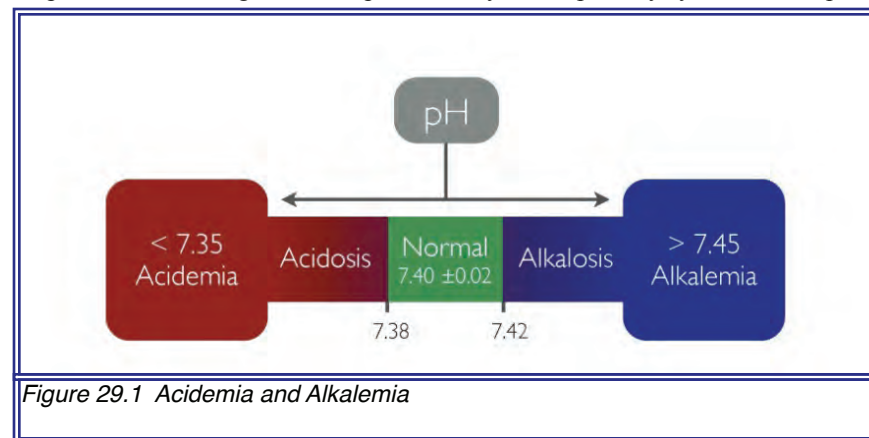

Figure 29.1 Acidemia and Alkalemia

metabolic disturbance.

It is prudent to always verify the accuracy of numbers reported on the ABG by comparing the $[H^+]$ from the modified Henderson equation. A quick method uses the 2 digits following the decimal point of the pH. By subtracting the 2 digits from 80, the resulting

number should equal the results from $(24 \times PaCO_2)/HCO_3^-$.

Example:

    ABG: 7.24/49/21/120

    $H^+ = 80-24 = 56$

    $H^+ = (24 \times PaCO_2)/HCO_3^- = (24 \times 49)/21 = 56$

Which confirms that the reported numbers are correct per Henderson's equation

Step 1: Is the pH acidemic or alkalemic?

The ABG pH deviation from the neutral point (7.40 ± 2) identifies the disorder as alkalemic or academic. (Figure 29.1)

Step 2: Is the primary disturbance respiratory or metabolic?

This step requires one to determine whether the disturbance affects primarily the arterial $PaCO_2$ (respiratory) or the serum HCO_3^- (metabolic). A respiratory disturbance alters the arterial $PaCO_2$ (normal value 40, range 38-42). Go to step 3. A metabolic disturbance alters the serum HCO_3^- (normal value 24, range 22-26).

-     If $HCO_3^- < 22$, metabolic acidosis is present. Go to step 4.
-     If $HCO_3^- > 26$, metabolic alkalosis is present, is respiratory compensation adequate? Go to step 6.

Step 3: For a respiratory disturbance, is it acute or chronic?

In respiratory acidosis, CO_2 retention occurs with the onset of hypercarbic respiratory failure. Acute changes will result in a pH reduction of 0.08 for every 10 mmHg rise of $PaCO_2$. However, in chronic respiratory acidosis, the HCO_3^- shift mediated by the kidney (compensation) will result in a lesser degree of pH reduction, only 0.03 per 10 mmHg rise of $PaCO_2$. Respiratory alkalosis results from hyperventilation due to multitude of reasons (see below) and the same rules apply to pH changes in the opposite direction. It is worth noting that the renal compensation will correct the pH toward normal but never completely so the pH will always indicate the direction of the primary

Table 29.2 Anion Gap reflects unmeasured Anions and Cations			
Unmeasured Anions		**Unmeasured Cations**	
Proteins (mostly albumin)	15 mEq/L	Calcium	5 mEq/L
Organic acids	5 mEq/L	Potassium	4.5 mEq/L
Phosphates	2 mEq/L	Magnesium	1.5mEq/L
Sulfates	1 mEq/L		
	23 mEq/L		11 mEq/L

disturbance unless a complex or mixed disorder exists.

Summary:

  Acute respiratory acidosis: pH decrease $= 0.08 \times (PaCO_2 - 40)/10$

  Chronic respiratory acidosis: pH decrease $= 0.03 \times (PaCO_2 - 40)/10$

  Acute respiratory alkalosis: pH increase $= 0.08 \times (40 - PaCO_2)/10$

  Chronic respiratory alkalosis: pH increase $= 0.03 \times (40 - PaCO_2)/10$

Step 4: For a metabolic acidosis, determine whether an anion gap is present.

A normal anion gap is approximately 10-12 mEq/L. The anion gap is the calculated difference between negatively charged (anion) and positively charged (cation) electrolytes, which are measured in routine serum assays.

$$\text{Anion gap} = Na^+ - (Cl^- + HCO_3^-)$$

Since the anions and cations are always in balance to maintain electrical neutrality, the anion gap reflects the unmeasured anion concentration. There are more unmeasured anions than cations (Table 29.2) and hence the normal difference expressed by the simple equation above.

The causes of an anion gap acidosis differ from those of a normal or non-anion gap acidosis (discussed in common acid-base disturbance). Except in rare situations, the anion gap determination is an excellent tool for narrowing the list of potential causes of a metabolic acidosis. Pay attention to patients with hypoalbuminemia as low levels of albumin (e.g. cirrhosis, nephrotic syndrome, malnutrition) reduce the normal anion gap
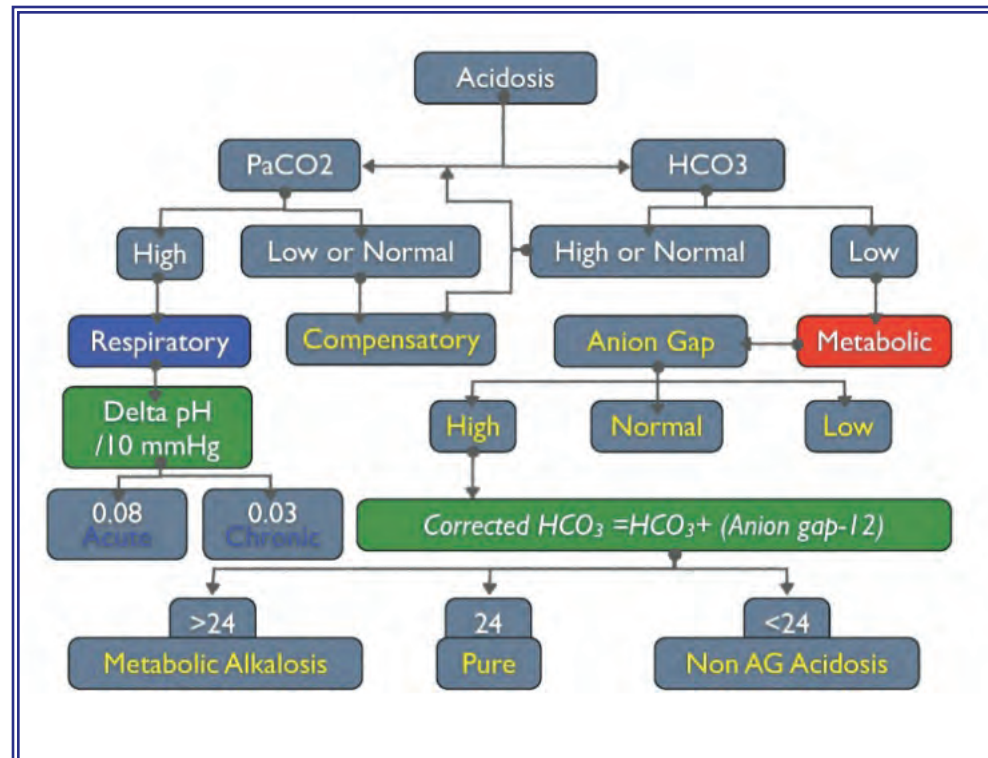

Figure 29.2 Flow diagram for the approach to an acidosis

and can mask a significant anion gap metabolic acidosis.

Step 5: Determine whether other metabolic disturbances co-exist with an anion gap acidosis.
A non-anion gap acidosis or a metabolic alkalosis may exist concurrently with an anion gap acidosis. This determination requires one to account for the increase in the anion gap and determine whether an additional variation in HCO_3^- exists. If no other metabolic disturbance exists, then the corrected bicarbonate would be 24

$$\text{Corrected } HCO_3^- = \text{measured } HCO_3^- + (\text{anion gap - 12})$$

If the corrected HCO3- varies significantly above or below 24, then a mixed or more complex metabolic disturbance exists. To be more specific, if the corrected HCO_3^- is greater than 24, a metabolic alkalosis co-exists. If the corrected HCO_3^- is less than 24 then a non-gap acidosis co-exists. (Figure 29.2)

Step 6. Assess the normal compensation by the respiratory system for a metabolic disturbance.
The respiratory system responds quickly to a metabolic disturbance (especially acidosis) and results in a linear reduction in $PaCO_2$. The Winter's formula (Figure 29.3) predicts the expected $PaCO_2$ in response to a change in HCO_3^-. In simple metabolic acidosis, the measured $PaCO_2$ will fall within the range predicted by Winter's formula. However, if the expected $PaCO_2$ falls outside the range, one should expect a mixed acid-base distur-

bance, usually respiratory in origin. For example:
• If the measured $PaCO_2$ is less than the Winter's expected range, the patient must have respiratory alkalosis in addition to the metabolic acidosis.
• If the measured $PaCO_2$ is more than the Winter's expected range, the patient must have respiratory acidosis in addition to the metabolic acidosis. (Figure 29.3)
It is important to recognize that the Winter's formula does not reliably predict the respiratory response to a metabolic alkalosis. Hypoventilation is the natural compensatory mechanism for a metabolic alkalosis. However the degree of $PaCO_2$ increase does not exhibit a linear relationship with the HCO_3^-. There are 2 general rules one can count on to predict the respiratory response to a metabolic alkalosis:
1. $PaCO_2$ may increase above normal but not usually > 50-55 mmHg to compensate for a metabolic alkalosis.
2. Compensation is usually incomplete, i.e, pH will improve toward normal but will remain > 7.42.
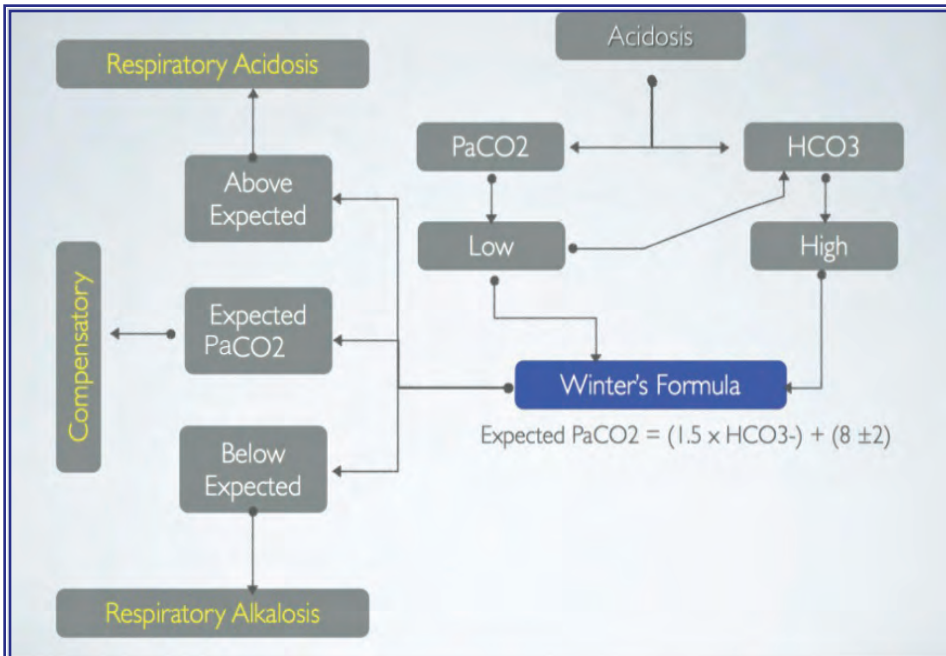
Common disturbances:

1. Respiratory acidosis:
Usually results from hypoventilation or the inability to eliminate CO_2 that is manifested as an elevation of $PaCO_2$ and a drop in pH.
Examples:
• Central nervous system depression (sedatives, central hypoventilation syndrome)
• Pleural disease (pneumothorax) or lung disease (COPD, pneumonia)
• Musculoskeletal disorders (severe scoliosis, Guillain-Barre, myasthenia gravis)

2. Respiratory alkalosis:
Usually results from hyperventilation that is manifested by a decrease in $PaCO_2$ and a rise in pH.
Examples:
• Catastrophic CNS event (CNS hemorrhage)
• Drugs (salicylates, progesterone)
• Pregnancy (especially the 3rd trimester)
• Decreased lung compliance (interstitial lung disease)
• Liver cirrhosis
• Anxiety and/or pain

3. Anion Gap Acidosis
Anion gap acidosis results from the accumulation of metabolic acids resulting in consumption of HCO_3^- in the presence of an anion gap (AG > 12).
Examples:
• Renal failure (uremia, unsecreted acids)
• Medications (INH, salicylates)
• Ketoacidosis (diabetic, alcoholic)
• Alcohol poisoning (methanol, isopropyl)
• Glycols (ethylene, propylene)
• Lactic acidosis (sepsis, heart failure)

4. Non-Anion Gap Acidosis
Non-anion gap acidosis (AG < 12) results from the loss of bicarbonate or the addition of

Figure 29.3 Respiratory compensation in metabolic acidosis and mixed disorders

external acid and is manifested by a low HCO_3^-.

Examples:

- GI loss of HCO_3^- (diarrhea)
- Renal loss of HCO_3^-
- Compensation for respiratory alkalosis
- Carbonic anhydrase inhibitor (acetazolamide)
- Renal tubular acidosis
- Ureteral diversion
- Hyperchloremia
- HCl or NH_4Cl infusion, TPN

5. Metabolic Alkalosis

Metabolic alkalosis results from an elevation of serum bicarbonate.

Examples:

- Volume contraction (vomiting, excessive diuresis, ascites)
- Hypokalemia (H^+ exchange with K^+)
- Alkali ingestion (bicarbonate)
- Excess gluco- or mineralocorticoids
- Recover from massive blood product resuscitation (metabolism of citrate)

6. Mixed and complex disorders

It is rare to find simple acid-base disorders in the critically ill patient, as many of these patients have significant chronic diseases with baseline acid-base disturbances. In addition, many therapies given to critically ill patients may result in additional alterations in their acid-base state, e.g. opioids, diuretics, total parenteral nutrition and continuous gastric suctioning. While one may find a simple primary disorder early in the course of critical illness affecting an otherwise healthy patient, with progression of the inciting disease and application of needed therapies, the disorder becomes complex and additional disorders are added to the acid-base milieu.

Often it is difficult to understand such complex acid-base states. It can be confusing when, for example, a patient could have an anion gap and a non-anion gap acidosis at the same time or a chronic respiratory acidosis and an acute metabolic alkalosis. Only when the etiology of each disorder is appreciated can one understand complex disorders. In the first instance, the patient may have had vomiting due to intestinal obstruction (causes non anion gap acidosis) and developed sepsis with hypoperfusion and lactic acidosis (anion gap acidosis). In the second instance, a patient with severe COPD and chronic respiratory acidosis with metabolic compensation (elevated HCO_3^-) is placed on mechanical ventilation with immediate normalization of the $PaCO_2$. The ABG will show
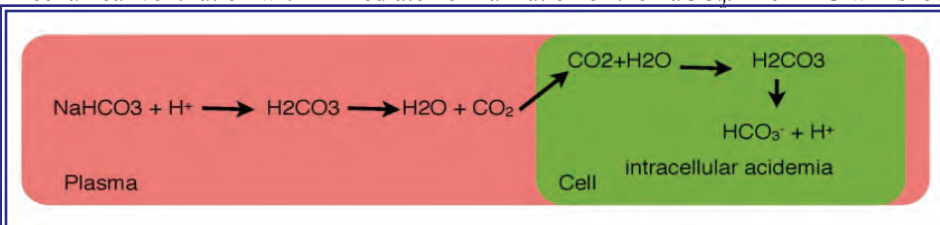
an elevated HCO_3^- and normal $PaCO_2$. This leads us to the diagnosis of an acute metabolic alkalosis if we are unaware of the history of COPD with chronic CO_2 retention. Thus, the medical history is crucial in understanding complex acid-base disorders.

Treatment

It is very rare for a clinician to treat acid-base disorders without also instituting treatment for the inciting pathology. For example, a patient with an anion gap metabolic acidosis secondary to severe sepsis must also receive treatment for the septic shock (restore perfusion and initiate antimicrobial therapy). When manipulating the acid-base state, it is important to keep a few important points in mind:

1. Most mild and moderate acid-base disturbances are self-limited and will resolve over time if the inciting pathology is treated.

2. Utilize and augment the normal compensatory mechanism when possible. For example, in a severe metabolic acidosis, one must augment respiratory compensation by assessing a patient's ventilation before resorting to administration of buffering agents.

3. Mild acidosis while a patient is under stress is likely beneficial and rarely of any harm. Mild acidosis augments oxygen unloading from hemoglobin and into tissues.

4. It is rarely beneficial to administer HCO_3^- to patients with a level above 10 mEq/L.

5. In situations when the pH is < 7.2, administration of intravenous HCO_3^- is indicated as a temporizing measure since severe acidosis could be harmful. Make sure CO_2 elimination is optimized and maximized. Giving IV HCO_3^- without proper ventilation will shift H^+ intracellularly; intracellular acidosis (Figure 29.4) is far more dangerous than its extracellular counterpart. Administer HCO_3^- slowly over time to allow for CO_2 elimination by the lungs.

6. Severe alkalosis (metabolic or respiratory, pH > 7.6) is as harmful as acidosis and acute treatment may be indicated. After correcting the primary pathology, metabolic alkalosis may be treated with a short course of carbonic anhydrase inhibitors (acetazolamide) for 24-48 hours. Respiratory alkalosis however may be difficult to treat especially if the inciting pathology is not acutely modifiable, e.g. catastrophic intracranial pathology.

7. $NaHCO_3$ is a hypertonic solution with a large Na^+ load. Be aware of the acute effect on intravascular volume especially in children and in patients with chronic hyponatremia. Intracranial hemorrhage can occur in neonates with rapid administration of $NaHCO_3$. Acute hypernatremia in patients with low Na^+ levels may result in central pontine myelinolysis.

8. THAM solution is another H^+ acceptor and could be used to correct a severe metabolic acidosis when Na^+ may be contraindicated. It is a weak buffer compared to $NaHCO_3$ but is less hypertonic.

Figure 29.4 Movement of extracellular bicarbonate into the cell resulting in an intracellular acidosis

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Questions

29.1 A 52 year-old man with a history of renal failure has an ABG showing pH 7.33, $PaCO_2$ 33 mmHg , and HCO_3^- 17 mmol/L What is the next best step?
   A.   Repeat the test due to an error
   B.   Administer 100 mEq of $NaHCO_3$
   C.   Initiate hemodialysis
   D.   Initiate BiPAP
   E.   Do nothing

29.2 A 66 year-old woman is admitted with fever and leukocytosis. She is found to have urosepsis. An ABG obtained for tachypnea shows pH 7.34, $PaCO_2$ 35 mmHg, PaO_2 78 mmHg, HCO_3^- 18 mmol/L, Na^+ 141 mmol/L, and Cl^- 105 mmol/L. The most appropriate response(s) after initiating antibiotics is/are:
   A.   Intubate and initiate mechanical ventilation.
   B.   Check lactate level as it is likely elevated.
   C.   Administer 50 mEq of $NaHCO_3$.
   D.   Increase IV fluids and monitor urine output.
   E.   Both B & D

29.3 A 22 year-old man is brought to the ED by ambulance after being in a minor motor vehicle accident. He states his chest hurts and it is difficult to breath. He has no other complaints. He is noted to have tachypnea and requires oxygen at 2 L/min to maintain a SpO_2 >95%. His chest x-ray shows multiple left-sided rib fractures with a small pneumothorax. His ABG shows pH 7.47, $PaCO_2$ 31 mmHg, PaO 81 mmHg, and HCO_3^- 22 mmol/L. What is the next best step?
   A.   Initiate acetazolamide therapy
   B.   Administer morphine to control pain and anxiety
   C.   Place a large bore IV and give 1L of 0.9 NS
   D.   Perform left thoracostomy to drain pneumothorax

30. Electrolyte Abnormalities

Anna M Allred MD and Sheena M Weaver MD

Key Points

• **Both disorders of electrolyte concentration and improper treatment can cause increased morbidity and mortality.**

• **As a general rule, the severity of the symptoms correlates with the severity of the disturbance and the rate at which it developed.**

• **If an error is suspected, there is no harm in repeating the laboratory analysis in a patient that is asymptomatic.**

• **Pharmacists can play an important role in determining the cause and in managing electrolyte disturbances.**

• **Equations and recommendations are commonly provided, but cannot replace clinical judgment and knowledge of the pathophysiology of electrolyte disorders.**

A 43 year-old woman with a past medical history of smoking and hypertension presented to the Neurointensive Care Unit 7 days ago with a confirmed subarachnoid hemorrhage (Hunt-Hess Grade 3). A 3-mm left anterior cerebral artery aneurysm was noted on angiography. It was successfully coil-embolized on hospital day 1 without complications. Her most recent laboratory values include: sodium 130 mEq/L (1 day prior 135 mEq/L); potassium 4.5 mEq/L; chloride 102 mEq/L; BUN 32 mg/dL (1 day prior 29 mg/dL); and creatinine 1.21 mg/dL (1 day prior 1.10mg/dL). Her urine output has been increasing over the past 24 hours.

INTRODUCTION

Electrolytes are necessary for many metabolic and homeostatic functions such as: nerve signal conduction; hormone function; muscle contraction; cardiovascular function; maintenance of cell membrane structure and function; bone composition; and acid-base/fluid regulation. Disorders of electrolytes are common in the adult ICU population. Multiple mechanisms are involved, including: altered absorption and distribution; excessive or inadequate administration; alterations in hormonal, neurologic and homeostatic mechanisms; gastrointestinal losses; altered renal losses; changes in fluid status and fluid shifts; and as side effects of medication administration. Below, disturbances in sodium, potassium, calcium, magnesium, and phosphorus are reviewed.

Sodium (Na⁺)

Hypernatremia – Associated with overall mortality rate of 40-70%.
    1. Definition: $Na^+ > 145$ mEq/L
    2. Causes – see Table 30.1
    3. Signs & Symptoms
      a. Lethargy
      b. Irritability
      c. Restlessness
      d. Thirst

e. Muscle irritability and spasticity

f. Hyper-reflexia

g. Seizures

h. Coma

i. Death

4. EKG Changes - none

5. Treatment - See Table 30.1

a. Achieve normal circulatory volume

b. Correct no more than 1-2 mEq/L/hr

c. Do not correct more than 15 mEq/L/24 hours

d. If > 170 mEq/L do not correct below 150 in the first 48-72 hours

e. Calculate water deficit

i. Water deficit (in liters) = Total body water x [(serum sodium/140)-1]

1) Replace first half of water deficit over 24 hours

2) Replace remainder over following 24 to 72 hours

ii. Replace using D5W or 0.45 % NS

6. Monitor – Check serum sodium every 2-4 hours if symptomatic; every 6-12 hours after symptoms resolved

---

Table 30.1 Causes and Treatment of Hypernatremia

Volume Status	Causes	Treatment
Hypovolemia	Loss of hypotonic fluids: - vomiting - diarrhea - nasogastric suctioning - osmotic diuresis - burns/open wounds - sweat (fever, sepsis) - lungs	NS or LR for hemodynamic instability Correct water deficit once hemodynamically stable
Isovolemia	Diabetes insipidus: - central (CDI) - Nephrogenic (NDI)	CDI: - ADH analog: Desmopressin NDI: - remove cause - Thiazide (use with caution)
Hypervolemia	Hypertonic saline (HTS) solutions Sodium bicarbonate solutions Mineralocorticoid excess: - hyperaldosteronism	Remove HTS Restrict sodium Loop or thiazide diuretic Can use hypotonic fluids: - 0.225% or 0.45% NS - D5W

Hyponatremia

1. Definition: $Na^+ < 135$ mEq/L

2. Causes – see Table 30.2

3. Signs & Symptoms

a. Headache

b. Lethargy

c. Disorientation

d. Muscle cramps or weakness

e. Depressed reflexes

f. Hyponatremic encephalopathy ($Na^+ < 120$ mEq/L)

i. Nausea/vomiting

ii. Seizures

iii. Coma

iv. Death

4. EKG Changes - none

5. Treatment – see Table 30.2

a. Recent and acute onset can be more rapidly corrected and is more likely to be symptomatic

b. Patients with severe manifestations, active seizures, or respiratory failure, can be treated with a bolus of 100 mL 3% saline over 10 minutes

i. Bolus can be repeated 1-2 times and followed by an infusion if symptoms persist

ii. Goal is to raise serum sodium 2 to 4 mEq/L.

c. Chronic hyponatremia should be corrected slowly and is usually not associated with severe symptoms

d. Calculate sodium deficit

i. Sodium deficit (mEq) = total body water x (140 – serum sodium)

1. Many use 125 or 130 instead of 140 in the calculation so as not to overcorrect

2. Correct for hyperglycemia if present; 1.6 mEq of Na/L is added for every 100 mg/dL increase of serum glucose above 100

ii. Replace fifty percent over first 24 hours

1) Do not correct more than 12 mEq/L in 24 hours

2) Correct acute hyponatremia at a rate of 1-2 mEq/L/hr

3) Correct chronic hyponatremia at rate of 0.5 mEq/L/hr

iii. Complete remaining replacement over 48 to 72 hours

e. Overcorrection can induce central pontine myelinolysis which can manifest gradually over one to six days after rapid correction. Hypertonic saline at more than 30 mL/hr increases the risk.

i. Findings include:

1) Pseudobulbar palsy

2) Quadriparesis

3) Seizures

4) Movement disorders

6. Monitor - Check serum sodium every 2-4 hours if symptomatic; every 6-12 hours after symptoms resolved

Potassium (K^+)

Hyperkalemia

1. Definition

a. $K^+ > 5.0$ mEq/L

Table 30.2 Causes and Treatment of Hyponatremia

Hypotonic (most common)	Hypovolemic: - excessive diuresis - hemorrhage - diarrhea - burns - cerebral salt wasting Isovolemic: - secondary to abnormalities of sodium wasting and water conservation - SIADH - adrenal insufficiency - hypothyroidism - medication side effect Hypervolemic: - secondary to inability to maintain normal volume status - cirrhosis - CHF - renal failure	Hypovolemic: - normal saline (NS) - Lactated Ringers (LR) Isovolemic: - water restriction - loop diuretics (i.e., furosemide 20-40 q6-12h) - hypertonic saline Hypervolemic: - diuresis - treat underlying illness
Isotonic	Hyperlipidemia Hyperproteinemia	Correct underlying cause Discontinue protein-based fluids
Hypertonic	Hyperglycemia: - DKA - HHS Hypertonic sodium-free solutions (i.e., mannitol)	Correct underlying cause Stop hypertonic solutions

   b. Life threatening is $K^+ > 6.5$ mEq/L

 2. Causes

   a. Extracellular shift in ions

     i. Metabolic acidosis

     ii. Trauma

     iii. Rhabdomyolysis

     iv. Bowel infarction

     v. Tumor lysis syndrome

     vi. Insulin deficiency – DM

   b. Medications

     i. Beta-blockers

     ii. Succinylcholine

     iii. Digoxin

   c. Excessive potassium ingestion

   d. Reduced potassium elimination

     i. Renal failure

     ii. Potassium-sparing diuretics

     iii. ARB & ACE inhibitors

     iv. NSAIDS

     v. Heparin

     vi. Cyclosporin & Tacrolimus

     vii. Hypoaldosteronism

 3. Signs & Symptoms (usually do not develop until $K^+ > 5.5$ mEq/L)

   a. Muscle twitching

   b. Nausea

   c. Cramping

   d. Weakness

   e. Paralysis

   f. Palpitations

   g. Cardiac arrhythmias → death

 4. EKG Changes

   a. Peaked T waves

   b. Widened QRS complexes

   c. Prolonged PR interval

   d. Shortened QT interval

   e. Sinusoid wave pattern

   f. Ventricular tachycardia or fibrillation

   g. Pulseless electrical activity

 5. Treatment

   a. Discontinue exogenous potassium

   b. IV calcium if symptomatic or EKG changes present: 1-2 g calcium gluconate or calcium chloride; repeat until EKG changes improve

   c. Promote intracellular shift of potassium ions (these medications will normalize serum potassium levels but WILL NOT affect total body potassium)

     i. 10 units of Insulin with 50-100 g dextrose (D50W)

     ii. Sodium bicarbonate 50-150 mEq IV

     iii. Albuterol inhaled

   d. Increase the elimination of potassium

     i. Loop diuretics – start with 40 mg furosemide (30 minutes to see effect)

     ii. Sodium polystyrene 30-90 g PO or PR (1-2 hours to see effect)

     iii. Emergency dialysis, if life threatening

 6. Monitor - Check levels frequently, every 2 to 6 hours

Hypokalemia

 1. Definition

   a. $K^+ < 3.5$ mEq/L

   b. Severe is $K^+ < 2.5$ - 3.5 mEq/L with symptoms

 2. Causes - usually multifactorial

   a. Decreased oral intake

   b. Increased losses

     i. Thiazide and loop diuretics

     ii. GI losses

       1. Diarrhea

       2. Vomiting

3. NGT drainage
   iii. RRT
  c. Intracellular shift
   i. Metabolic alkalosis
   ii. Catecholamine's
  d. Iatrogenic - Infusion of potassium free fluids
  e. Medications
   i. Albuterol
   ii. Insulin
   iii. Theophylline
  f. Caffeine
  g. Refeeding a malnourished patient
  h. Hypomagnesemia can cause refractory hypokalemia
3. Signs & Symptoms
  a. Weakness
  b. Muscle cramps
  c. Respiratory compromise
  d. Paralysis
  e. Cardiac arrhythmias
  f. Death
4. EKG Changes
  a. T wave flattening
  b. T wave inversion
  c. ST segment depression
  d. Prolonged PR interval
  e. Prolonged QRS complexes
  f. Presence of U waves
5. Treatment
  a. IV and enteral replacement are both effective; replace IV if symptomatic
  b. K^+ 3.0 - 3.4 mEq/L – start with 20-40 mEq IV potassium
  c. K^+ < 3.0 mEq/L may require as much as 200 mEq of potassium
   i. Start with 40-80 mEq IV replacement at 10-20 mEq/hr (rate depends on peripheral or central access) and recheck level
   ii. High concentration or rapid infusion of replacement potassium may necessitate continuous ECG monitoring; especially if > 40 mEq/hr (rare)
   iii. Larger doses in setting of ongoing renal or gastrointestinal losses (rare)
  d. Restoration of normo-kalemia relies on normo-magnesemia
  e. Avoid dextrose containing solutions
  f. Monitor acid-base status – levels will fall 0.6 mEq/L for every 0.1 increase in pH
6. Monitor - Check levels frequently, every 2 to 6 hours

Calcium (Ca^{2+})
Hypercalcemia
  1. Definition

   a. Ca > 10.2 mg/dL
   b. Severe is Ca ≥ 13 mg/dL
  2. Causes
   a. Malignancy
   b. Primary hyperparathyroidism
   c. Adrenal insufficiency
   d. Paget's disease
   e. Milk alkali syndrome
   f. Rhabdomyolysis
   g. Medications
    i. Thiazide diuretics
    ii. Lithium
    iii. Vitamin D
    iv.Vitamin A
  3. Signs & Symptoms
   a. Fatigue
   b. Confusion
   c. Anorexia
   d. Arrhythmias
   e. Severe
    i. Obtundation
    ii. Acute renal failure
    iii. Ventricular arrhythmias
    iv. Coma
   f. Chronic
    i. Nephrolithiasis
    ii. Metastatic calcifications
    iii. Renal failure
  4. EKG Changes
   a. Bradycardia
   b. Prolonged PR interval
   c. Wide QRS complex
   d. Short QT interval
  5. Treatment
   a. Mild to moderate hypercalcemia – commonly only need hydration
   b. Severe hypercalcemia needs immediate treatment with hydration; NS at 200-300 ml/hr
   c. After hydration, use loop diuretics to increase renal elimination
   d. RRT if severe or in renal failure
  6. Monitor - Check daily calcium levels while in ICU

Hypocalcemia
  1.Definition
   a. Ca < 8.6 mg/dL

   b. Ionized Ca^{2+} < 1.1 mmol/L
2. Causes
  a. Hypoalbuminemia
  b. Hypomagnesemia
  c. Hyperphosphatemia
  d. Sepsis
  e. Pancreatitis
  f. Hypoparathyroidism
  g. Vitamin D deficiency
  h. Renal insufficiency
  i. Citrated blood products
3. Signs & Symptoms
  a. Tetany
  b. Chvostek & Trousseau signs
  c. Altered mental status
  d. Chronic
   i. Hair loss
   ii. Dermatitis
   iii. Eczema
   iv. Grooved nails
4. EKG Changes
  a. Prolonged QT interval
  b. Bradycardia
5. Treatment
  a. Do not need to treat asymptomatic patients
  b. For every 1 g/dL decrease in serum albumin below 4 g/dL, the serum calcium concentration will decrease by 0.8 mg/dL.
  c. Treat when Ca < 7.5 mg/dL or ionized Ca^{++} < 0.9 mmol/L
   i. IV calcium chloride (13.6 mEq/10 mL)
   ii. IV calcium gluconate (4.56 mEq/10 mL)
    1) Start with 1-3 g
    2) Undergoes hepatic metabolism
6. Monitor – Check 2 hours after dose is completed to follow improvement, if warranted.

Magnesium (Mg^{2+})
Hypermagnesemia
  1. Definition – Mg > 2.4 mg/dL
  2. Causes
   a. Renal insufficiency
   b. Iatrogenic
  3. Signs & Symptoms
   a. Asymptomatic until Mg > 4.0 mg/dL
   b. Moderate Mg 4-12.5 mg/dL

   i. Nausea/vomiting
   ii. Hypotension
   iii. Bradycardia
   iv. Loss of DTR's
  c. Severe Mg > 12.5 mg/dL
   i. Respiratory paralysis
   ii. Refractory hypotension
   iii. Atrioventricular block
   iv. Cardiac arrest
4. EKG Changes
  a. Wide QRS complex
  b. Prolonged PR interval
  c. Bradycardia
5. Treatment
  a. Discontinue magnesium continuing medications
  b. 1 g IV calcium to stabilize cardiac membrane (over 5 min)
  c. Loop diuretics
  d. Renal replacement therapy
6. Monitor – check levels daily while correcting

Hypomagnesaemia
  1. Definition
   a. Mg < 1.5 mg/dL
   b. Severe is Mg < 1.0 mg/dL
  2. Causes
   a. GI losses
   b. Pancreatitis
   c. Malnutrition
   d. Renal losses
   e. Surgery
   f. Trauma, Burns
   g. Sepsis
   h. Alcoholism
   i. Medications
    i. Thiazide and loop diuretics
    ii. Amphotericin
    iii. Cisplatin
    iv. Cyclosporine
    v. Digoxin
  3. Signs & Symptoms
   a. Cardiac arrhythmias
   b. Seizure
   c. Coma
   d. Death

4. EKG Changes
    a. Prolonged QT interval
    b. Atrial and/or ventricular ectopy
5. Treatment
    a. Replace IV or PO; IV preferred because enteral is slowly absorbed and magnesium containing products can promote diarrhea
    b. Mild to moderate can be treated with 1-4 g of IV magnesium sulfate or 8-32 mEq of magnesium
    c. Severe hypomagnesemia usually requires 4-6 g (32-48 mEq)
    d. If symptomatic, start with 1-2 g (8-16 mEq) over 10 minutes
    e. Decrease dose if renal function reduced by > 50%
6. Monitor – Check Serum levels as needed; may be falsely elevated due to magnesium's slow distribution into body tissues
7. Magnesium as Treatment
    a. Severe preeclampsia or eclampsia
      i. Loading dose 4-6 gm IV
      ii. Continuous infusion 1-3 gm/hr
    b. Torsade de pointes
      i. Loading dose 1-2 gm IV over 30-60 seconds; repeat q 5-15 minutes as needed
      ii. Continuous infusion 0.5–1 g/hr
    c. Tolerate serum levels as high as 6-9 mg/dL as long as patient is asymptomatic

Phosphorus (PO_4^{2-})

Hyperphosphatemia
1. Definition: > 4.5 mg/dL
2. Causes
    a. Renal insufficiency
    b. Excessive administration
    c. Acidosis
    d. Hemolysis
    e. Rhabdomyolysis
    f. Tumor lysis syndrome
    g. Hypoparathyroidism
3. Signs & Symptoms (secondary to calcium-phosphorus precipitation)
    a. Crystal formation causes hypocalcemia
    b. Crystals deposit into soft tissues causing organ damage
    c. Nephrocalcinosis
    d. Hypotension
    e. Impending CV collapse
4. EKG Changes – none
5. Treatment
    a. Patients on renal replacement therapy need to decrease PO phosphorus in diet
    b. Phosphate binders – reduce absorption from the GI tract
    c. Monitor feeding formulas to adjust phosphorus content

    d. Acute dialysis
6. Monitor – Depends on severity

Hypophosphatemia
1. Definition
    a. Mild: < 2.7 mg/dL
    b. Severe: < 1.5 mg/dL
2. Causes
    a. Malnutrition
    b. Alcoholism
    c. Alkalosis
    d. Diabetic ketoacidosis
    e. Gastrointestinal losses
    f. Renal replacement therapy
    g. TPN
    h. Medications
      i. Diuretics
      ii. Antacids
      iii. Sucralfate
      iv. Amphotericin B
      v. Corticosteroids
3. Signs & Symptoms
    a. Impaired diaphragmatic contractility - hypoventilation
    b. Acute respiratory failure
    c. Impaired myocardial contractility
    d. Weakness – proximal extremities
    e. Paresthesias
    f. Seizure
    g. Platelet dysfunction
4. EKG Changes – none
5. Treatment
    a. Replace orally if mild and patient asymptomatic
    b. If severe or symptomatic replace with IV potassium phosphate or sodium phosphate
      i. Ordered in mmol
      ii. One mmol phos = 31 mg phos
6. Monitor – recheck 2 to 4 hours after infusion complete

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Questions

30.1 All of the following are common causes of hypokalemia EXCEPT:
   A.   Loop diuretic use
   B.   Hyper-secretion of mineralocorticoids
   C.   Hypoaldosteronism
   D.   Excessive vomiting, diarrhea or other GI losses

30.2 Select the best set of parameters for Cerebral Salt Wasting, which would help differentiate it from SIADH:
   A.   Hyponatremia + Euvolemia + Urine Na+>>40mEq/L + polyuria
   B.   Hyponatremia + Hypovolemia + Urine Na+>>40mEq/L + polyuria
   C.   Hyponatremia + Hypovolemia + Serum Osm < 270mOsm/kg + oliguria
   D.   Hypernatremia + Hypovolemia + Serum Osm > 285mOsm/kg + polyuria

30.3 Which of the following are considered sequelae of hypophosphatemia?
   A.   Metabolic encephalopathy secondary to ATP depletion
   B.   Paralytic ileus
   C.   Rhabdomyolysis and Hemolysis
   D.   Impaired myocardial contractility
   E.   All of the above

30.4 The appropriate initial therapy for this tracing is:
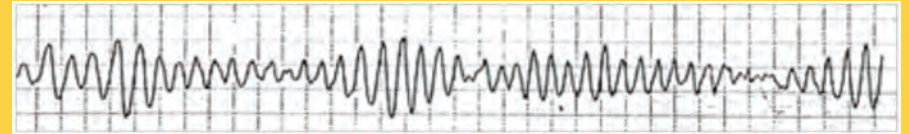
   A.   1-2 g calcium chloride
   B.   50 mEq sodium bicarbonate
   C.   Synchronized cardioversion
   D.   1-2 g magnesium sulfate

30.5 All of the following are associated with hypercalcemia EXCEPT:
   A.   Autoimmune Hypoparathyroidism
   B.   Primary Hyperparathyroidism
   C.   Sarcoidosis
   D.   Multiple Myeloma
   E.   Milk-Alkali Syndrome

31. Fluid Management in the ICU

Luke Parr MD and Aaron Joffe DO

Key Points

• In the average 70-kg man, 60% of the body's weight is water.

• Human albumin should not be routinely administered and synthetic colloids (HES, dextrans, gelatin) should not be administered to patients with sepsis.

• The Surviving Sepsis Guidelines and ATLS guidelines provide recommendations for fluid management in severe sepsis/septic shock and traumatic hemorrhagic shock, respectively.

A 55 year-old, 130-kg man with poorly controlled diabetes is admitted to the ICU with severe redness, pain, and swelling of his right leg.

T (°C) 38.6
HR (bpm) 128
RR (bpm) 24
BP (mmHg) 74/53
Saturation 98%

WBC (x10⁹/L) 22
Hg (g/dL) 9.0
Na⁺ (mEq/L) 140
K⁺ (mEq/L) 4.2
Creatinine (mg/dL) 2.0
Lactate (mg/dL) 6.8

Where's the water?

Paramount to understanding fluid management is an appreciation of the various compartments into which the total body water (TBW) is distributed (Figure 31.1). TBW is related to the amount of lean body mass as fat is relatively anhydrous. Thus, men and women are considered to be approximately 60% and 50% water, respectively. The "third space" refers to body compartments that do not readily communicate with the vasculature such as peritoneal, pleural, or synovial cavities. Third spacing may occur in cases of insults such as surgery, trauma and infection. Although rarely termed this way, the intracellular and extracellular compartments represent the "first" and "second" spaces.
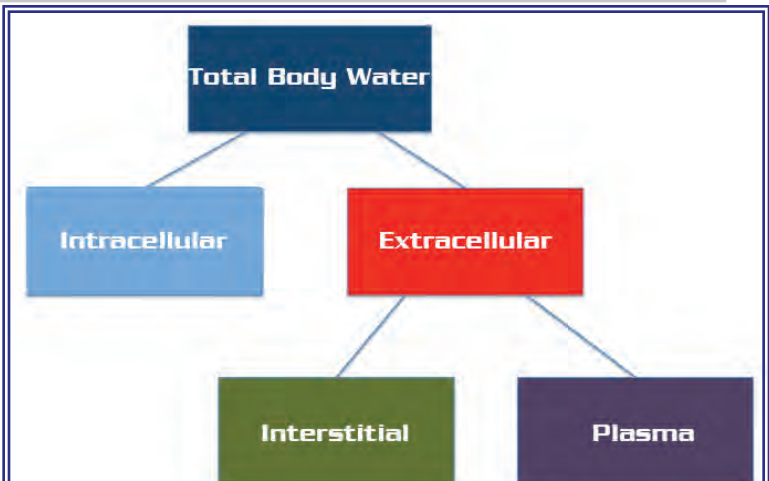
Figure 31.1 Proportions of Total Body Water. In the average 70kg man, TBW = 42 kg, ICW = 28 kg, ECW = 14 kg, Interstitial = 10.5 kg and Plasma = 3.5kg

What drives water movement between compartments?

Osmolality describes the number of osmoles per kilogram of solvent; osmolarity is the number of osmoles per liter of solution. Since the human body is comprised of mainly water, there is little difference between the two. For practical purposes, osmolality is easier to measure than osmolarity and is the laboratory value reported. Normal serum osmolality is 285-295 mOsm/kg. It can be estimated by the formula:

$$(Na^+ [mEq/L] \times 2) + (glucose [mg/dL] / 18) + (BUN [mg/dL] / 2.3).$$

Although the equation is estimating serum osmolality, one should keep in mind that this formula does combine both principles of osmolarity and osmolality (the use of 18 for glucose and 2.3 BUN converts to the values to mOsm/kg). Tonicity refers to "effective osmoles" which result in solute-free water moving across two compartments divided by a semi-permeable membrane. Net transcapillary fluid flux is determined mainly by the hydrostatic pressure gradient between the capillary lumen and the subendothelial space. Colloid osmotic pressure differences between the same two spaces have minimal impact on fluid exchange over a wide variety of physiologic conditions.[1]

What fluids do you administer?

Fluid options for administration include crystalloids, colloids, and blood products. Crystalloid solutions are the most commonly administered IV fluids. They include normal saline (NS), balanced electrolyte solutions such as Plasmalyte-A and Ringer's Lactate (LR) and dextrose containing solutions. Colloids are preparations of insoluble molecules dispersed throughout a water-based diluent. The perceived benefit to colloids is that they are more likely to stay intravascular. The general rule of thumb that three times as much crystalloid as colloid is required for equal intravascular volume expansion has been shown to be false and is more on the order of less than 1.6:1. Colloids are considered natural (albumin) or synthetic (gelatins, hydroxyethyl starches, and dextrans). The relative components of a number of commonly used solutions are presented in Table 31.1

Blood components are typically prepared as fractionated components rather than whole blood. One unit of packed red blood cells is about 250 ml in volume with a hematocrit of 70%. Fresh frozen plasma and platelets can be transfused contemporaneously in an attempt to approximate transfusion of whole blood. Definitive data regarding the optimal ratio of plasma to red cell transfusion during massive hemorrhage is currently lacking.

How do you assess the need for fluid?

Clinical assessment of the state of the extracellular fluid compartment is challenging. Detection of hypovolemia without shock is difficult even for the most seasoned physician as the history and physical exam provide limited information.[2] Profound changes in orthostatic vital signs may be helpful in the absence of confounding medications. Additionally, in the absence of ongoing fluid losses, a lack of peripheral or pulmonary edema with an expanded third space makes a low circulating blood volume likely.[3] Serum chemistries assaying acid-base status, renal function, or urine electrolyte concentrations may also be useful.

The optimal type of resuscitation fluid remains undetermined. Balanced electrolyte solutions may be associated with less renal injury than 0.9% sodium chloride solutions. Synthetic colloids have not been shown to improve outcomes and may be detrimental in critically ill patients. When a colloid solution is indicated, human albumin, rather than a synthetic colloid should be used. All colloids are contraindicated in patients with traumatic brain injury.

Critically ill patients are often anemic. With the exception of acute anemia resulting from active bleeding or hemorrhage, the transfusion threshold can be safely set at 7 g/dL with a post-transfusion goal of 7-9 g/dL.[4,5,6]

How do you diagnose and treat shock?

Shock is defined as a state of inadequate oxygen delivery to support aerobic metabolism. General signs of shock include hypotension, tachycardia and low urine output. The presence of a metabolic acidosis, hyperlactatemia, base deficit, or low mixed venous/central venous oxygenation saturation are further clues. A directed bedside assessment can be used to broadly categorize shock states as shown in Table 31.2.

Hypovolemic shock can occur from a variety of causes and includes hemorrhage, profound diarrhea, and severe dehydration. Regardless of etiology, correction of hypovolemic shock includes rapid replacement of intravascular volume until hemodynamic goals of resuscitation are met.

A highly effective protocol for management of hemorrhagic shock in a trauma patient has been developed and is clearly presented in the Advanced Trauma Life Support (ATLS) Guidelines. The guidelines provide recommendations for the initial stabilization and evaluation of the trauma patient. Primary fluid management includes the insertion of 2 large bore (16 gauge or larger) intravenous catheters in a peripheral vein or a 9 French central venous

Table 31.1 Composition of commonly used crystalloids and colloids

Solution	Na$^+$ (mEq/L)	K$^+$ (mEq/L)	Cl$^-$ (mEq/L)	Other Ions	Osmolality (mMol/L)	pH
Normal Saline (0.9% NaCl)	154	0	154		308	4.5-7.0
Lactated Ringers	130	4	109	lactate, calcium	273	6.0-7.5
Plasmalyte	140	5	98	magnesium, acetate, gluconate	294	6.5-7.6
D5W	0	0	0	dextrose	278	5.0
Albumin 5%	145	0	145		300	6.9
Albumin 25%	145	0	145		1500	6.9
HES 130/0.4 (Voluven®)	154	0	154		308	4.0-5.5
HES 450/0.7 (Hespan®)	154	0	154		309	5.9

catheter, control of bleeding, and a 2 liter fluid challenge. Transient and non-responders need blood products for volume and to control coagulopathy. An FFP/PRBC ratio greater than or equal to 1:1.5 is associated with lower mortality. Ultimately, source control is the most important intervention in traumatic hemorrhagic shock.[7]

Cardiogenic shock is caused by the heart's inability to pump effectively, whether due to intrinsic myocardial disease, arrhythmia or valvular disease. Diastolic heart failure is usually a "compliance" problem, whereas systolic heart failure is primarily a failure of the heart to pump. Management of cardiogenic shock often involves manipulating preload (diuresis and/or nitrates), afterload (vasopressors, ACE inhibitors, intra-aortic balloon pump), and/or contractility (inotropes). Pulmonary artery catheters have historically been used to help clinicians in the management of cardiogenic shock but its use has not been shown to improve survival.

Distributive shock is due to loss of vascular tone and/or increase in vascular permeability leading to hypotension and tissue hypoperfusion. Specific etiologies may include sepsis, anaphylaxis, fulminant hepatic failure, and endocrine dysfunction such as adrenal crisis or thyroid storm. Neurogenic shock is related to a loss of sympathetic tone from the spinal cord leading to flaccid vasculature, often with bradycardia, and is best treated with fluids, vasopressors, and inotropes. Septic shock is by far the most common form of distributive shock.

The Surviving Sepsis campaign recommends initial resuscitation targets of a CVP 8-12 mmHg, MAP ≥ 65 mmHg, UO ≥ 0.5 ml/kg/h, and central venous oxygen saturation greater than 70% for patients in severe sepsis and septic shock. Crystalloids are the fluid of choice with an initial challenge of at least 2 liters or 30 mL/Kg. Albumin may have a role only after substantial amounts of crystalloids are given. Synthetic colloids are contraindicated in these patients. Barring other indications for transfusion, a goal hemoglobin of 7-9 g/dL is adequate and FFP is not indicated, except in the presence of bleeding or planned procedures.[8]

Obstructive shock, which can be conceptualized as intra- or extra- cardiac obstruction to either inflow or outflow, may result from cardiac tamponade, tension pneumothorax, pulmonary embolism, or severe aortic stenosis. Administration of fluid is merely a temporizing measure, as correction of obstructive shock requires rapid correction of the underlying problem.

Table 31.2 Findings differentiating the 4 classic categories of shock

Type	Mean RAP (neck veins)	Mean LAP (lungs)	Stroke Volume (pulse volume)	SVR (skin)	Mixed Venous O2
Hypovolemic	↓, flat	↓, clear	↓	↑, cool/mottled	↓
Cardiogenic	↑	↑, rales	↓	↑, cool/mottled	↓
Distributive	↓, flat	↓, clear	↑↓	↓, warm/diaphoretic	↑
Obstructive*	↑	↓, clear	↓	↑, cool/mottled	↓

*Classic findings of a massive pulmonary embolism. Findings vary if the etiology is tension pneumothorax or cardiac tamponade.

This patient has septic shock. Hemodynamic resuscitation goals as described by the Surviving Sepsis Campaign guidelines should be targeted. Hypotension and tachycardia have further resulted in demand ischemia. Other etiologies of his shock including hemorrhagic and pulmonary embolism are less likely.

Fluid resuscitation with an initial bolus of 20-30 mL/kg is appropriate. Central access should be considered. A urinary catheter and arterial line should be placed. If the initial fluid bolus does not resolve his hypotension and tachycardia, a vasopressor should be started to maintain his mean arterial pressure greater than 65 mmHg. Although his hemoglobin is greater than 7 g/dL, a packed red cell transfusion may be appropriate, but only after other hemodynamic goals have been reached. Aggressive resuscitation, in conjunction with treatment of the infection, gives this patient his best chance at survival and optimal recovery.

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Questions

31.1 The use of colloid solutions in fluid management is preferred in which of the following patients?
- A. Acute traumatic brain injury
- B. Acute pancreatitis
- C. Septic shock
- D. None of the above

31.2 An elevated central mixed-venous oxygen saturation is classically found in which of the following conditions?
- A. Hemorrhagic shock
- B. Septic shock
- C. Cardiogenic shock
- D. Massive pulmonary embolism

31.3 Which of the following is the best indicator of hypovolemia
- A. Gastric tonometry
- B. Pulse pressure variation
- C. Stroke volume variation
- D. Orthostatic vital signs

32. Renal Replacement Therapy

Matthew J F Sigakis MD and Edward A Bittner MD PhD

Key Points

• Renal Replacement Therapy (RRT) is a common therapy provided in the ICU.

• RRT can be performed continuously (CRRT) or intermittently (IHD); one has not been demonstrated to be superior over the other.

• Although CRRT is preferred in hemodynamically unstable patients, the final modality will depend on physician preference and hospital resources.

• 3 major principles in RRT are ultrafiltration, diffusion, and convection.

A 72 year-old man is admitted to the ICU after open repair of a thoraco-abdominal aortic aneurysm. His postoperative course is complicated by acute kidney injury, respiratory failure and hypotension. On post-operative day (POD) # 3, renal replacement therapy is initiated via continuous veno-venous hemodialysis. After 1 week, there is improvement in his hemodynamics and he is transitioned to conventional intermittent hemodialysis. He is transferred to the floor on POD#9.

Introduction

Acute kidney injury (AKI) in the Intensive Care Unit (ICU) is common and can range from mild elevation in creatinine to anuric renal failure. Once a patient has developed severe AKI, the therapeutic options are limited with the mainstay of treatment being renal replacement therapy (RRT).

Indications for RRT

There is a paucity of evidence to guide the optimal time to initiate RRT. In most instances, the decision to initiate RRT is based on development of life threatening conditions (Table 32.1). There is no generally accepted azotemia threshold for RRT initiation. Once a decision to commence RRT is made, the components of the prescription include the modality, anticoagulation, and intensity of treatment.

Principles of RRT

RRTs are classified by the transport process used to remove solutes and toxins from the blood. All forms of RRT rely on the principle of allowing water and solute movement through a semipermeable membrane and then discarding the waste products, normally down the drain.

Ultrafiltration is the process by which the movement of water occurs across a semipermeable membrane due

Table 32.1 Indications for RRT

Primary	Secondary
Alcohol and drug intoxications	Endotoxic shock
Fluid management for oliguria/anuria	Acute hepatic failure
Hyperkalemia	Plasmapheresis (in lieu of)
Hypothermia	Severe dysnatremia
Metabolic acidosis (pH < 7.1)	Severe rhabdomyolysis
Rapidly climbing urea/creatinine	
Refractory fluid overload	
Uremia with acute signs of pericarditis, neuropathy, mental status changes or refractory bleeding	

to a trans-membrane pressure gradient.

Diffusion and *convection* are two processes by which solutes move across a semipermeable membrane (Figure 32.1).[3] Diffusion is the movement of solutes from an area of higher solute concentration to an area of lower solute concentration across a semipermeable membrane. Convection occurs when the trans-membrane pressure gradient drives water across a semipermeable membrane (ultrafiltration) and "drags" solutes with it. In this process, membrane pore diameter limits the size of the solutes that can pass though it.

Modalities of RRT

RRT modalities include intermittent hemodialysis, continuous renal replacement therapy, peritoneal dialysis and newer "hybrid" therapies, such as extended duration dialysis or sustained low-efficiency dialysis.

The distinguishing characteristics of these modalities include the fluid transport process (hemodialysis vs. hemofiltration), duration (intermittent vs. continuous) and membrane permeability.[4]

Fluid Transport Process (Figure 32.2)

Hemodialysis
Blood is pumped through an extracorporeal system where it is physically separated from a crystalloid solution (dialysate) by a semi-permeable membrane. Solutes move across the membrane along their concentration gradient from one compartment to the other by Fick`s laws of diffusion. For example, bicarbonate moves from dialysate to blood (higher concentration in dialysate) whereas urea and potassium move from blood to dialysate (lower concentration in dialysate). In order to maintain concentration gradients and, therefore, enhance the efficiency of the system, the dialysate flows counter-current to the flow of blood (i.e., they flow in opposite directions of each other). When removal of water is required, the pressure on the blood-side of the membrane is increased to force water molecules to pass into the dialysate. Hemodialysis is typically chosen for removal of small molecules < 500 Daltons and electrolytes (potassium,

lithium, urea) and fluid.

Hemofiltration
Blood is pumped through an extracorporeal system that incorporates a semi-permeable membrane. The hydrostatic pressure that is created on the blood-side of the membrane drives plasma across the membrane (ultrafiltration). Molecules that are small enough to pass through the membrane (typically <50,000 Daltons) are "dragged" across the membrane with the water by the process of convection. The filtered fluid (ultrafiltrate) is discarded and a replacement fluid is added in an adjustable (in volume and composition) fashion. Hemofiltration is typically used for moderate to large molecules (5,000 to 50,000 Daltons) such as cytokines and compliment.

Hemodiafiltration
A combination of dialysis and ultrafiltration, it has the benefits of both techniques but to a lesser extent than when the individual techniques are used on their own.

Slow continuous ultrafiltration
Used when the only requirement is water removal. It can remove up to 6 liters of fluid in a day. Solute removal is minimal.
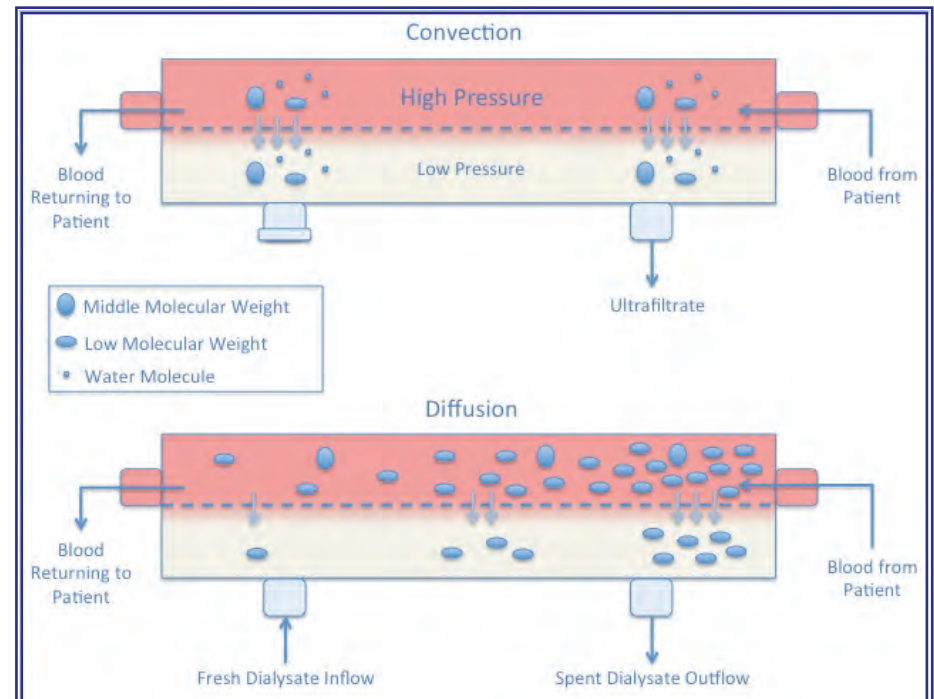

Figure 32.1 Transport of solutes across a semipermeable membrane by convection and diffusion. [Adapted from Tolwani, et al]
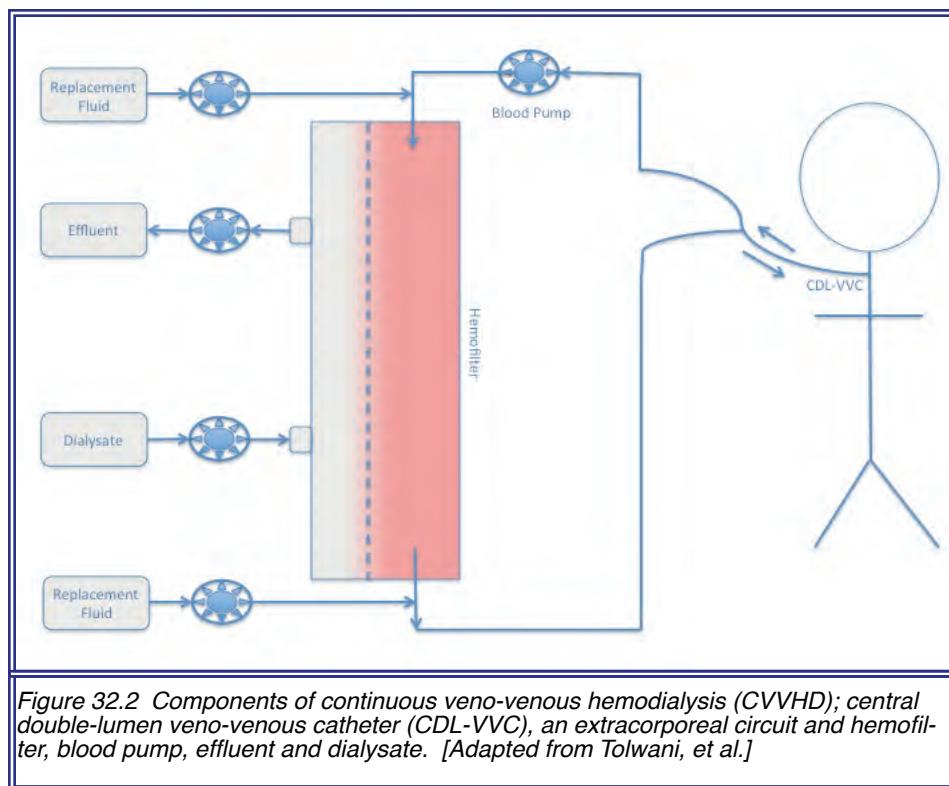
Figure 32.2 Components of continuous veno-venous hemodialysis (CVVHD); central double-lumen veno-venous catheter (CDL-VVC), an extracorporeal circuit and hemofilter, blood pump, effluent and dialysate. [Adapted from Tolwani, et al.]

Duration

Intermittent Hemodialysis (IHD)

Traditionally, severe AKI has been managed with IHD that is empirically delivered over 3-5 hours per session, 3-6 sessions per week. Decisions regarding dialysis session duration and frequency are based on patient metabolic control, volume status, and presence of hemodynamic instability. A major advantage of IHD is rapid solute and volume removal. In addition, IHD usually has a decreased need for anticoagulation compared with other types of RRT because of the faster blood flow rate and shorter duration of therapy. The main disadvantage of IHD is the risk of hypotension resulting from rapid electrolyte and fluid removal. Rapid solute removal from the intravascular space can result in cerebral edema limiting this modality for patients with head trauma or hepatic encephalopathy.

Continuous veno-venous hemodialysis (CVVHD), hemofiltration (CVVH) and hemodiafiltration (CVVHDF)

Continuous in duration with lower flow rates, there tends to be less hemodynamic disturbance. In addition, solute and electrolyte removal occur over a longer period of time resulting in less acute osmolar changes. These modalities require continuous anticoagulation and are more expensive to utilize than IHD. Components of CRRT include central access with a large bore (at least 10 French) double-lumen venous catheter, an extracorporeal circuit with filter, a blood pump, and an effluent pump (Figure 32.2).[3]

Sustained Low-Efficiency Dialysis (SLED) and Extended Day Dialysis (EDD)

SLED and EDD are dialytic modalities that use conventional hemodialysis machines. These machines are able to provide slower blood and dialysate flows. They combine the advantages of CVVH and IHD to allow for improved hemodynamic stability through gradual solute and volume removal as in CRRT while providing high solute clearances as in IHD. These treatments can be performed intermittently based on the needs of the patient and do not need to be interrupted for various beside diagnostic and therapeutic procedures that may be required in critically ill patients.

Membrane permeability

Low flux (Cellulose based)

Low permeability to water and is typically used for hemodialysis.

High flux (Synthetic)

High permeability to water and is typically used for hemofiltration.

Other forms of RRT

Peritoneal Dialysis (PD)

Dialysate is placed into a patient's abdomen where the peritoneum is used as a membrane across which fluids and solutes (electrolytes, urea, glucose, albumin and other small molecules) are exchanged from the blood. The dialysate is removed and replaced periodically. High volume and continuous PD does exist. It is rarely used in the ICU to treat AKI.

Arterio-venous RRT

Used to treat AKI via temporary central arterial (outflow) and venous (inflow) catheters. Arterio-venous RRT is associated with greater vascular morbidity than veno-venous access and depends on an adequate arterial blood pressure to drive blood flow. As a result, it has largely been replaced by veno-venous RRT.

Arterio-venous fistula or graft

Surgically created communication between the native artery and vein in an extremity, allowing blood to bypass capillaries and flow more freely. A 14-gauge needle is inserted in the vein or graft in a location that is proximal to the artery. This access diverts blood to the dialysis machine. A second 14-gauge needle is inserted in the vein or graft in a location that is distal to the artery that allows dialyzed blood to return to the patient (Figure 32.3). A patent graft typically has a palpable or auscultatory thrill. An arterio-venous fistula or graft cannot be used for CRRT as it is nearly impossible to the secure the needles to prevent dislodgement.

Modality and Outcome

Studies which compare modalities have failed to demonstrate any survival advantage for continuous versus intermittent therapy. However, these studies have been limited by issues related to study design, such as exclusion of patients with hemodynamic instability, improper randomization, differences in baseline characteristics between study populations and high crossover rates between modalities. In the absence of data suggesting benefit of one over another, choosing a modality should be guided by the patient's clinical status, local medical and nursing expertise, and availability of RRT modalities.

Transitions in modality are common due to the changing needs of patients during their hospital course.

Technical considerations

Access
- Central venous access via double lumen catheter (11–14 Fr)
- Internal jugular or femoral vein is preferred.
- Subclavian vein is used with caution given propensity for stenosis and inability to compress in the event of hemorrhage.
- The proximal port removes blood and it is returned through the distal lumen at the catheter tip to minimize recirculation of filtered blood.
- Tunneled catheters can be placed if dialysis is to be prolonged.

Anticoagulation
- RRT can activate the clotting cascade given contact between blood and non-biological surface.
- Anticoagulation is typically used for both intermittent and continuous forms of RRT.
- Most common anticoagulant is unfractionated heparin; citrate is a common second-choice agent (see below).
- Other approaches exist to minimize clotting within the extracorporeal circuit and can be utilized when there is increased risk of bleeding (see below).

Table 32.2 Drugs cleared by RRT	
Barbiturates	Antibiotics:
Ethylene glycol	- Aminoglycosides
Lithium	- Carbapenems
Metformin	- Cephalosporins
Methanol	- Metronidazole
Salicylates	- Penicillins

Resources
- CRRT is more labor intensive and more expensive than IHD.
- Clinician experience may be important.

Pharmacokinetics

- Drugs are more readily cleared by RRT if they are water-soluble and not highly protein-bound. As a patient's protein level falls, the free fraction of the drug increases causing greater clearance. (See Table 32.2)
- Drugs given between intermittent periods of dialysis will not be cleared until a subsequent session.

Patient factors impacting RRT

Increased risk of bleeding
- Anticoagulation may be needed for IHD or CRRT to prevent clotting of the filter.

- Currently, heparin is administered systemically or pre-filter, if needed.
- Intermittent flushing with saline or pre-filter hemodilution may be used as an alternative to anticoagulation to prevent filter clotting.
- Short runs of dialysis (<2 hours) may be performed without anticoagulation.
- Runs can be extended for patients with thrombocytopenia or coagulation disorders.
- PD can be an alternative RRT modality for patients with an extreme mortality/morbidity risk from anticoagulation.
- RRT without anticoagulation is common in patients with coagulation abnormalities.
- Regional heparin/protamine anticoagulation:
No longer recommended. Protamine administration can result in a number of severe side effects including anaphylaxis, hypotension, cardiac depression, leukopenia and thrombocytopenia. There is also risk of a rebound anticoagulant effect, due to the shorter half-life of protamine compared with heparin.

Figure 32.3 Typical access for chronic hemo-dialysis. [http://commons.wikimedia.org/wiki/File:Fistola_radiocefalica.svg, licensed under Cretative Commons Attribution]

Heparin-induced thrombocytopenia
- Heparin anticoagulation is contraindicated; therefore the dialysis system must also be heparin free.
- Regional citrate anticoagulation:
Citrate is infused into the blood of the afferent limb, which binds to ionized calcium inhibiting coagulation. Citrate is removed during the dialysis process, but may enter the systemic circulation leading to hypocalcemia. Intravenous calcium supplementation is frequently required. In patients with reduced citrate metabolism, such as in liver failure and in patients with pre-existing hypocalcemia and/or hypomagnesemia, extra caution is warranted.
- Argatroban, a direct thrombin inhibitor, is sometimes used (off label use):
Argatroban is hepatically metabolized and safe in patients with intact hepatic function. Argatroban has a short half-life of approximately 35 minutes in patients with end-stage kidney disease (ESKD). Monitor with activated clotting and partial thromboplastin times (NOT PT and/or INR).

Hemodynamic instability
- Several precautions must be taken including less aggressive ultrafiltration, longer runs, and use of blood volume measurements to guide ultrafiltration.
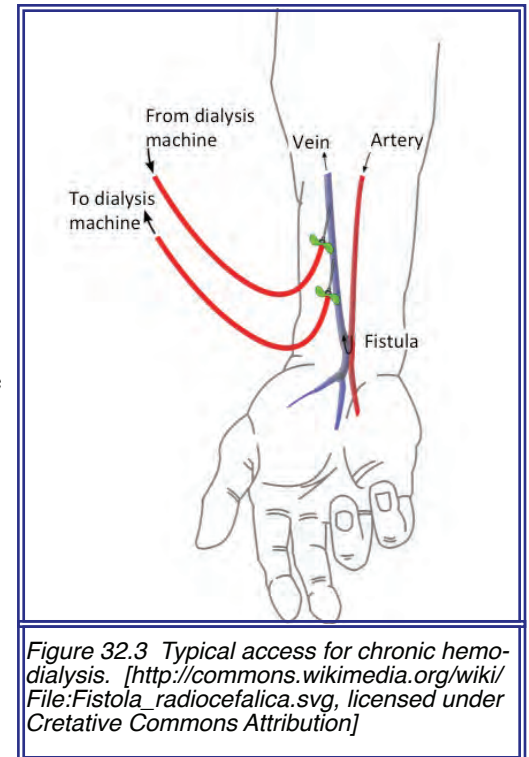
• CRRT, when available, is preferred over IHD because there is less hemodynamic disturbance.

• RRT may help to stabilize the hemodynamic status by correction of blood pH.

Cerebral edema or intracranial hypertension

• CRRT is preferred over intermittent RRT:

There are less frequent decreases in systemic blood pressure that could lead to cerebral ischemia. In addition, there are less frequent tonicity/osmolarity changes of the systemic circulation that can worsen cerebral edema.

Traumatic brain injury with risk of intracranial bleed

• Consider RRT without anticoagulation.

• PD is an option. However, increased abdominal pressure from dialysate may translate into increased intracranial pressure. In addition, intra-abdominal hypertension may decrease systemic preload and increase afterload, leading to lower blood pressure and decreased cerebral perfusion pressure.

Hyponatremia

• Chronic hyponatremia corrected rapidly may cause osmotic demyelination syndrome.

• Renal replacement fluid with reduced sodium concentration may be used. However, this may also decrease plasma chloride and/or bicarbonate concentrations. Frequent monitoring of sodium, bicarbonate, and pH is warranted.

Elevated serum urea

• Urea >175 mg/dl

• Risk of dialysis disequilibrium syndrome, a neurological condition characterized by nausea and headache. The mechanism is thought to be a decrease in serum osmolarity (due to decreased serum urea during dialysis), with slower equilibration of intracranial urea concentration leading to cerebral edema. Preventative measures to maintain serum osmolarity include decreasing the dose of dialysis, slowing treatment time, or initiation of RRT with ultrafiltration followed by dialysis.

Table 32.3 Complications of RRT	
Air emboli	Catheter related:
Altered drug kinetics	- Bleeding
Blood loss	- Infection
Electrolyte imbalances	- Line disconnection/malfunction
Hemodynamic instability	- Pain
Hypothermia	- Pneumothorax
Platelet consumption	- Thrombosis
Anticoagulation related: bleeding, HIT	

Acute liver failure or acute on chronic liver failure

• AKI may be secondary to hepatorenal syndrome.

• Cerebral edema, increased intracranial pressure and hyponatremia may be present.

• CRRT with special attention for hemodynamic stability and maintenance of cerebral perfusion pressure is warranted.

Complications

Vary in nature relating to the dialysis catheter, the extracorporeal circuit, and therapy, itself. (See Table 32.3)

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Questions

32.1 The following statements about Continuous Renal Replacement Therapy (CRRT) are true, except:
A.   CRRT is more cost effective than IHD
B.   CRRT is preferable to IHD in patients with acute brain injury or cerebral edema.
C.   There is no known survival benefit using CRRT versus IHD.
D.   CRRT is preferred in patients who have an unstable cardiovascular status.

32.2 The following statements regarding RRT are true, except:
A.   Internal jugular or femoral vein central access is preferred over subclavian vein for dialysis catheter placement.
B.   Water-soluble drugs are more easily removed by RRT than protein-bound drugs.
C.   Regional citrate anticoagulation can be used during RRT for patients with HIT.
D.   There is an established role for RRT in the ICU for treatment of septic shock in patients with normal renal function.

33.3 The following statements comparing dialysis with filtration are true, except:
A.   Filtration is more effective than dialysis at removing water.
B.   A low flux membrane is typically used for filtration and a high flux membrane is typically used for dialysis.
C.   Filtration in more effective than dialysis at removing cytokines and dialysis is more effective at removing small molecules.
D.   Filtration depends on convection and dialysis depends on diffusion.

Section 8: Hematology and Transfusion

Chapters

- **Thromboembolic Disease**
- **Coagulopathies in the ICU**
- **Transfusion Therapy**
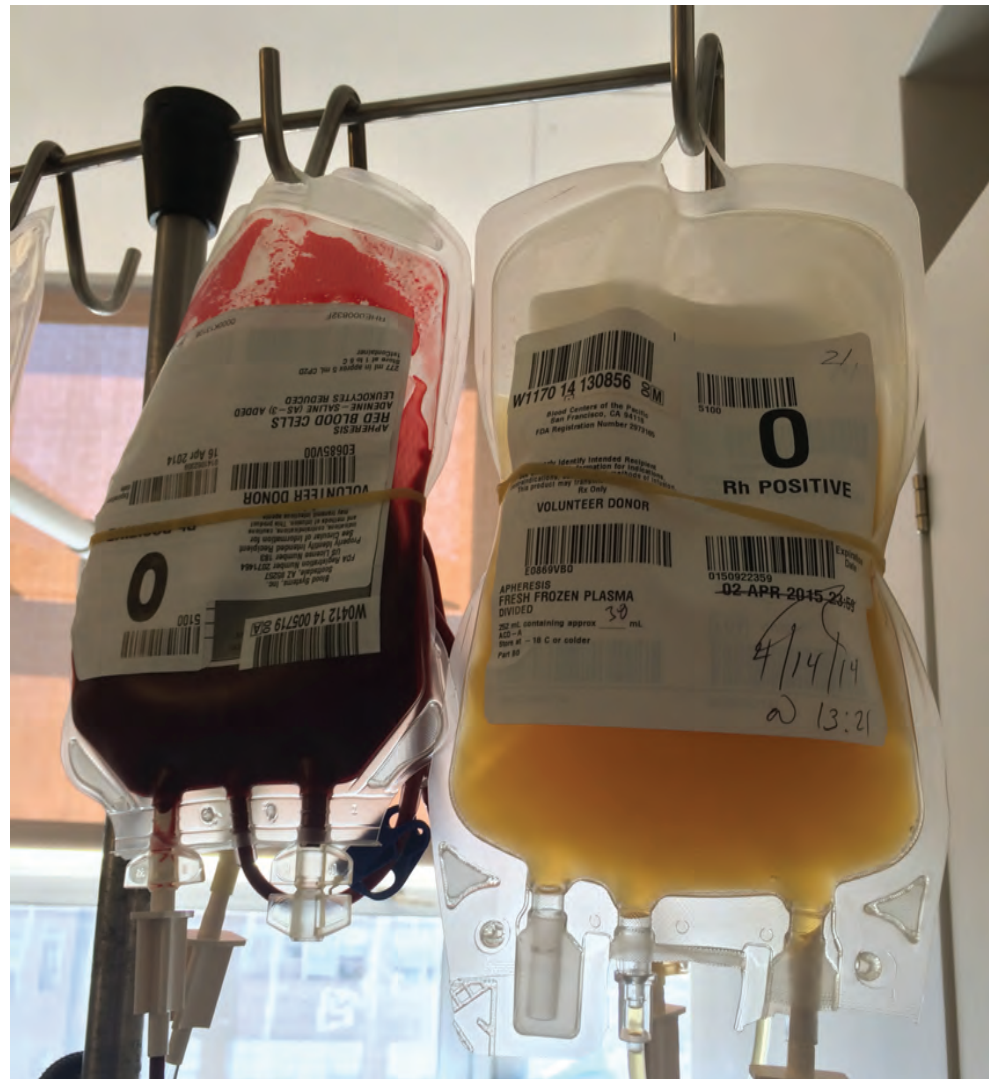
33. Thromboembolic Disease

Tracy Jobin McGrane MD

Key Points

• **The clinical presentation may vary from a patient being asymptomatic to one in shock, making it a challenging diagnosis if it is not thought of as part of the differential diagnosis.**

• **Diagnostic workup corresponds to the severity of the patient's clinical presentation.**

• **Anticoagulation is the mainstay of therapy.**

• **Hemodynamically unstable patients may require thrombolysis or surgical embolectomy.**

A 32 year old female is admitted to the neurological intensive care unit status post a craniectomy for resection of a frontal lobe high grade glioma. Three days after admission, she is tachycardic and complains of shortness of breath. Her physical exam is otherwise unremarkable. Her chest radiograph (CXR) and arterial blood gas analysis are normal. Later that day, she develops sudden respiratory distress with hypotension and hypoxia. A helical computed tomography (CT) scan reveals a pulmonary embolus.

INTRODUCTION

Venous thromboembolism (VTE) is a pathologic clot formation within the veins and can refer to either a deep venous thrombosis (DVT) or a pulmonary embolism (PE). It is estimated that greater than one million people in the United States are affected by a PE each year, with approximately 10-20% resulting in death, but the true incidence is believed to be much higher based on post mortem data. The majority of preventable deaths associated with PE are related to a missed diagnosis rather than a failure of existing therapies. Many screening studies for venous thromboembolism (VTE) lack sensitivity and specificity. Several noninvasive diagnostic techniques have been developed to improve the accuracy of the diagnosis; however, no single noninvasive diagnostic test is sensitive or specific enough for the diagnosis in all patients. The cornerstone of management involves identification of high risk groups and treatment with adequate prophylactic measures.

Epidemiology

  A. Exact incidence unknown but studies estimate more than one million cases in the US each year.

  B. The majority of VTE deaths are caused by PE.

  C. Initial clinical presentation is sudden death in approximately 20% of all cases.

  D. Mortality of untreated PE is approximately 30%; once diagnosed and treated, mortality is 2.5%.

  E. Risk Factors for VTE

    1. History of VTE

    2. Age > 40 yr

3. Surgery
4. Prolonged immobility
5. Cerebrovascular accident
6. Congestive heart failure
7. Malignancy
8. Trauma
9. Obesity
10. Pregnancy or recent delivery
11. Estrogen therapy
12. Inflammatory bowel disease
13. Inherited or acquired defects in blood coagulation factors

Pathophysiology

A. Virchow's triad: venous stasis, hypercoagulable state, and vascular endothelial injury

B. Approximately 50% of patients with a VTE will have more than one risk factor

Prophylaxis

A. Pharmacologic agents
1. Heparins
   a. Unfractionated heparin-monitoring not needed for prophylaxis
   b. Low molecular weight heparin (LMWH)-monitoring: not needed
     i. Recent meta-analysis has shown LMWH to be superior to unfractionated heparin in preventing PE.
   c. Complications
     i. Bleeding
     ii. Thrombocytopenia–secondary to immune IgG-mediated response; may lead to arterial thrombosis
     iii. Resistance to heparin–antithrombin III deficiency
     iv. Osteoporosis–occurs in approximately 30% treated with long-term unfractionated heparin therapy
2. Vitamin K antagonist
   a. Warfarin
   b. Complications
     i. Bleeding
     ii. Skin necrosis–in patients with protein C or S deficiency
B. Mechanical agents
1. Early ambulation, leg elevation, physiotherapy
2. Graduated compression stockings
3. Intermittent pneumatic compression
4. Prophylactic IVC filter–if anticoagulation contraindicated or patient has VTE recurrence despite adequate anticoagulation

Diagnosis of VTE/PE

A. Clinical presentation-extremely varied ranging from asymptomatic to any of the symptoms below
  1. VTE–limb edema/pain, differential limb circumference, Homan's sign, distended collateral veins, increased temperature if infection present
  2. PE–dyspnea, pleuritic pain, tachypnea, tachycardia, hypoxemia, hypocarbia, hemoptysis, infiltrate on CXR, or sustained hypotension without an obvious cause
B. Clinical probability assessment
  1. Suspected PE based on clinical presentation and risk factors
     a. Clinical judgment is heavily weighted in most diagnostic algorithms
     b. Clinical probability tools such as Wells Criteria, Geneva Score and Pulmonary Embolism Severity Index (PESI) help stratify patients based on probability of PE
C. Diagnostic workup
  1. Hemodynamically stable
     a. Low or intermediate clinical probability → check D-Dimer (usually omitted in hospitalized patients because specificity is reduced in this population)
        i. D-Dimer normal → PE is ruled out
        ii. D-Dimer elevated → proceed with CTA to either rule out or confirm diagnosis (if this is not available or if patient has chronic kidney disease or patient has allergy to contrast dye, ventilation-perfusion scanning is an acceptable alternative)
     b. High clinical probabililty → proceed with CTA
  2. Hemodynamically unstable
     a. If safe to transport, proceed with CTA, if available, or echocardiography if CTA not available
     b. If patient unsafe to transport and high clinical probability, proceed with transthoracic or transesophageal echocardiography to evaluate for right ventricular (RV) dysfunction to either rule out or confirm diagnosis of PE
        i. rarely a thrombus can be seen within the pulmonary arteries or RV
D. Diagnostic options
  1. Pulmonary angiography–considered the gold standard but is rarely performed today
     a. Requires expertise in performance and interpretation, is invasive, and has associated risks
     b. Usually reserved for patients with chronic thromboembolic pulmonary hypertension
     c. Comparable outcome results between pulmonary angiography and CTA of approximately 1% VTE rate within 6 months
  2. Contrast enhanced helical CT scan
     a. Reported sensitivity ranges from 57-100% and its specificity ranges from 78-100%
     b. Sensitivity and specificity vary with the location of the emboli, ranging from 90% for emboli involving the main and lobar pulmonary arteries to much lower rates for segmental and subsegmental pulmonary vessels
     c. A normal CT scan may indicate a substantially reduced likelihood of embolism but negative predictive value is lower than with a negative V/Q scan
  3. Ventilation perfusion (V/Q) scan

a. Previously had a central role in the diagnosis of embolism; can be a valuable tool when CTA contraindicated and the results are definitive

b. A normal scan rules out the diagnosis of embolism, and a high probability one is strongly suggestive of embolism

c. Large trials have demonstrated that most patients with suspected PE who undergo V/Q scan do not have findings that are considered definitive

d. High clinical suspicion and high probability lung scan: PE in 96%

e. Low clinical suspicion and low probability lung scan: PE in 4%

f. Patients must have a normal chest xray and normal ventilation patterns for this exam.

4. Echocardiography

a. Massive PE is associated with right ventricle (RV) enlargement, RV free wall hypokinesis with preservation of apical contractility, dilation of pulmonary arteries, and elevated RV pressure.

b. According to the International Cooperative Pulmonary Embolism Registry, RV hypokinesis predicted an increased risk of death within 30 days in patients with SBP > 90 mm Hg. 30 day survival rates in patients with or without RV hypokinesis were 84% and 91% respectively.

5. Magnetic Resonance Angiography/Venography (MRA/MRV)

a. Shown to have insufficient sensitivity and a high rate of technically inadequate images when used for diagnosing PE (PIOPED III)

6. Review of other diagnostic workup

a. Electrocardiogram

i. The classic S1Q3T3 pattern (deep S-wave in lead I, Q-wave in lead III, and inverted T-wave in lead III) suggests right heart strain and should prompt consideration for PE work up

ii. Neither sensitive nor specific for PE; this pattern is only seen in a small percentage (approximately 10%) of patients with a PE

b. ABG

i. Previous studies have shown that a PE cannot be excluded with a normal alveolar-arterial gradient

c. CXR

i. May see ipsilateral elevation of the diaphragm on affected side, wedge-shaped infiltrate, focal oligemia, or an enlarged right descending pulmonary artery but these are neither sensitive nor specific

d. D-dimer

i. Endogenous marker for fibrinolysis

ii. Highly sensitive but nonspecific screening test for suspected VTE

iii. Elevated levels present in nearly all patients with VTE but can also be elevated with advance aged, pregnancy, trauma, recent surgery, inflammation, and cancer

e. Troponin

i. Elevated level not specific for PE

ii. Elevated level in presence of PE correlates with worse RV function

iii. Normal level has a 97-100% negative predictive value for in-hospital mortality

f. Brain Natriuretic Peptide (BNP)

i. Released from cardiac ventricular cells in response to high ventricular filling pressures; is an indicator of myocardial wall stress and hypoxia

ii. In one series, serum BNP was elevated in 80% of patients with acute PE and significant RV overload

E. Diagnosis of DVT

1. Contrast venography

a. The reference standard for the diagnosis of VTE

b. Noninvasive tests have supplanted the venogram

2. Impedance plethysmography (IPG)

a. Overall sensitivity and specificity of 83% and 92% respectively

b. False positive results with tensing of the leg muscles, reduces arterial flow and compression by an extravascular mass

3. Ultrasonography with color Doppler flow (duplex scan)

a. Sensitivity for DVT is 97%; specificity is 99%

b. Does not identify deep pelvic DVT

c. Cannot distinguish between occlusion from external pressure vs. thrombosis

d. Less sensitive in identifying asymptomatic, isolated calf vein and recurrent thrombosis

e. Predicted value is greater than that of IPG

Treatment

A. Local measures–elevation of extremity, warm compresses; to be used as adjunct to other measures

B. Anticoagulation (should begin before diagnostic studies if PE is intermediate or high probability)

1. Unfractionated heparin infusion-adjusted dose

a. Adjust to keep PTT ≥1.5 - 2.0 times control

b. Follow with warfarin within 24 hours; continue warfarin for at least 3 months

2. LMWH–fixed dose, subcutaneous (SC) regimens proven as effective treatment for VTE and PE, usually not monitored

3. Direct thrombin inhibitors-adjusted dose

a. Does not require antithrombin III cofactor

b. Used mainly for patients with heparin induced thrombocytopenia

c. Can have unpredictable anticoagulation, need for intensive lab monitoring, and potential drug-drug interactions

C. Thrombolytic therapy

1. Considered in patients deteriorating despite aggressive medical therapy; and normotensive patients with evidence of RV impairment.

2. Agents: Streptokinase; Urokinase; Alteplase.

D. Pulmonary embolectomy

1. For hemodynamically unstable patients with PE and in whom thrombolysis is contraindicated

2. Historically accompanied by a high mortality rate (up to 30%)

E. Inferior Vena Cava filter (IVC)

1. For patients who have contraindications to anticoagulant therapy or an inability to be adequately anticoagulated

2. Higher long term incidence of DVT but lower risk of PE
3. Retrievable IVC filter should be considered and removed as soon as possible to avoid endothelialization

CONCLUSIONS and RECOMMENDATIONS

VTE can be difficult to diagnosis due to its varied clinical presentation. Suspected PE in the stable critically ill patient should receive a CTA, unless contraindicated. If patient is unstable, consider urgent echocardiogram to rule out right ventricular strain or anticoagulate until stable enough for diagnosis to be obtained. Consider thrombolytic therapy in patients with PE and rapid deterioration or pulmonary embolectomy for unstable patients in whom thrombolysis is contraindicated.

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Questions

33.1 A 76-year-old man is 5 days post intracranial hemorrhage and develops dyspnea with pleuritic chest pain. Vitals: T = 38.6C, BP - 82/48, P = 125. CXR and ECG are unrevealing. ABG on room air shows: pH = 7.48, $PaCO_2$ = 32, PaO_2 = 72. What should be the next step?
   A. Intravenous heparin and no further diagnostic testing.
   B. Intravenous heparin followed by thrombectomy.
   C. Echocardiogram followed by possible embolectomy.
   D. CTA followed by intravenous heparin.
   E. Pulmonary arteriography.

33.2 A 58-year-old woman with renal failure develops acute dyspnea 7 days after hip replacement surgery. She has a history of 90 pack-years of smoking, and has received heparin, 5000 IU SQ Q12 hrs since her admission. Which one of these measures is most appropriate at this point?
   A. Discontinue heparin, as the dyspnea may be a complication of therapy.
   B. Obtain a pulmonary arteriogram, because a V/Q scan is unreliable in heavy smokers.
   C. Obtain a V/Q scan, then anticoagulate if scan is high probability.
   D. Anticoagulate with IV heparin (PTT ≥1.5 normal), then start warfarin in 5 to 7 days.
   E. Obtain a CTA, then anticoagulate if scan is high probability.

33.3 Which one of the following statements is true about the initial presentation/diagnosis of acute PE?
   A. Normal findings on ABG exclude the possibility of PE.
   B. Absence of elevated hemidiaphragm on CXR excludes possibility of PE.
   C. CTA is considered the gold standard for diagnostic testing of PE.
   D. Hormone replacement therapy in postmenopausal women is a risk factor for venous thromboembolism.
   E. Patients with clinically significant PE have characteristic manifestations that suggest its presence.

34. Coagulopathies in the ICU

Nicholas Pesa MD and John Klick MD

Key Points

• Coagulation is an incredibly complex and elegant system that must be understood well in order to recognize and treat the coagulopathic ICU patient.

• There are numerous causes of hyper- and hypocoagulability that can overlap and coexist in the ICU patient.

• Antithrombotic agents are useful pharmacological agents in the ICU patient but must be understood well for safe use.

• Pharmacological agents promoting hemostasis can be vital in the hemorrhagic patient and must be considered in lieu of/in addition to blood product transfusion.

A 72 year-old man is taken emergently to the OR from the cath lab in cardiogenic shock. He had received ticagrelor, an allosteric ADP receptor antagonist, in the cath lab and angiography revealed severe triple vessel disease including a 95% left main coronary artery occlusion, at which point he was rushed to the OR. After CABG while attempting to wean off cardiopulmonary bypass, severe right ventricular dysfunction was encountered, prompting a return to CPB and placement of an Abiomed right ventricular assist device. He received 8 units of PRBC in the OR, as well as 5 units of FFP, 2 units of platelets, and 2 units of cryoprecipitate. He is on multiple inotropic and vasopressor agents. His first hour in the ICU he has over 300 cc of sanguineous output from the chest tubes. His first hematocrit is 19 in the ICU.

There is a constant balance in any given patient between hemostasis, thrombosis, and hemorrhage. Critical illness, organ dysfunction, physiologic insults, and medications can all tip this balance in one direction or the other. Knowing which variables to target and prioritize can help achieve hemostasis in the coagulopathic patient. Venous thromboembolism and transfusion are discussed separately in this manual.

Physiology of Coagulation

Coagulation is a complex interplay of multiple variables, initially triggered by tissue injury (Figure 34.1). Abnormalities in the coagulation cascade are commonly encountered in the ICU, and an understanding of the complexity of the coagulation pathways is essential in proper management of the ICU patient.

Acquired Coagulopathies

A. Hypocoagulable States

1. Factor Deficiencies

Hepatic dysfunction, vitamin K deficiency, biliary obstruction, and other nutritional deficits can lead to various factor deficiencies. For example, in the case of Vitamin K deficiency, levels of factors II, VII, IX, and X along with Protein C, Protein S, and Protein Z are reduced, as they are dependent on Vitamin K for synthesis, causing an overall hypocoagulable state.
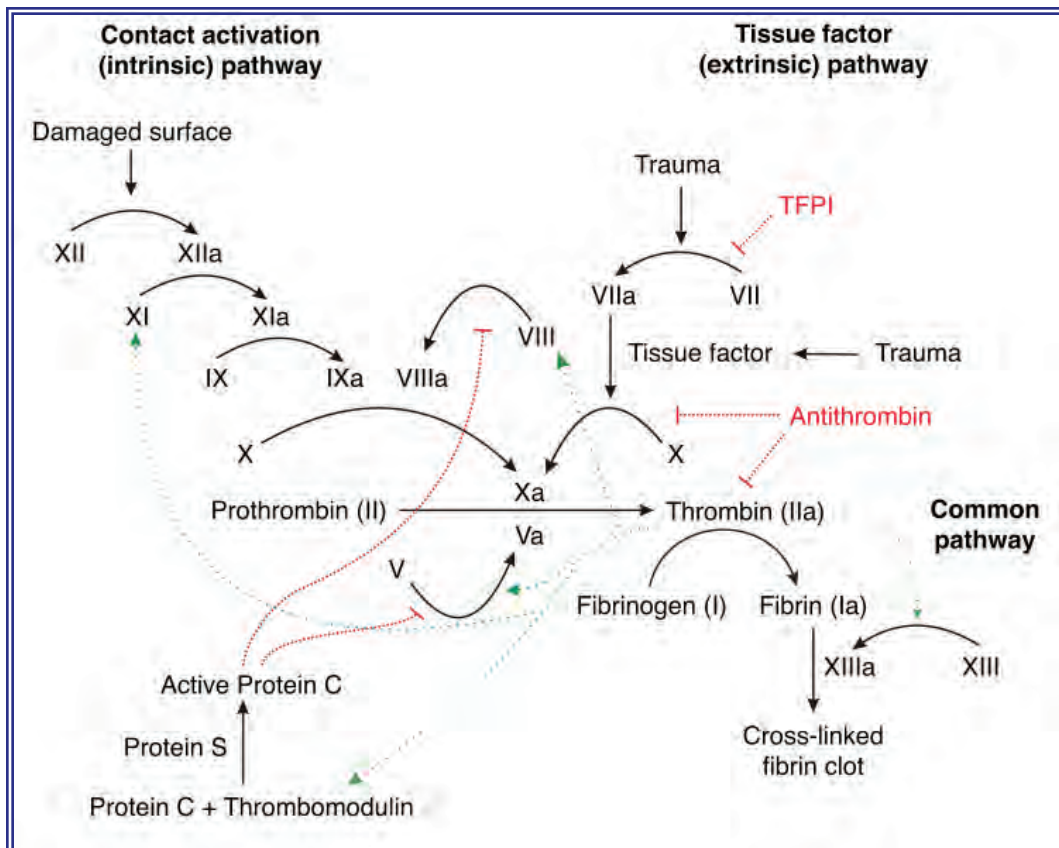
Figure 34.1 The Coagulation Cascade. [http://en.wikipedia.org/wiki/File:Coagulation_full.svg]

2. Consumptive Coagulopathies

Disseminated Intravascular Coagulation (DIC) is a pathological activation of the coagulation cascade that results in widespread thrombosis and subsequent depletion of the various proteins necessary for normal coagulation. Thrombocytopenia, thrombin-induced factor consumption, and plasmin generation thus result in a hypocoagulable state.

3. Platelet Dysfunction and Deficiency

In addition to the myriad of pharmacological agents that affect platelet function (as discussed below) there are also many pathological states that can lead to platelet function inhibition and/or thrombocytopenia. The most commonly encountered in the critically ill patient include hypothermia, uremia, acidosis, and extracorporeal circulation (such as hemodialysis, cardio-pulmonary bypass, ECMO, or ventricular assist devices.

4. Hemodilution

In the patient requiring massive transfusion, transfusion of packed red blood cells without the appropriate additional transfusion of fresh frozen plasma, platelets,

cryoprecipitate, and/or factor concentrates will result in a relative dilution of the native coagulation proteins. Large-volume crystalloid/colloid resuscitation can have the same result.

B. Hypercoagulable states

1. HIT

Heparin-induced thrombocytopenia is the abnormal thrombocytopenia that results from administration of one of the various forms of heparin. The underlying pathology of this disease is the formation of abnormal antibodies in response to heparin that bind and activate platelets. This activation leads to thrombosis and platelet consumption.

2. Hypercoagulability of Malignancy

Malignancy can result in a prothrombotic state through tumor cell secretion of procoagulants and inflammatory cytokines, physical interaction of tumor cells and blood, disruption of the normal endothelial layer, acute phase reactant production, and inflammation from necrosis.

3. Pregnancy

Normal pregnancy is accompanied by increases in fibrinogen and thrombin (promoting thrombosis) and increased plasminogen activator inhibitor levels (impairing fibrinolysis). Pregnancy can also result in a pathological state of HELLP (hemolysis, elevated liver enzymes, low platelets) that can cause spontaneous hepatic hemorrhage and even maternal death.

4. Trauma

Major trauma induces a hypercoagulable state, which is thought to arise from increased and persistently elevated levels of thrombin in addition to dysregulation of its breakdown.

5. Sepsis

Sepsis causes a systemic response to infection that includes a robust inflammatory response. This inflammatory response includes increased levels of cytokines that can activate the coagulation cascade and increased levels of procoagulants such as thrombin.

6. Other

Hyperhomocysteinemia, TTP/HUS, nephrotic syndrome, and antiphospholipid antibody syndrome are other important hypercoagulable states.

Congenital coagulopathies

A. Hypocoagulable States

1. Hemophilia A

Hemophilia A is a sex-linked recessive deficiency of factor VIII that can have a wide range of severity that relate to factor VIII activity level. Mild hemophiliacs can use DDAVP to stimulate release of factor VIII while treatment of the hemorrhaging patient involves replacement of factor VIII with traditional FFP/cryoprecipitate or with newer factor VIII concentrates. In cases of severe hemorrhage or for patients with factor VIII inhibitors, NovoSeven can be used as an alternative (discussed below).

2. Hemophilia B

Hemophilia B is a sex-linked recessive deficiency of factor IX that has a similar clinical presentation to hemophilia A. Replacement of factor IX with concentrates is the indicated treatment in this patient population.

3. vWD

Von Willebrand Disease is the most common hereditary coagulopathy (but can also be acquired) that results from a qualitative and/or quantitative deficiency of von Willebrand factor (vWF). A bleeding tendency results that is more prominent in tissues having high blood flow shear stress, where vWF is most active.

4. Other Rare Disorders

The various dysfibrinogenemias, factor XIII deficiency, the rare factor deficiencies (V, VII, X, XI), and prothrombin deficiency (Factor II) are also important considerations in the differential diagnosis of the coagulopathic patient.

B. Hypercoagulable States

1. Factor V Leiden

Factor V Leiden deficiency is an autosomal dominant point mutation in the gene coding factor V that results in production of a mutant factor V that is resistant to cleavage by protein C. It is frequently associated with DVTs and is found in up to 20% of patients presenting with their first DVT.

2. Antithrombin III Deficiency

As ATIII is the most potent inhibitor of coagulation, deficiency of ATIII results in a much higher thrombotic risk than factor V Leiden or Protein C/S deficiencies. A homozygous genetic defect in ATIII production is not compatible with life.

3. Protein C and S Deficiency

Protein C deficiency is a heterozygous genetic defect that results in lack of inhibition of factors V and VIII. This causes an increased risk of VTE. LMWH, heparin, or warfarin can be used for prophylaxis. Protein S deficiency is more rare and results in a mild increase in hypercoagulability.

Antithrombotic Agents

A. Unfractionated Heparin (UFH)

UFH forms a complex with antithrombin causing inhibition of factor II (prothrombin) activity and activated factor X activity. It causes a dose dependent prolongation of both the aPTT and the activated clotting time (ACT). Half-life of the anticoagulant effect is approximately 1.5 hours irrespective of dose. Effect may be monitored by aPTT, ACT, whole blood heparin concentration, or anti-factor Xa activity. Up to 4 hours may be necessary for anticoagulant effects to dissipate enough to undertake an elective surgical procedure. Intravenous protamine sulfate can be administered to rapidly neutralize UFH's anticoagulant effect at a dose of 0.7-1.3mg/100 units UFH administered.

B. Low Molecular Weight Heparin (LMWH)

LMWH is produced from UFH as a smaller molecule with potent anti-activated factor X activity. Dose adjustment is required in the presence of renal insufficiency. Numerous LMWH preparations are available for clinical use. Elimination half-life varies from 3-5 hours. The drug should be stopped 24 hours prior to elective surgical procedures. The anticoagulant effect may be partially (about 60-70%) reversed by protamine sulfate at a dose of 1mg/100mg of LMWH.

C. Fondaparinux

Fondaparinux is an activated factor X inhibitor that requires interaction with antithrombin to exert its anticoagulant effect. The elimination half-life is 17-21 hours. Although no evidence-based recommendations exist, a conservative management strategy is to delay elective surgery for 5 half-lives, or 4 days. Dose adjustment is required for patients with renal insufficiency.

D. Direct thrombin inhibitors

The direct thrombin inhibitors (DTI) include dabigatran, lepirudin, argatroban, and bivalirudin. They interact with free or clot bound thrombin to inhibit the conversion of fibrinogen to fibrin. The half-lives of the drugs vary. Conservative management strategies suggest that patients on intravenous infusions of DTIs should have the drug discontinued five elimination half-lives before elective surgery or neuraxial blockade. There is no reversal agent for DTI related bleeding. DTIs are useful to prevent and treat thrombotic events related to heparin induced thrombocytopenia type II (HIT). The anticoagulant effect of the drug may be followed by either the aPTT or the ACT. Dabigatran is currently the only FDA approved oral DTI available in the U.S. and has a half-life of 17 hours in patients with normal renal function. The drug should be stopped 4-5 days prior to elective surgery or neuraxial blockade.

E. Coumarins

Warfarin is the only coumarin approved by the FDA. It inhibits the hepatic synthesis of the vitamin K dependent coagulation factors (II, VII, IX, X, as well as proteins C and S). The PT or the International Normalized Ratio (INR) can be used to follow the drug's anticoagulant effects. Warfarin is metabolized by the liver and has a half-life of 20-60 hours. Administration of vitamin K will decrease the time for the effects of warfarin to abate. Administration of fresh frozen plasma will acutely reverse the anticoagulant effects of warfarin, however warfarin has a longer half-life than FFP. Prothrombin complex concentrates represent another option for rapid and effective reversal of warfarin's effects. A conservative strategy is to discontinue warfarin five days prior to elective surgery or neuraxial blockade.

F. Antiplatelet Agents

1. Non-steroidal anti-inflammatory drugs (NSAIDS)

Aspirin works by irreversibly inhibiting the platelet enzyme cyclooxygenase, resulting in a blockade of platelet activation and aggregation. The normal circulating life span of a platelet is approximately 10 days. Aspirin has a half-life of 15-20 minutes in the plasma and undergoes hepatic and plasma esterase metabolism. The antiplatelet effects of aspirin may only be overcome by platelet transfusion. Other NSAIDS such as ibuprofen, ketorolac and naproxen produce reversible platelet cyclooxygenase inhibition so the return of platelet function correlates with the half-life of the drug.

2. Glycoprotein IIb/IIIa inhibitors

The GPIIb/IIIa inhibitors are only available as IV preparations and are extremely potent inhibitors of platelet function. Abciximab, eptifibatide, and tirofiban are currently approved for use in the Untied States. These drugs inhibit platelet aggregation via the interaction of GPIIb/IIIa receptors and either fibrinogen or von Willebrand factor. These drugs are primarily used in the setting of interventional procedures for acute coronary syndromes or neurologic processes. Depending on the drug half-life, these agents may increase bleeding during emergent cardiac surgery.

3. Platelet ADP Receptor Antagonists

Clopidogrel, ticlopidine, and prasugrel are the FDA approved adenosine diphosphate (ADP)-receptor antagonists. They selectively and irreversibly inhibit ADP-induced platelet aggregation by blocking the P2Y12 ADP receptor on the platelet's surface. Clopidogrel is FDA approved to reduce thrombotic events related to recent myocardial infarction, stroke, and peripheral arterial disease. It is also approved for medical management and PCI treatment of acute coronary syndrome. Clopidogrel undergoes extensive hepatic metabolism and has a half-life of about 8 hours. Its irreversible nature makes five to seven days necessary before functional platelets are restored. Emergent cardiac surgery for patients on clopidogrel is associated with significant bleeding and transfusion requirement. Ticlodipine is approved for coronary stenting and prophylaxis of thromboembolic stroke. The half-life is reported to be 12.6 hours but increases dramatically to 5 days with repeated dosing. It is used much less frequently than clopidogrel due to its association with neutropenia, agranulocytosis, and thrombotic thrombocytopenic purpura. A 14-day delay is recommended prior to neuraxial blockade. Prasugrel is a recently approved drug used in patients with acute coronary syndromes managed with PCI. The effects are analogous to clopidogrel and abate 5-9 days after discontinuation. Metabolism is via the liver and by serum esterases.

I. Platelet Adhesion Inhibitors

Dipyridamole is available in oral and iv formulations. Its complex mechanism of action ultimately inhibits platelet aggregation by blocking their activation by ADP, collagen and platelet activating factor. It is FDA approved to be used as an adjunct to warfarin for prophylaxis against thromboembolic events in patients with prosthetic cardiac valves as well as being approved for use with thallium in myocardial imaging studies. It primarily undergoes hepatic metabolism and has a half-life of 9-13 hours. Cilostazol inhibits phosphodiesterase III leading to an increase in intracellular cyclic adenosine monophosphate (cAMP). The result is a reversible inhibition of platelet aggregation. A conservative approach would be to delay elective surgery or neuraxial blockade for 48 hours following administration.

Pharmacologic Agents for Achieving Hemostasis

A. Fibrinogen Concentrate

Human fibrinogen concentrate is available as a concentrated lyophilized protein created from pooled human plasma. It is FDA approved for congenital fibrinogen deficiency but there is extensive experience with its off label use to treat bleeding relating to fibrinogen deficiency in cardiac surgery. The product has higher fibrinogen content per milliliter (1000mg/50cc, 20mg/cc)) than either cryoprecipitate (~150mg/15cc, 10mg/cc) or fresh frozen plasma (~500mg/250cc, 2mg/cc). (www.riastap.com)

B. Antifibrinolytics

Epsilon aminocaproic acid and tranexamic acid are lysine analogues that can reduce blood loss in patients at risk for major hemorrhage. These agents work principally by inhibiting the process of fibrinolysis that accompanies major surgery. They are used extensively in cardiac surgery with the use of cardiopulmonary bypass.

C. DDAVP (desmopressin)

Intravenous administration of DDAVP will increase vWF and factor VIII levels in patients with type I von Willebrand Disease. DDAVP can also be a useful adjunct in patients with end-stage renal disease who suffer from uremic platelet dysfunction.

D. Activated Factor VII (Novoseven)

FDA approved for the treatment of patients with hemophilia A or B who have inhibitors to factor VIII or IX and for patients with congenital factor VII deficiency. There is extensive experience with its off-label use in the treatment of traumatic and surgical bleeding. The drug works by enhancing the generation of thrombin on activated platelets. There are no formal guidelines as to the use of this drug in the setting of uncontrolled bleeding. Due to the risk of significant thrombotic complications, we suggest that its use be limited to the setting of life-threatening bleeding without an identifiable surgical source where there has been a failure to respond to blood component therapy.

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Questions

34.1 Which of the following is the most reliable method of restoring normal coagulation within 2 hours for a patient receiving argatroban?
   A.   Administration of protamine
   B.   Administration of vitamin K
   C.   Discontinuation of argatroban
   D.   Administration of cryoprecipitate

34.2 A 24-year-old man is scheduled to undergo arthroscopic knee surgery. He has hemophilia A without history of spontaneous hemorrhages. Laboratory studies have not detected any inhibitors to factor VIII. Which statement about the management of this patient is most likelytrue?
   A.   Spinal anesthesia is absolutely contraindicated.
   B.   Recombinant factor VIII should be administered before surgery.
   C.   Recombinant factor VIIa should be administered before surgery.
   D.   Recombinant factor VIII therapy should be discontinued 48 hours post-op.

34.3 A patient with known type 1 von Willebrand disease presents for emergency splenectomy following a motor vehicle collision. Which of the following is the most appropriate initial treatment?
   A.   Intravenous desmopressin (DDAVP)
   B.   Cryoprecipitate
   C.   Platelets
   D.   FFP

34.4 Following massive fluid resuscitation with crystalloid and PRBC's, the best initial treatment for trauma-associated coagulopathy is the early use of
   A.   Recombinant factor VIIa
   B.   FFP
   C.   Desmopressin
   D.   Cryoprecipitate

35. Transfusion Therapy

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Key Points

• Indications for allogeneic blood product administration include: insufficient oxygen carrying capacity/delivery thought to be at least partially due to either inadequate volume of total red blood cells or plasma; replacement of coagulation cascade constituents to correct severe coagulopathy and inadequate quantity and/or dysfunction of platelets.

• There are no universally accepted absolute thresholds for transfusion therapy.

• It is important to balance the various patient characteristics, disease processes and potential risks prior to making transfusion decisions.

A 57 year-old man sustained a motor vehicle accident with multiple fractures (pelvic, femur, ribs), a splenic laceration and a closed head injury. In the ED, he is intubated and two large bore IVs are obtained. He is brought to the OR emergently for surgical intervention. Vital signs include temperature 35.2° C, HR 133/minute, BP 84/66 mmHg, and SpO_2 95%. Baseline laboratory data, and a type and screen are pending, but CT scan provides evidence of a large abdominal/pelvic fluid collection consistent with blood.

Overview

There are three primary indications for allogeneic blood product administration:

1. Insufficient oxygen carrying capacity/delivery thought to be at least partially due to either inadequate total red blood cell mass or circulating plasma.
2. Replacement of coagulation cascade constituents to correct severe coagulopathy.
3. Inadequate quantity and/or dysfunction of platelets

There are a number of products available for transfusion, each with their own specific indications. In order to utilize these resources appropriately, it is best to understand how we obtain the various products.

Whole blood consists of red cells, white cells, and platelets suspended in plasma. These various components are separated through a centrifugation process wherein the supernatant (plasma) is separated from whole cells. Once the cells are removed, the platelets are then collected. The plasma can then be frozen [fresh-frozen plasma (FFP)] or further separated through a freeze-thaw cycle into a precipitate (cryoprecipitate) and factor-poor plasma. Cryoprecipitate is rich in clotting factors including fibrinogen and von Willebrand factor (vWF). The result is no less than 4 separate components (PRBC, FFP, cryoprecipitate, platelets) (Figure 35.1) with

varying transfusion indications. Additionally, each component carries with it a unique set of considerations.

The goal of this section is to outline the various safety considerations, indications and controversies surrounding each individual blood product component.

Whole Blood

Rarely utilized given inefficient storing requirements, reduced longevity of storage compared to its separated products and increased incidence of harmful donor-recipient interactions, whole blood is principally used in acute blood loss settings. Discussed later in this chapter, whole blood administration may be more effective in prevention of transfusion related coagulopathy and has been shown to improve outcomes specifically associated with trauma.

Storage

Whole blood is refrigerated and stored for as long as 21-35 days, according to regulations set by the Food and Drug Administration (FDA) and utilized by blood collection, storage and/or distribution agencies such as the American Red Cross. Until recently, surgeons employed an autologous whole blood transfusion strategy for surgeries with an anticipated large amount of blood loss. Patients typically donated up to 2 units of whole blood as much as 2-4 weeks prior to surgery. This practice was very common in the 1980's and early 1990's when the risk of viral transmission from donor blood was much greater than today. Autologous whole blood transfusion has fallen out of favor outside of isolated circumstances given the increased cost and logistical difficulties as well as the increased incidence of preoperative anemia due to insufficient time to allow for adequate erythropoiesis.

Packed Red Blood Cells (pRBCs)

Informally, when the phrase "blood transfusion" is used, most providers are referring to a pRBC transfusion. It is quite a common practice with the administration of nearly 15 million units of packed red blood cells (pRBCs) reported in 2009 alone. A unit of pRBCs typically represents about 200-250 ml of volume at a hematocrit (hct) of about 60-70%. Administration of 1 unit classically results in an increase in hemoglobin concentration (Hb) of 1 g/dL. Most centers in the United States now employ universal leukoreduction. By reducing the number of leukocytes there is evidence for less adverse effects including certain types of transfusion reactions.

Storage

According to the FDA, depending upon the anticoagulant used, pRBCs can be stored up to 42 days in a refrigerated environment (1-6° C) without significant degradation of red cell components. Studies have suggested, however, that fresher blood may be more suitable for critically ill patients given better maintenance of 2,3-DPG stores. Most recently, researchers have shown reduced red cell membrane deformability with older pRBCs. Due to a lack of definitive studies, controversy exists regarding just how long stored red cells can be utilized. Regardless, most consider younger/fresher stores to have greater clinical benefit.

Indications for pRBC Transfusion

Packed red blood cells are indicated to address insufficient oxygen carrying capacity. This includes excessive blood loss or anemia, the extent of which exceeds the ability of crystalloid/colloid administration alone to provide adequate volume expansion.
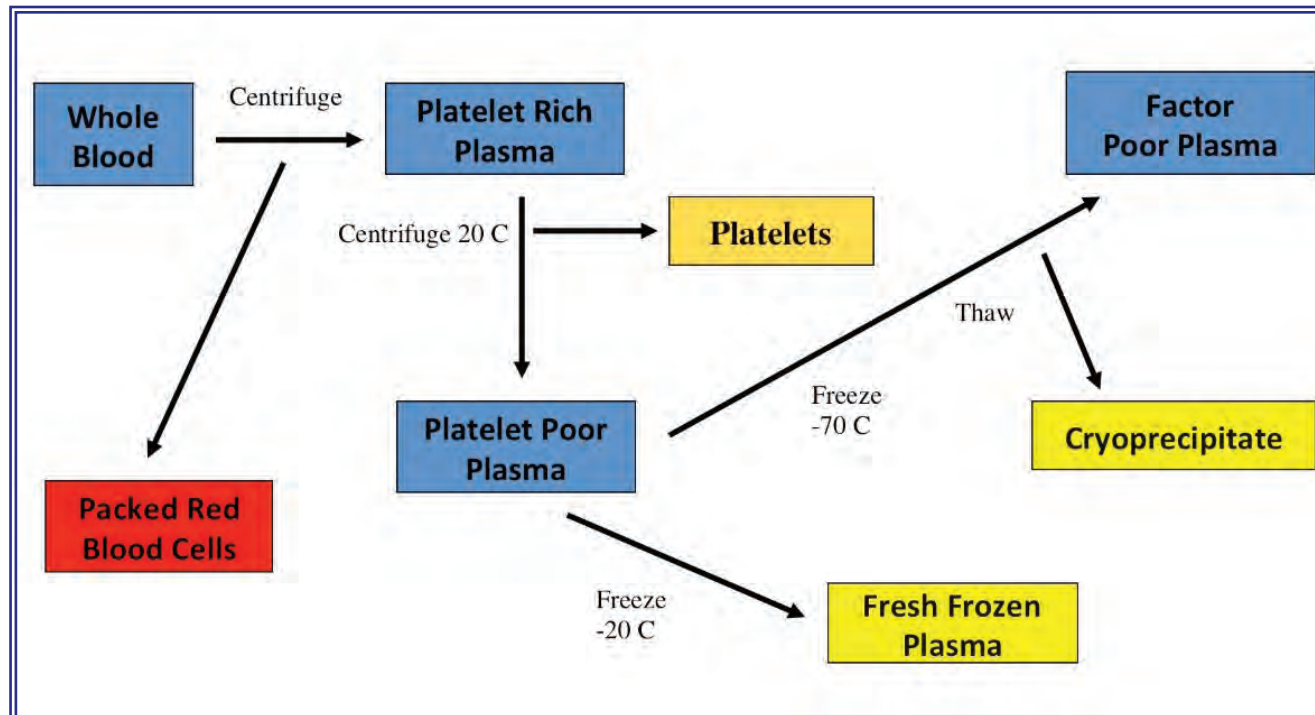
Figure 35.1 Processing whole blood into components

Over the past decade, several large randomized trials have been published along with four society-endorsed guidelines all supporting hemoglobin transfusion thresholds of 7-8 g/dL in patients that are not actively bleeding. In fact, virtually all the large randomized trials have shown no benefit to higher hemoglobin triggers of 9-10 g/dL, and two of the trials have shown increased morbidity with higher hemoglobin triggers in certain subsets of patients. It is well recognized, however, that the hemoglobin level alone is not always a sufficient reason to transfuse and that decreased intravascular volume and evidence of end-organ ischemia may also be indications for transfusion. Certainly, the decision to transfuse should be based on a global combination of careful

monitoring of patient characteristics, metabolic state, disease processes and end-organ perfusion (demand) as well as ongoing blood loss/production and current hemoglobin concentration (supply).

Although cases exist in the literature to support extreme examples of transfusion practice (as can be seen in Jehovah's Witness patients), the Annals of Internal Medicine recently released a clinical practice guideline (with formal review of all available transfusion trial data) to summarize the evidence available. Their summary is as follows:

1. Strong recommendation with high quality evidence to adhere to 7-8 g/dL (strict transfusion strategy) in hospitalized, hemodynamically stable patients with normal intravascular volume.

2. Providers should adhere to a restrictive strategy in patients with preexisting cardiovascular disease, including consideration of transfusion only if hemoglobin levels are below 8 g/dL or symptoms of anemia arise.

3. No recommendation can be provided for patients with acute coronary symptoms.

Although a great deal of research has been devoted to transfusion triggers in hemodynamically stable patients, much less is understood regarding similar triggers in acute bleeding and massive transfusion strategies (see below). Confounders such as severity of disease, type of potential surgical intervention, mechanism of various trauma, degree of resuscitation and quality of monitoring lead to a large variety of accepted transfusion practices.

Summary
Packed RBC transfusion is chiefly utilized to improve oxygen carrying capacity and delivery in patients with reduced or ineffective native RBCs. Most studies support transfusion trigger levels of 7-8 g/dL depending upon patient characteristics and clinical situation. Rare exceptions exist and further studies are warranted to determine appropriate hemoglobin levels in high-risk patients.

Table 35.1 Major Blood Groups and Rh Factor		
Blood Group	**Antigen on Erythrocytes**	**Plasma Antibodies**
A	A	Anti-B
B	B	Anti-A
AB (RBC universal recipient)	AB	None
O (RBC universal donor)	None	Anti-A, Anti-B
Rh	Rh	None

Fresh Frozen Plasma (FFP)
As previously described, FFP is the result from immediately freezing the supernatant from a freshly centrifuged unit of whole blood. FFP contains all existing clotting factors, plasma albumin, electrolytes and physiologic anticoagulants. Anticoagulants (protein S, alpha-2 antiplasmin, etc.) are just as important as clotting factors as they

maintain an appropriate balance upon administration to avoid excessive clotting which can lead to thrombotic events. Single unit preparations typically range in volume from 250-350 ml and contain roughly 80-85% of the native clotting factors in the original unit of whole blood.

Storage
Shelf life can range in upwards of 1 year if properly stored at the suggested -18° C. Once thawed to 4° C, it must be administered within 24 hours. Of note, although the storage process improves longevity, it reduces the effectiveness of certain factors (especially factors V, VII, VIII) by as much as 20%. As discussed later, this has led to the development of recombinant factors and cryoprecipitate for profound coagulopathies.

Indications for FFP Transfusion
In order to hold a meaningful discussion regarding FFP transfusion practices, it is first important to review the coagulation cascade. Knowledge of the interaction between upstream factors, existing platelets and various platelet activators, and resultant downstream products is important to understanding how FFP administration can affect the overall balance of this tightly regulated system.

The main indication for FFP administration is replacement of coagulation cascade constituents to correct severe coagulopathy. This can include known coagulopathy secondary to innate coagulation factor deficits (hemophilia) as well as acquired coagulopathies secondary to sepsis, DIC, medication administration (warfarin, heparin) or even dilutional effects (large volume crystalloid, pRBC administration).

Though possibly less controversial than pRBC transfusion, the decision to administer FFP is no less complicated. And unlike red blood cell transfusions, no widely accepted body of guidelines exists regarding the appropriate use of fresh frozen plasma. An overall lack of well-conducted clinical trials determining the appropriate use of FFP has led to a larger variability in its use when compared to other products.

The most common indication for the use of FFP is the prevention of or intervention upon bleeding in patients with prolonged bleeding tests. Parameters such as PT/INR (extrinsic cascade) and PTT (intrinsic) are monitored, with FFP usage typically limited to patients with elevations in these parameters to greater than 1.5 times the upper limit of normal. Currently, the use of a thromboelastogram (TEG) is becoming more popular as it evaluates the entire coagulation process (quality).

Fresh frozen plasma administration has been described in patients with prolonged bleeding times and:

1. Correction of congenital (hemophilia) or acquired (DIC, severe nutrition deficiency, liver failure, severe acidosis) coagulopathies associated with risk of potential blood loss (scheduled or emergent surgery) or active blood loss (GI bleeds,, intracranial bleeding).

2. Correction of coagulopathies associated with supratherapeutic medication administration (warfarin).

3. Co-administration as part of a massive transfusion protocol (dilutional and consumptive coagulopathies).

Cryoprecipitate

Cryoprecipitate, as its name suggests, is the precipitate that forms during the thawing of fresh frozen plasma when it has been frozen to -70° C. A single unit of cryoprecipitate is approximately 10-20 mL and multiple units are administered at once. It contains a concentrated amount of certain clotting factors (fibrinogen, factor VIII, factor XIII, von Willebrand factor) with minimal volume. Cryoprecipitate is used primarily to replete stores of coagulation factors lost through various processes including dilutional co-agulopathy, disseminated intravascular coagulation (DIC), end-stage liver disease, or congenital clotting factor deficiencies.

Storage

Cryoprecipitate can be stored at similar length and by similar means to its FFP counter-part. Once thawed, it must be administered within 24 hours.

Indications for Cryoprecipitate Transfusion

Cryoprecipitate is most notably utilized to treat patients with known hemophilia and von Willebrand disease with planned surgical procedures, sustained trauma or spon-taneous bleeding. In addition, it is often utilized in incidents of massive transfusion protocol, disseminated coagulopathies or other consumption-related bleeding (discussed later). Additionally, cryoprecipitate remains the only adequate fibrinogen concentrate available. In clinical situations involving ongoing bleeding associated with low levels of specific coagulation factors (i.e. fibrinogen), cryoprecipitate administration should be considered. A fully comprehensive discussion falls outside the scope of this chapter.

Summary for Fresh Frozen Plasma and Cryoprecipitate

Fresh frozen plasma, perhaps, has the most variable usage pattern among all blood prod-ucts. Freezing products permits lengthy storage practices. Fresh frozen plasma and its constituents should be reserved for correction of reversible coagulopathy from a variety of etiologies. Coagulation specific laboratory studies including PT, aPTT, INR and fibrinogen, at the very minimum, should be monitored to ensure proper utilization.

Platelets

Platelets can be collected from its separation from a donated unit of whole blood (random donor) or obtained from an individual donor with no other blood products collected (apheresis). Combining multiple single-donor units create a unit of random donor platelets (typically 6 units collected from whole blood from 6 donors). A unit of apheresis platelets is created by extracting the amount of platelets contained in six units of whole blood from one donor by only collecting the platelets while returning all other blood products back to the donor during one donation. An apheresis preparation can range from 200-300 ml in volume and typically increases the circulating platelet count by 40-60 x 10^9/L.

Storage

Unlike other blood cell components, platelets are stored at room temperature. This is done to prevent denaturation of platelet proteins necessary for coagulation. Accord-ingly, shelf life is reduced to approximately 5 days. Given concomitant isolation of leukocytes with platelets, it may be necessary to perform additional pre-storage leuko-cyte reduction or depletion by washing preparations with saline if the risk for transfu-sion reaction is particularly high. Patients with known prior anaphylaxis or significant febrile reactions secondary to platelet transfusion may benefit from premedication and leukoreduction practices.

Indications for Platelet Transfusion

Although no universally accepted lower limit exists, a reasonable consensus has been drawn regarding necessary platelet transfusion levels. Platelet transfusion to treat acute bleeding, multiple trauma or coagulopathy associated with platelet counts < 50 x 10^9/L is highly recommended. Beyond that, there is significant variability in transfusion prac-tice.

Provided there are no signs of coagulopathy and platelets are fully functional (i.e. no platelet inhibiting medications), clinicians generally agree that patients are at no greater risk of bleeding during invasive procedures when platelet counts are greater than 50 x 10^9/L. However, depending upon the procedure, it may be reasonable to consider a prophylactic platelet transfusion in individuals with counts < 50 x 10^9/L.

Outside of the perioperative period, severe and life-threatening hemorrhage is a risk when platelet counts drop below 5-10 x 10^9/L. It is reasonable to consider prophylactic platelet transfusion in these patients regardless of known hemostatic challenge (surgery, coagulopathy, platelet inhibiting medications) to prevent spontaneous bleeding.

Summary

Platelets represent the scaffolding upon which the coagulation factor mortar is applied. In order to reduce bleeding associated with platelet loss, destruction or consumption, one should consider platelet administration. To prevent denaturation, platelets are stored for short periods at room temperature. Leukocyte depleted preparations are available to reduce risk of various reactions.

Safety

Transfusion Reaction

Each transfusion of a blood product, in essence, represents a tissue transplant. There are two significant measures utilized to avoid 'rejection' or severe host-donor interactions.

1. To appropriately select blood products for administration, initial blood typing is required. Individual patient antigens (A, B, Rh) on the membranes of erythrocytes are identified and these indirectly determine the various antibodies (anti-A, anti-B) present as well. This initial screening allows providers to select type-specific blood (A, B, and O with Rh). Given this first step alone, the chance of a significant hemolytic reaction (major ABO incompatibility; hemolytic reaction) related to the transfusion should be small.

2. In addition to blood typing, donor and recipient blood undergo both major and minor cross-matching. Traditionally, this required incubation of donor erythrocyte

with recipient plasma (major) and donor plasma with recipient erythrocyte (minor) to determine if agglutination occurs.

Agglutination would represent an incompatible cross-match. Recent advances have permitted most labs to simply screen a recipient's whole blood sample against an extensive panel of well-known antibodies to establish an appropriate cross-match. This process has improved efficiency without increasing frequency of transfusion reactions. At present, our best estimate of the incidence of all reactions with the above employed type and cross-match process is approximately 1 in 5,000 transfusions. The most common etiology of an incompatible transfusion reaction remains clerical error with the wrong unit administered to the patient.

Emergency Transfusion

If a transfusion is required prior to completion of the formal type and cross-match process, one may use either type-specific, non-cross-matched blood or the more commonly preferred type O-negative pRBCs. This product is kept as an emergency supply in most facilities given that it lacks surface A, B, and Rh antigens. (Table 35.1) Emergency blood administration has proven quite safe according to recent studies, with reported minor transfusion reactions of less than or equal to 1 in 1,000 transfusions. (Table 35.2)

Table 35.2 Summary of Storage for Various Blood Components

	Whole Blood	pRBCs	FFP	Cryoprecipitate	Platelets
Conditions	Cooled (4°C)	Cooled (4°C)	Frozen (-18°C)	Frozen (-18°C)	Room (24°C)
Shelf Life	21-35 days	42 days	1 year (24 hours once thawed)	1 year (24 hours once thawed)	5 days
Volume	250-500 ml/unit	200-300 ml/unit	250-400 ml/unit	10-20 ml/unit	200-300 ml/apheresis unit
Indication	Acute blood loss (trauma)	Anemia	Coagulopathy	Component specific coagulopathy	Thrombocytopenia

Transfusion-Related Acute Lung Injury (TRALI)

Another growing area of concern related to blood product administration is transfusion-related acute lung injury. This reaction, occurring by definition within 6 hours of transfusion, results in dyspnea, arterial hypoxemia and pulmonary edema. Resultant chest radiographs show diffuse infiltrates and the reaction can evolve into acute respiratory distress syndrome (ARDS). Although the true mechanism is debated, it is believed to be a reaction between donor antibodies and recipient leukocytes (as a result, the incidence is considerably higher in plasma and platelet transfusions). Similar reactions may be the basis for a spectrum of transfusion-related reactions. These range from fever and localized infusion site erythema to full blown anaphylaxis.

Although many cases are insidious and often go undiagnosed as part of other ongoing pathology, TRALI is the number one cause of transfusion-related death. Overall incidence has been estimated to be approximately 1:5000 to 1:10000 plasma-containing transfusions. Interestingly, the rate has been declining in parallel with the institution of plasma mitigation (exclusion of female multiparous donors).

Transfusion-Related Circulatory Overload (TACO)

In much the same way excessive crystalloid administration can lead to volume overload, excessive blood product administration can do the same. Although presentation can be similar to TRALI, transfusion-related circulatory overload is not thought to be a leukocyte-derived process. Patients develop respiratory distress, pulmonary edema, peripheral edema and typically increased blood pressure. Clearly, the risk is increased with larger volumes of blood products.

Given the reduced overall incidence of large volume blood product administration or massive transfusions, the incidence of TACO is likely less than TRALI. However, the morbidity associated with TACO is underappreciated and no less clinically important.

Transfusion-Related Infection and Sepsis

Major reactions (ABO incompatibility, Rh incompatibility, TRALI) and minor reactions (simple febrile non-hemolytic) are not the sole potential pitfalls of a transfusion. Although rates of viral transmission have dropped significantly secondary to donor blood testing, there still remains a risk of transmission of infectious diseases such as Hepatitis B (1 in 277,000), Hepatitis C (1 in 2 million), HIV (1 in 2 million), and West Nile Virus (1 in 350,000). This reduction in communicable transmission rates is owed directly to improvements in both awareness and employment of efficient nucleic acid screening technology.

Another less appreciated, but equally devastating outcome of a transfusion is transmission of bacterial contamination (roughly 1 in 38,000 blood transfusions and 1 in 5,000 platelet transfusions). As mentioned above, platelets carry a considerably higher risk given its storage at room temperature, permitting survival of most bacterial species. Although several detection methods are employed to reduce bacterial transmission rates, the phenomenon remains among the most common preventable negative consequence of blood product transfusion.

Risk of transmission of parasites, fungus and prion disease, especially in endemic areas, should remain a consideration to practitioners as well. Rates vary considerably on a regional basis.

Transfusion-Related Immunomodulation

Blood transfusion has been shown to suppress cell-mediated immunity. This, in conjunction with innate post-surgical immunosuppression, may place patients at increase harm for both opportunistic infection and even cancer recurrence. As indicated above, FFP and platelets carry higher risk than pRBCs given the inclusion of leukocytes within preparations. Leukocyte reduction/depletion (not elimination) practices have significantly reduced leukocyte-derived transfusion reactions, but they remain a significant consideration.

Summary

Although blood product transfusion is recognized among the greatest advancements in the history of medicine, it is important to know and understand its potential negatives. Even if one discounts the devastating consequences of a major ABO incompatibility or rare transmission of Hepatitis or HIV viral infections, pitfalls remain. The growing evidence surrounding febrile transfusion reactions, lung injury, immunosuppression and potential for less appreciated communicable diseases should make each provider think twice before ordering a transfusion. In an era of increasing need for proper resource allocation and better safety practices, the decision to transfuse should not be made lightly.

Massive Transfusion

Blood transfusion practices have evolved dramatically over the past decade and one area of particular interest is the concept of "massive transfusion". The idea was borne from the concept of using whole blood transfusion for trauma-related hemorrhage. Simply stated, it seemed most reasonable to replace whole blood loss through hemorrhage with whole blood product. Given that our blood procurement processes typically preferentially separate blood components, researchers sought to determine if altering the ratio of blood product administration would affect patient mortality in situations involving massive bleeding.

The rationale is simple: administration of an inappropriate ratio of products would increase the risk of dilutional coagulopathy (low effective coagulation factors, fibrinogen, or platelets) secondary to large crystalloid, colloid or pRBC administration. Blood product administration ratios that approach those found in whole blood would be most effective.

Several studies have retrospectively analyzed blood product administration to identify the optimal ratio to effectively treat hemorrhage and ultimately increase survival. Borgman, et al. initially reviewed 246 patients in a combat support hospital who received greater than 10 units of packed red blood cells (PRBCs) in a 24-hour period and found that as the ratio of PRBCs to FFP approached 1:1, the overall mortality rate improved in conjunction with reduced rates of ongoing hemorrhage. These findings were later validated in a large, multi-center retrospective study on 466 civilian trauma patients. Not only did they find improved mortality rates with transfusion ratios of FFP:pRBCs and platelets:pRBCs < 1:2, but improved morbidity measurements such as ventilator, ICU and hospital-free days.

As a direct result of both the above studies and individual anecdotal evidence, centers began to adopt a Massive Transfusion Protocol (MTP). One example of such a protocol, developed at The Johns Hopkins Hospital, is as follows:

MTP would be initiated in patients with
   (a) projected or observed loss of an entire blood volume in a 24hr period
   (b) projected or observed loss of 50% of blood volume in a 3hr period
   (c) ongoing bleeding of > 150ml/min or
   (d) rapid bleeding with circulatory failure despite volume replacement through alternative means (i.e., crystalloid or colloid administration)

The MTP would provide blood products in an organized fashion in coolers with pre-determined product ratios of 1:1:1 pRBCs:FFP:platelets, respectively. Given platelets are typically prepared as a "six-pack" with effectively 6 individual units of platelets in each pack, the effective administration ratio would be 6:6:1 of pRBCs:FFP:platelets. If an active type and cross-match is present, appropriately cross-matched products will be provided along with apheresis platelets. Otherwise, uncrossed emergency blood will be utilized in a manner discussed above.

Monitoring

No discussion of large-volume blood product administration is complete without highlighting the importance of close laboratory monitoring. Aside from consistently checking markers of coagulation and hemoglobin levels, it is important to regularly check patients for metabolic disturbances including acidosis, hyperkalemia and hypocalcemia. Acidosis and hyperkalemia can be a direct result of increased hydrogen ion and potassium associated with blood product storage. Hypocalcemia can result from citrate anticoagulant binding with native calcium. Thoughtful treatment of these various laboratory disturbances is important to prevent severe arrhythmias, muscle weakness and alteration of drug metabolism.

Close monitoring of patient temperature is important when large volumes of refrigerated/fresh frozen components are administered quickly. Small decreases in core body temperature can lead to shivering, resulting in greater metabolic/oxygen demand and worsening infection risk. Fluid and surface body warmers may be required to maintain normothermia.

Chapter Summary

In review, the three primary indications for allogeneic blood product administration include:

   1. Insufficient oxygen carrying capacity/delivery thought to be at least partially due to either inadequate volume of total red blood cells or plasma.
   2. Replacement of coagulation cascade constituents to correct severe coagulopathy.
   3. Inadequate quantity and/or dysfunction of platelets

At its base, the decision to use blood products in a clinical situation appears to be relatively simple. However, limited blood product supplies, increased recognition of harmful transfusion reactions, infectious disease transmission, and a growing culture of blood conservation has lead to a complicated ongoing discussion regarding appropriate transfusion practices. The discussion above represents only a basic outline of what the medical community understands about blood product utilization.

Moving forward, it is important to constantly balance the various patient characteristics, disease processes and potential risks prior to making the weighty decision to transfuse.

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Questions

35.01 Choose the most correct statement regarding the patient presented at the beginning of the chapter:
    A. The Massive Transfusion Protocol should be started after adequate crystalloid resuscitation.
    B. Blood product administration should be delayed until the T&S is obtained.
    C. The patient is at increased risk for both TRALI and TACO.
    D. It is only important to increase blood oxygen carrying capacity regardless of coagulation status in this patient.

35.02 Which blood product carries both the highest risk of transfusion-related infection and transfusion-related reaction?
    A. Fresh frozen plasma
    B. Packed red blood cells
    C. Platelets
    D. Whole blood

35.03 Which of the following is a true statement regarding transfusion practices?
    A. Hemoglobin level is the primary determinant of oxygen delivery independent of individual patient characteristics.
    B. Transfusions should be limited to the fewest number of products needed to correct each abnormality.
    C. TRALI is most commonly associated with administration of cryoprecipitate.
    D. Platelets should be administered to patients with platelet counts less than 50×10^9/L.

Section 9: Infectious Diseases

Chapters

- **Severe Sepsis and Septic Shock**

- **Infections and Antibiotic Management**

- **Management of the Immunocompromised Patient**
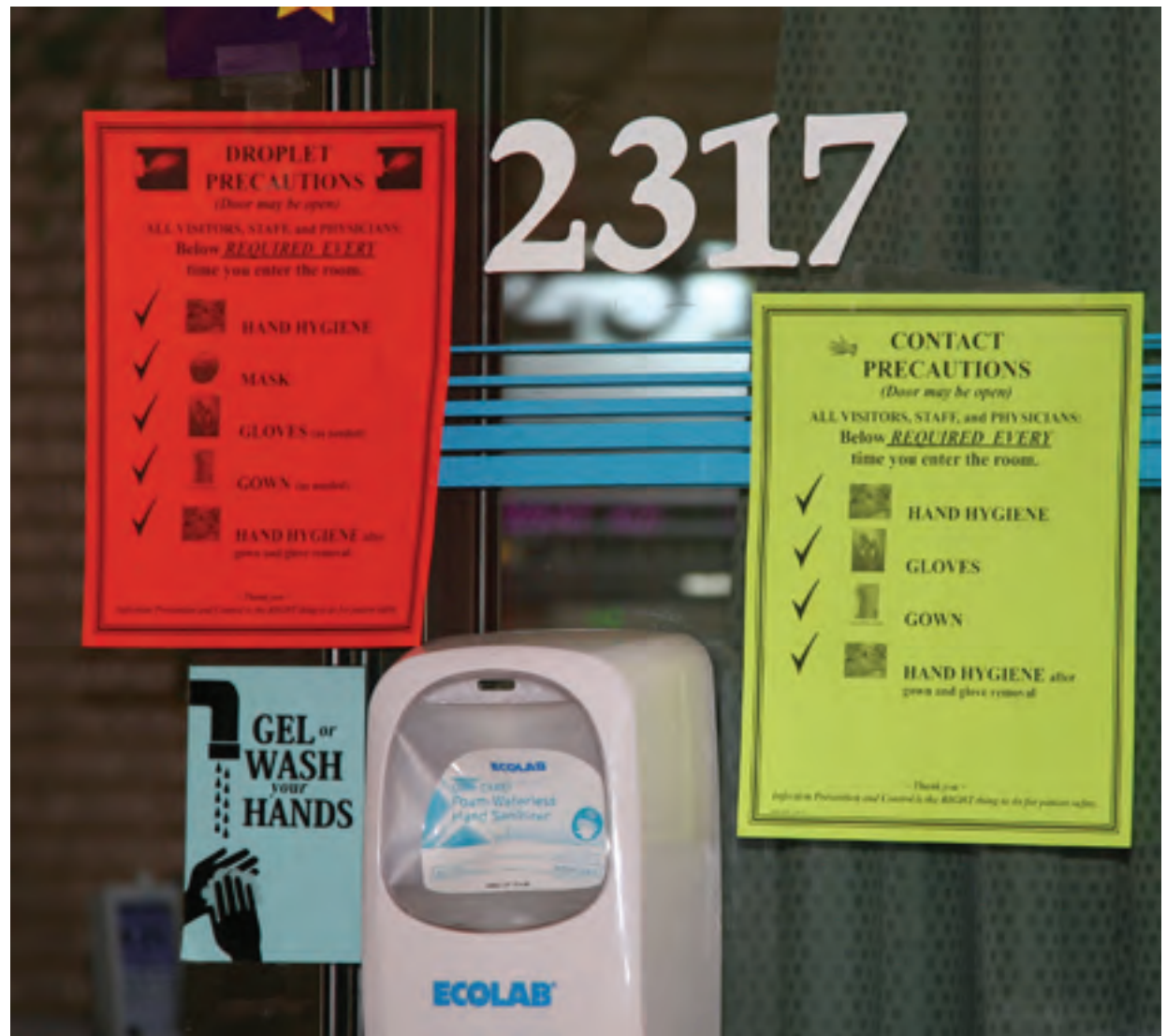
36. Severe Sepsis and Septic Shock

Judson Mehl DO and Deborah Rohner MD

Key Points

- Sepsis is common in the intensive care unit setting. It can present with a variety of signs and symptoms and providers must always have a high index of suspicion.

- Early goal directed therapy of patients with sepsis and septic shock should utilize crystalloid boluses targeting defined resuscitation endpoints. In the face of ongoing hypotension, pressors, inotropes, and steroids may be required to meet the defined endpoints.

- Early broad-spectrum antibiotic therapy is critical in the setting of severe sepsis and septic shock. Cultures should be obtained prior to administration when possible, but should not delay administration.

- Despite aggressive treatment, patients may still progress to multisystem organ failure and death

A 26 year-old woman is admitted to the intensive care unit with altered mental status, tachycardia and hypotension. A family member denies medical history but reports that she injects heroin daily. In addition to her hypotension and tachycardia, she has minimal urine output and her temperature is 35.2°C. A CBC shows a mild normocytic anemia and leukocytosis. Serum lactate is 5.6 mmol/L. Broad-spectrum antibiotics are ordered while blood and urine cultures are obtained. Despite a 30ml/kg crystalloid bolus, she remains hypotensive. An arterial catheter and central venous catheter are placed. An infusion of norepinephrine is begun with subsequent improvement in the patient's blood pressure. An echocardiogram of the heart demonstrated moderate tricuspid insufficiency. Over the next 24 hours the patient's blood pressure improves, allowing for weaning of vasopressors. Empiric antibiotic coverage is continued until blood cultures return with growth of S. Aureus at which time antibiotic therapy is de-escalated

Introduction

Sepsis is a systemic, deleterious host response to infection leading to severe sepsis (acute organ dysfunction secondary to documented or suspected infection) and septic shock (severe sepsis plus hypotension not reversed with fluid resuscitation). The systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic shock are a continuum of increasing severity of the body's response to inflammation and infection[1].

Severe sepsis strikes about 750,000 Americans annually[2]. It's been estimated that between 28 and 50 percent of these people die[3].

The Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012 was published by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine[1]. It provides an evidence-based medicine approach to sepsis using the GRADE approach. This system classifies quality of evidence as high (grade A), moderate (grade B), low (grade C), very low (grade D), or ungraded (UG). The GRADE system further classifies recommendations as strong (grade 1) or weak (grade 2). These grades are presented in this chapter.

Diagnosis and Initial Resuscitation, Antimicrobials

Historically, patients meeting two of the four SIRS criteria with an identifiable or suspected infection were said to meet the criteria for sepsis. These definitions have since been relaxed to include patients with a docu-

Table 36.1 Sepsis Diagnostic Criteria

Suspected or documented infection, plus any of the following:

Temperature > 38.3 or < 36.0 °C	Lactate > 1 mmol/L
Heart Rate > 90	INR > 1.5 or aPTT > 60 sec
Tachypnea	Platelets < 100,000
Altered mental status	WBC > 12,000 or < 4,000
Decreased capillary refill	WBC > 10% immature forms
Hyperglycemia (glucose > 140 mg/dL)	Urine output < 0.5 ml/kg/hr*
Hypoxemia PaO$_2$:FiO$_2$ < 300	Systolic blood pressure < 90 mmHg
Creatinine increase > 0.5mg/dL	Mean arterial pressure < 70 mmHg
Bilirubin > 4 mg/dL	

in the absence of pre-existing oliguria and following adequate fluid resuscitation.
Adapted from Dellinger, et al.[1]

mented or suspected infection and meeting any number of the criteria listed in Table 36.1.

Patients meeting the sepsis criteria and demonstrating acute tissue hypoperfusion or organ dysfunction are said to have "severe sepsis." The criteria for severe sepsis are listed in Table 36.2.

Primary resuscitation endpoints have been identified to guide initial therapy in sepsis and septic shock. They include:
   - Central venous pressure of 8-12 mmHg
   - Mean arterial pressure greater than or equal to 65 mmHg
   - Urine output greater than or equal to 0.5 mL/kg/hr
   - Central venous or mixed venous oxygen saturation of 70% or 65%, respectively (grade 1C)
   - Targeting lactate normalization after initial elevated lactate (grade 2C)

These goals must also be tailored to individual patients. For example, in patients with known pulmonary hypertension or heart failure, central venous pressure may not accurately reflect resuscitation status. Likewise, in patients with long-standing hypertension, a MAP of 65 mmHg may not provide adequate end-organ perfusion.

Once the diagnosis of sepsis has been made or suspected, a search for the source including cultures, imaging studies, and specific assays like 1,3 beta-D-glucan, for detection of invasive fungal infections, should be expeditiously performed (2C). Importantly, antimicrobial administration should not be delayed for cultures if culture collection is expected to take >45 minutes (1C). The goal is to administer IV antibiotics within 1hr of recognition of septic shock (1C). Blood cultures should be drawn from a percutaneous site as well as each vascular access device, especially those placed >48hrs prior to

diagnosis (1C).

Some of the more frequently encountered pathogens in sepsis are listed in Table 36.3, along with the first-line antimicrobials for treatment. However, familiarize yourself with your unit's commonly occurring pathogens and their sensitivities and tailor. Initial antimicrobial therapy should be broad and selected to penetrate the suspected tissue (1B).

Patients with neutropenia and those suspected infections involving multi-drug resistant bacteria such as Acinetobacter or Pseudomonas warrant combination empiric therapy (2B).

Just as important as initiating antimicrobials broadly, is the daily re-evaluation and de-escalation once susceptibilities are known (2B). In general, empiric therapy should not be continued for more than 3-5 days (2B). A total 7-10 days of targeted antibiotic treatment is sufficient to treat most infections (2C), but there are some exceptions such as patients with immunosuppression and those with undrainable foci. Certain organisms may also require an extended duration of therapy. Specific lab tests such as procalcitonin, a biomarker for sepsis, may guide discontinuation of therapy (2C).

If a specific source is identified, intervention to remove that source should occur within

Table 36.2 Criteria for Severe Sepsis

Severe sepsis = sepsis-induced tissue hypoperfusion or organ dysfunction (any of the following thought to be due to the infection)

Sepsis-induced hypotension
Creatinine > 2 mg/dL
Platelet count < 100,000
INR > 1.5
Increased serum lactate
PaO$_2$:FiO$_2$ ration < 200 in presence of pneumonia or < 250 in absence of pneumonia
Bilirubin > 2 mg/dL
Urine output < 0.5ml/kg/hr for more than 2 hours, despite adequate fluid resuscitation

Adapted from Dellinger, et al.[1]

12 hours, if feasible (1C). Peripancreatic necrosis is a notable exclusion where demarcation is preferred (2B).

Ventilated patients should receive oral chlorhexidine gluconate for VAP prevention (2B).

Support of Failing Circulation in Severe Sepsis and Septic Shock
Crystalloid is the recommended resuscitation fluid (1B), though albumin is also an option in patients requiring large amounts of crystalloid (2C). The use of hydroxyethyl

starches is not recommended (1B).

An initial crystalloid challenge of 30 mL/kg should be given with sepsis-induced tissue hypoperfusion, repeat boluses may be utilized when patients continue to demonstrate hemodynamic improvement with the fluid challenge (1C).

When an adequately volume-resuscitated patient with septic shock remains hypotensive, the initial vasopressor of choice is norepinephrine (1B). For profound refractory shock, epinephrine may be concurrently administered or substituted for norepinephrine (2B). Vasopressin in doses of 0.03 (and up to 0.04) units/minute is utilized as an adjunct to norepinephrine in patients with refractory septic shock (UG). Administration of vasopressors and their titration require placement of an arterial catheter (UG).

Phenylephrine is not recommended in the treatment of septic shock except in circumstances where norepinephrine is associated with serious arrhythmias, cardiac output is known to be high and blood pressure persistently low, or as salvage therapy when combined inotrope/vasopressor drugs and low dose vasopressin have failed to achieve MAP target (1C).

Dopamine should not be used to provide renal protection (1A). Dopamine may be considered in only highly selected patients such as those with low risk for tachyarrhythmias or have bradycardia (2C).

In patients demonstrating ongoing tissue hypoperfusion or decreased cardiac output after appropriate volume resuscitation and addition of vasopressors, the possibility of cardiac dysfunction should be considered. Invasive monitoring may demonstrate increased cardiac filling pressures and decreased cardiac output (ie cardiogenic shock). In these cases, the addition of dobutamine may help improve hemodynamics. A trial of dobutamine up to 20mcg/kg/min may be administered or added to a vasopressor (1C). The goal of inotropes is to achieve a normal cardiac index, not a supranormal level (1B).

Patients who remain hypotensive after adequate volume resuscitation and vasopressor therapy should be give hydrocortisone 200mg IV/24 hours (2C) as a continuous infusion (2D). Steroids should not be used to treat sepsis in the absence of shock (1D) and should be tapered when vasopressors are no longer required (2D). There is no role for ACTH stimulation testing (2B).

Adjunct Therapies in Sepsis

Patients with sepsis often have failure of other organ systems. Patients with respiratory failure will frequently require ventilator support. In patients meeting the Berlin definition of acute respiratory distress syndrome, a lung-protective ventilation strategy should be employed (1A and 1B).

A hemoglobin concentration of 7-9g/dL in adults is sufficient in the absence of myocardial ischemia, severe hypoxemia, acute hemorrhage, or ischemic heart disease (1B). Additionally, erythropoietin does not have a role (1B) nor does FFP to correct lab abnormalities in the absence of bleeding or planned procedures (2D). Platelet counts often fall in the septic patient. In the absence of bleeding, platelet counts of $\geq 20,000/mm^3$ are accepted in patients without significant risk factors for bleeding. Platelet counts $\geq 50,000/mm3$ are suggested for active bleeding, surgery, or invasive procedures. Additionally, platelets are suggested prophylactically when counts drop to counts $\leq 10,000/mm3$ even in the absence of bleeding (2D).

Sedation and analgesia should target specific titration endpoints (1B). Neuromuscular blocking agents should be withheld in patients without ARDS. If they must be used, train-of-four monitoring should be used (1C) and should not be used for more than

Table 36.3 Frequently Encountered Pathogens in Sepsis and Suggested Antimicrobials for Treatment

Source	Likely Pathogen	First Line Empiric Therapy	Alternate Empiric Therapy
Abdominal	GNRs Enterobacter Enterococci Bacteroides	Piperacillin-Tazobactam Ertapenem	Fluoroquinolone+Metronidazole Tigecycline
	Severe, life threatening peritonitis	Imipenem Meropenem Doripenem	Ampicillin+Metronidazole+ Fluoroquinolone or Aminoglycoside
Kidney/Bladder	Enterococci Enterobacter Pseudomonas	Piperacillin-Tazobactam Ampicillin+Gentamycin	Fluoroquinolone Cefepime
Lung	S. pneumoniae H. influenzae GNRs	Fluoroquinolone	Ceftriaxone+Azithromycin
	If recent viral influenza, cover S. aureus	Vancomycin+Fluoroquinolone	Linezolid+Fluoroquinolone
	If Pseudomonas suspected	Piperacillin-Tazobactam+Fluoroquinolone Piperacillin-Tazobactam+Aminoglycoside+Azithromycin	
	VAP	Imipenem Meropenem	
Central Line (CLBSI)	S. epidermidis S. aureus	Vancomycin	Daptomycin if no response to Vancomycin
	In impaired host, neutropenia, severe illness	Vancomycin+Cefipeme or Piperacillin-Tazobactam	

Adapted from Gilber, et al.[4]

48hours (2C).

In those with kidney injury, renal replacement therapies are often required. Continuous and intermittent hemodialysis are equivalent (2B), but continuous therapy is often hemodynamically tolerated better (2D).

Blood glucose is often elevated in response to the systemic inflammation of sepsis. Blood glucose should be treated to maintain blood sugars less than 180 mg/dL (1A). Hypoglycemia should be avoided and aggressively treated when present.

Patients with severe sepsis or septic shock who have risk factors should receive stress-ulcer prophylaxis with either a H2-blocker or proton pump inhibitor (1B), favoring a proton pump inhibitor (2D).

Many clinicians use bicarbonate therapy to correct the academia from a lactic acidosis despite a lack of evidence-based medicine to support this. The surviving sepsis guidelines recommend not using sodium bicarbonate for the purpose of improving hemodynamics or reducing vasopressor requirements with a pH≥7.15 (2B).

Patients should receive daily pharmacoprophylaxis for venous thromboembolism (1B) or a combination of pharmacoprophylaxis plus compression devices (2C).

Current nutrition recommendations suggest that there may be some benefit in utilizing enteral or parenteral nutrition within the first 48 hours of sepsis and septic shock (2C). However, if feeding is initiated it should be at low-dose and advanced only as tolerated (2B).

Summary

Sepsis is associated with high morbidity and mortality in critically ill patients and is a continuum of disease spanning SIRS to multiple system organ failure and septic shock. There is still much to be learned about sepsis. As for now, following the Surviving Sepsis Campaign 2012 guidelines as outlined in this chapter provides a consensus from which to direct care.

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Questions

36.1 You are called to the intensive care unit for a patient in septic shock. A CT scan of the abdomen was performed in the emergency department and demonstrated peripancreatic necrosis. Nursing staff have been unable to obtain a peripheral blood culture despite multiple attempts over the last hour. The next appropriate step in management of this patient include:
   A.   Placement of a central venous catheter to obtain a blood culture and serum lactate levels
   B.   Immediate initiation of empiric broad-spectrum antibiotics
   C.   Placement of an arterial catheter to better manage hemodynamics
   D.   Initiate norepinephrine at 0.2 mcg/kg/min and titrate to MAP goals

36.2 The most appropriate initial fluid choice for resuscitation of sepsis and septic shock is:
   A.   Hetastarch
   B.   0.9% Saline
   C.   5% Albumin
   D.   Fresh frozen plasma

36.3 A patient in septic shock is deemed adequately volume resuscitated. He remains hypotensive despite maximal vasopressor support. His cardiac output is 7 liters/min. Another reasonable choice in the treatment of this patient includes:
   A.   Hydrocortisone 200 mg/day
   B.   Dobutamine 20 mcg/kg/min
   C.   Activated protein C
   D.   Dopamine 10 mcg/kg/min

36.4 Which of the following is not an initial resuscitation goal in the treatment of severe sepsis and septic shock:
   A.   CVP 8-12 mmHg
   B.   Urine output of 0.5 ml/kg/hr
   C.   Cardiac output greater than 3 liters/min
   D.   Mean arterial pressure greater than or equal to 65 mmHg

37. Infections and Antibiotic Therapy

Peter von Homeyer MD

Key Points

• Infections are a major cause of mortality for ICU patients; mortality increases in septic patients by 7.6% each hour appropriate antibiotics are delayed.

• Tissue penetration, patient's organ dysfunction, side effects, and drug interactions should all be considered.

• Common sources of infections in the ICU are lungs, blood stream/lines, urinary tract, and wounds.

• Empiric therapy should be narrowed and converted to targeted therapy as soon as possible.

A 54 year-old man with no PMH is admitted to the ICU with respiratory distress and hypoxia requiring high FiO$_2$ delivery via face mask. CXR showed bilateral diffuse infiltrates. In the ED, he was given vancomycin and piperacillin/tazobactam after cultures were sent. In the ICU, antibiotics were changed to vancomycin/ ceftriaxone/ and azithromycin since the likely diagnosis was community-acquired pneumonia. Oseltamivir was also added pending results from the respiratory viral panel.

Introduction

Infections remain a major cause of mortality in patients admitted to the intensive care unit (ICU). Antibiotic drugs are a mainstay of therapy and are more often used than in other patient populations. Overuse and uncritical initiation of therapy has significantly increased resistance to antibiotic drugs in the last 20 years.[1, 2] Multi-drug resistant bacteria are increasingly present, and there are very few therapeutic options to treat infections caused by:

- Methicillin-resistant Staphylococcus aureus (MRSA)
- Multi-drug resistant coagulase-negative staphylococci
- Vancomycin-resistant enterococci (VRE)
- Extended-spectrum beta-lactamase (ESBL) producing enterobacteria
- Multi-drug resistant non-lactose fermenting gram-negative rods (i.e. Pseudomonas aeruginosa, Acinetobacter baumanii)

Absence of an indication for antibiotic therapy and wrong drug choices increase selection and promote development of resistant bacteria. It is, therefore, of utmost importance to limit and rationalize the use of antibiotic drugs to reduce further selection and maintain therapeutic options for the treatment of the most severe infections for our patients and the entire population. Most likely, there will not be any new antibiotic drug development in the near future particularly for the treatment of gram-negative bacteria, so preserving the effectiveness of existing drugs is an important principle. In addition to overuse, inadequate dose or duration of therapy and

using the same antibiotic drug for the same indication over a long period of time can also increase selection.

Therapeutic Strategies (General Principles)

The two major principles of antibiotic therapy are targeted and empiric therapy. Targeted therapy requires culture acquisition and diagnosis with speciation of the causing organism. This is followed by a highly specific drug choice, and this is generally the most effective and rational method of antibiotic therapy. (See Table 37.1) Empiric therapy is often required in ICU patients due to acute illness and necessity of immediate initiation of treatment. As the causing organism is unknown, the antibiotic drug or sometimes combination of drugs chosen has to have a broader antimicrobial spectrum. It should, however, be thoughtful and potential sources and expected organisms should be taken into consideration. One should always go through a checklist of the most common sources for ICU infections that includes:

- Lungs
- Blood stream and indwelling catheters
- Urinary tract
- Wounds

For critically ill patients, for example, with severe pneumonia or sepsis, an immediate start of antibiotic therapy can be life-saving and must not be delayed. One study found that in septic patients mortality increases by 7.6% for every hour without effective antibiotic therapy.[3] "The Tarragona Strategy" defined some of the principles for early empiric treatment of severe infections in the ICU.[4] These include:

- "Look at your patient" (Clinical presentation and comorbidities)
- "Hit hard and early" (Adequate drug choice and dosage)
- "Listen to your hospital" (Knowledge of the local antibiogram)

In addition to those overarching principles, one should consider all aspects of antibiotic drug pharmacology, including tissue penetration, patient's organ dysfunction, side effects, and drug interactions. (Table 37.1)[5]

Empiric antibiotic therapy should always include acquisition of cultures and samples before initiation (if at all possible). Upon receipt of the culture results and speciation, antibiotic therapy must be narrowed and so converted to targeted therapy.

Antibiotic Drug Choice

I. Spectrum of Organisms

It is important to understand the differences in the spectrum of organisms when dealing with community-acquired versus nosocomial infections. Community-acquired infections are relatively easy to predict. It becomes more problematic with so called health-care-acquired infections in patients that are transferred from long-term care facilities, dialysis units, or nursing homes. Finally, nosocomial infections are hardest to predict in terms of the causative organism, and multi-drug resistant bacteria are more common. The effectiveness of antibiotic drugs is highly dependent on the local resistance situation.

II. Antibiotic Drug Mechanism of Action

There is no antibiotic drug that covers all bacteria, some are only against gram-positive bacteria, others only against gram-negative bacteria, some against aerobic and others against anaerobic bacteria, or they have varying stability against bacterial beta-lactamase. For example, newer generation cephalosporins are more stable when exposed to bacterial beta-lactamase than first and second-generation cephalosporins. Another example is that certain antibiotics have no therapeutic effect on certain bacteria, i.e. cephalosporins are not effective against enterococci. Most common antibiotics are not effective against Pseudomonas aeruginosa, as this particular bacterium has very small pores, which most antibiotic molecules cannot penetrate.

III. Antibiotic Tissue Penetration

Adequate tissue concentration at the site of the infection is important for effective antibiotic therapy. This has an impact on antibiotic drug choice. As a general principle, in well-perfused organs such as the lungs or the bladder, most antibiotics will reach adequate tissue concentrations. Certain antibiotics will not penetrate less-well perfused organs, such as bones or the central nervous system and meninges, due to molecule size. For example, vancomycin is a large molecule and does not penetrate well into the cerebrospinal fluid. Other antibiotics tend to accumulate in certain tissues, i.e. clindamycin in bones. The worst penetration is seen in poorly perfused areas such as abscesses or

Table 37.2 Principles of Antibiotic Drug Choice

Organism	Patient	Antibiotic Drug
Spectrum - community acquired - health-case acquired - nosocomial	Clinical presentation and risk factors	Spectrum
Antibiogram and local resistance patterns	Predisposing comorbidities	Side effects
	Antibiotic "history"	Tissue penetration
	Organ dysfunction	Pharmacology
	Allergies, age, pregancy	

necrotic tissue, i.e. diabetic gangrene foot or necrotizing fasciitis. In these cases, source control becomes more important than antibiotic therapy.

IV. Types of Antibiotic Drugs

Some antibiotics are bactericidal, some are bacteriostatic, and in some the effect depends on the organism present. Bactericidal antibiotics kill almost all targeted bacteria in a matter of about 24 hours. Bacteriostatic antibiotics mainly inhibit bacterial growth, but can also reduce the amount of bacteria slowly over time. Antibiotic drugs targeting the cell wall are generally bactericidal; drugs interfering with the protein synthesis usually are bacteriostatic. Some antibiotics are bactericidal against some bacteria, but bacteriostatic against others, i.e. linezolid is bactericidal against streptococci, but only bacteriostatic against staphylococci and enterococci. (Table 37.3)

Table 37.1 Antibiotic Drugs and Their Characteristics

Drug	Spectrum	Comments
Aztreonam	Gram-negative, including Pseudomonas aeruginosa	Inactivated by ESBL, safe in patients with penicillin allergy
1st Generation Cephalosporins (i.e., cefazolin)	Gram-positive, methicillin susceptible Few Gram-negative	
2nd Generation Cephalosporins (i.e., cefuroxime)	Less Gram-positive than 1st generation, more Gram-negative than 2nd generation	
3rd Generation Cephalosporins (i.e., ceftazidime)	Few Gram-positive Broad gram-negative coverage, including Pseudomonas aeruginosa in some	Penetrate the CNS
4th Generation Cephalosporins (i.e., cefepime)	Similar to 3rd generation, but greater resistance to beta-lactamases	
Clindamycin	Gram-positive cocci (including some MRSA) Anaerobes	High incidence of Clostridium difficile associated diarrhea
Colistin	Gram-negative rods, including multi-drug resistant Pseudomonas, Acinetobacter and Klebsiella	Nephrotoxic. Older drug which fell out of favor. Often a last resort for multi-resistant GNRs
Daptomycin	Gram-positive cocci, including MRSA	Severe skin and soft tissue infections and endocarditis
Macrolides (i.e., azithromycin)	Gram positive cocci Haemophilus influenzae	Usually for treatment of mild infections
Aminoglycosides (i.e., gentamicin)	Gram-negative rods Synergy against some Gram-positive cocci	Nephrotoxic and ototoxic
Carbapenems (i.e., meropenem)	Ultra-broad coverage	Imipenem can cause seizures
Linezolid	Gram-positive cocci, including MRSA and VRE	Last resort antibiotic for severe gram-positive infections
Metronidazole	Anaerobes Entameba hystolitica Clostridium difficile	
Penicillins	mostly Gram-positive cocci Some penicillins cover Gran-negative rods	Decreasing efficacy due to beta-lactamase producing bacteria Increased efficacy in conjunction with beta-lactamase inhibitor, i.e., tazobactam
Fluoroquinolone (i.e., ciprofloxacin)	Gram-negative rods Some Gram-positive cocci (Streptococcus usually resistant)	Only ciprofloxacin has sufficient Pseudomonas coverage Moxifloxacin provides no coverage for urinary tract infections
Vancomycin	Gram-positive cocci including MRSA Clostridium difficile (oral administration only)	Nephrotoxic and ototoxic Can cause Red Man Syndrome Needs loading dose and adequate trough serum levels to avoid development of resistance
Tigecycline	Gram-positive cocci, including MRSA Some Gram-negative rods (not Pseudomonas)	Last resort antibiotic for severe Gram-positive infections

V. Pharmacodynamics

The minimum inhibitory concentration (MIC) is the lowest concentration of an antibiotic that will inhibit the visible growth of an isolated microorganism after overnight incubation (18-24 hours). The minimum bactericidal concentration (MBC) is the lowest concentration of a bactericidal antibiotic required to kill a particular microorganism. A bacterium is sensitive to a certain antibiotic if the MIC is such that an adequate tissue concentration can be achieved without administering toxic doses of the drug.

VI. Patient Factors

Particularly in the ICU setting where we treat critically ill patients who frequently have comorbidities, antibiotic therapy must be tailored considering all relevant patient factors that may interfere with the drug chosen. The severity of the infectious illness is an important factor impacting drug choice as well as predisposing factors such as immunodeficiency or diabetes. Drug allergies, recent exposure to antibiotic drugs, and pregnancy also play an important role. Certain antibiotics should not be used in children, as their effect on growth is not completely understood (fluoroquinolones, tetracycline).

The most common acute patient factors influencing antibiotic drug choice and dosage in the ICU are organ dysfunction, especially renal and hepatic dysfunction. As most antibiotics are metabolized via hepatic or biliary excretion or renal clearance, doses and/or dosing interval have to be adjusted accordingly if these organs are dysfunctional. Also, patients with acute kidney injury should not receive nephrotoxic antibiotics, i.e. aminoglycosides.

VII. Combination of Antibiotic Drugs

When combining different antibiotic drugs to treat a severe infection, it makes sense to combine different types of antibiotics, for example a bactericidal and a bacteriostatic drug, i.e. cephalosporin and fluoroquinolone. The two main reasons for combination therapy in the critically ill patient are broadening of the spectrum of organisms and antibiotic synergy. The addition of beta-lactamase inhibitors to penicillins is a means to broaden the spectrum of the penicillin, which would have otherwise been inactivated by bacterial beta-lactamase. On the other hand, the combination of antibiotics with the

Table 37.3 Types of Antibiotic Drugs

Bactericidal	Dependent on Organism	Bacteriostatic
Penicillins	Linezolid	Chloramphenicol
Cephalosporins	Chloramphenicol	Sulfonamides
Carbapenems	Erythromycin	Tetracycline
Aminoglycosides	Azithromycin	Clindamycin
Fluoroquinolones	Clindamycin	Linezolid
Rifampin		Tigecycline
Vancomycin		Macrolides
Daptomycin		

same mechanism of action is generally not helpful and can in fact promote the development of resistance, i.e. carbapenem therapy can induce the production of specific beta-lactamases that make the bacteria resistant to penicillins and cephalosporins.

VIII. Reevaluation of Antibiotic Therapy

As a general principle, any antibiotic therapy should be reevaluated after two to four days of therapy. If the patient continues to have fevers or otherwise does not show clinical improvement, antibiotic therapy should be changed or broadened after careful review of culture results. The antibiotic drug may not be effective, but other reasons for ineffective therapy include the development of secondary resistance or growth of a second organism.

IX. Review of Microbiological Culture Results

It is important to recognize the difference between colonization and infection. The mere finding of an organism in a culture is no proof of clinically relevant infection. So again, the patient's clinical presentation has to correlate with the culture findings to justify antibiotic therapy.

Pneumonia

I. Community-Acquired Pneumonia (Non-aspiration Risk)

Diagnosis: Send sputum gram stain and culture, chest X-ray, and blood cultures
- Ceftriaxone 1 gm IV q24 hours PLUS
- Azithromycin 500 mg PO/IV q24 hours
- If previous MRSA colonization: Consider adding vancomycin 2 gm IV x 1 if > 70 kg, 1.5 gm IV x 1 if < 70 kg (loading dose), then 15 mg/kg IV q12 hours (maintenance)
- Typical duration: 7 days

II. Community-Acquired Pneumonia with Cavitary Lesions

- Consider oral anaerobes and MRSA
- Ampicillin/Sulbactam 3 gm IV q6 hours PLUS
- Vancomycin 2 gm IV x 1 if > 70 kg, 1.5 gm IV x 1 if < 70 kg (loading dose), then 15 mg/kg IV q12 hours (maintenance)
- Typical duration: 10-21 days

III. Health-Care Acquired Pneumonia

Diagnosis: Send sputum gram stain and culture, chest X-ray, and blood cultures. For ventilated patients, send quantitative BAL culture
- Consider MRSA, gram-negative rods, and oral anaerobes
- Cefepime 2 gm IV q8 hours PLUS
- Vancomycin 2 gm IV x 1 if > 70 kg, 1.5 gm IV x 1 if < 70 kg (loading dose), then 15 mg/kg IV q12 hours (maintenance)
- Typical duration: 7 days, unless pseudomonas or MRSA, then 14 days

IV. Ventilator Associated Pneumonia

Diagnosis: Send quantitative BAL culture, chest X-ray, and blood cultures

- For patients > 4 days of mechanical ventilation or hospitalization
- Consider MRSA, resistant gram-negative rods including pseudomonas, acinetobacter, and ESBL
- Cefepime 2 gm IV q8 hours PLUS vancomycin 2 gm IV x 1 if > 70 kg, 1.5 gm IV x 1 if < 70 kg (loading dose), then 15 mg/kg IV q12 hours (maintenance)
- Ciprofloxacin 400 mg IV q12 hours if dual gram negative coverage is needed
- Typical duration: 7 days, unless pseudomonas or MRSA, then 14 days

V. Other Considerations

- Cefepime, vancomycin, and ciprofloxacin need dose and/or interval adjustment for renal insufficiency
- If the patient has cystic fibrosis or is status post lung transplantation, consult infectious disease or pulmonology service for advice, as these patients frequently have chronic infection with resistant organisms and need early aggressive treatment
- Yeast in the lung rarely represents true infection and generally needs no antifungal therapy
- In case of a severe penicillin allergy:

  o For community-acquired pneumonia: Replace ceftriaxone or ampicillin/sulbactam with moxifloxacin 400 mg PO/IV q24 hours

  o For healthcare-acquired or ventilator-associated pneumonia: Replace cefepime with ciprofloxacin 400 mg IV q8 hours (PLUS/MINUS aztreonam 2 gm IV q8 hours)

Bloodstream Infection

I. Suspected Line Infection

Diagnosis: Immediate initiation of antibiotic therapy. You may draw paired, simultaneous blood cultures from all central line lumens AND one peripheral site. Depending on your hospital, line infection is suspected if the central line colony forming units (CFU) is more than twice as high as the peripheral CFU, or the central line cultures become positive 2 hours before the peripheral cultures.

- Vancomycin 2 gm IV x 1 if > 70 kg, 1.5 gm IV x 1 if < 70 kg (loading dose), then 15 mg/kg IV q12 hours (maintenance) PLUS
- Cefepime 2 gm IV q8 hours
- Consult with infectious disease service for management of line (i.e. removal versus salvage, timing)

II. Suspected Endocarditis, hemodynamically stable with no valve insufficiency

Diagnosis: Draw 3 sets of blood cultures prior to initiation of antibiotic therapy

- Vancomycin 2 gm IV x 1 if > 70 kg, 1.5 gm IV x 1 if < 70 kg (loading dose), then 15 mg/kg IV q12 hours (maintenance) PLUS
- Ceftriaxone 2 gm IV q24 hours

III. Suspected Endocarditis, hemodynamically unstable or valve insufficiency

Diagnosis: Immediate initiation of antibiotic therapy. Consult with cardiology and infectious disease services

- Vancomycin 2 gm IV x 1 if > 70 kg, 1.5 gm IV x 1 if < 70 kg (loading dose), then 15 mg/kg IV q12 hours (maintenance) PLUS
- Ceftriaxone 2 gm IV q24 hours PLUS
- Gentamicin 1 mg/kg IV q8 hours
- For prosthetic valves, add rifampicin 600 mg PO q24 hours

IV. Other Considerations

- Cefepime, ceftriaxone, vancomycin, and gentamicin need dose and/or interval adjustment for renal insufficiency
- Duration of treatment will vary based on microbiology and patient factors, surgical intervention and possible intraoperative tissue culture results

Urinary Tract Infections (UTI)

I. Community-Acquired Pyelonephritis

Diagnosis: Clean catch mid-stream urine analysis with reflexive gram stain and culture.

- Consider enteric gram-negative rods
- Ceftriaxone 1 gm IV q24 hours
- If patients are hemodynamically unstable, add levofloxacin 750 mg PO/IV q24 hours
- Typical duration: 3 days for uncomplicated infection in females, 7 days for complicated infections or in males
- Neutropenic or otherwise immunosuppressed patients will need coverage even without significant amount of white blood cells in urine analysis, if clinical presentation suggest pyelonephritis

II. Catheter Associated UTI (CAUTI)

Diagnosis: Obtain specimen from new urinary catheter or from sterilized port on existing urinary catheter, not from collection bag. Send urine analysis and reflexive gram stain and culture.

- Consider resistant gram-negative rods
- Ceftazidime 2 gm IV q8 hours
- If previous colonization or concerns for highly-resistant gram-negative organism such as acinetobacter or pseudomonas, consider meropenem 1 gm q8 hours instead of ceftazidime
- If gram-positive cocci on gram stain, add vancomycin 2 gm IV x 1 if > 70 kg, 1.5 gm IV x 1 if < 70 kg (loading dose), then 15 mg/kg IV q12 hours (maintenance)
- Deescalate or discontinue if other cause for patient's symptoms is found
- White blood cells and bacteria in urine analysis suggest infection, but colonization is not uncommon

III. Other Considerations

- Ceftriaxone, ceftazidime, meropenem, levofloxacin, and vancomycin need dose and/or interval adjustment for renal insufficiency

• In case of a severe penicillin allergy: Replace ceftriaxone, ceftazidime, and meropenem with levofloxacin 750 mg PO/IV q24 hours (PLUS/MINUS aztreonam 2 gm IV q8 hours)

Intra-Abdominal Infection

I. Community-Acquired Intra-Abdominal Infection
• Consider enteric gram-negative rods and anaerobes
• Ceftriaxone 1 gm q24 hours PLUS
• Metronidazole PO/IV q8 hours
• For uncomplicated biliary infection, anaerobic coverage with metronidazole is usually not necessary
• Typical duration: 5-7 days

II. Hospital Acquired Intra-Abdominal Infection
• Patients with severe physiological disturbance, advanced age, often immunocompromised
• Consider resistant gram-negative rods and anaerobes
• Vancomycin 2 gm IV x 1 if > 70 kg, 1.5 gm IV x 1 if < 70 kg (loading dose), then 15 mg/kg IV q12 hours (maintenance) PLUS
• Piperacillin/tazobactam 4.5 gm IV x1 (loading dose), then 4 hours later 3.375 gm IV q8 hours (maintenance)
• If previous colonization or concerns for highly-resistant gram-negative organism such as acinetobacter or pseudomonas, consider meropenem 1 gm q8 hours instead of piperacillin/tazobactam
• Typical duration: 5-7 days

III. Other Considerations
• Vancomycin is needed to cover enterococci
• Ceftriaxone, vancomycin, piperacillin/tazobactam, and meropenem need dose and/or interval adjustment for renal insufficiency
• In case of a severe penicillin allergy: Replace ceftriaxone, piperacillin/tazobactam, and meropenem with levofloxacin 750 mg PO/IV q24 hours PLUS metronidazole 500 mg PO/IV q8 hours

Sepsis with Unknown Infection Site

Diagnosis: Culture blood, urine, and sputum. Deescalate antibiotic therapy dependent on culture results, other laboratory findings, and clinical course.
• Consider MRSA and resistant gram-negative organisms
• Vancomycin 2 gm IV x 1 if > 70 kg, 1.5 gm IV x 1 if < 70 kg (loading dose), then 15 mg/kg IV q12 hours (maintenance) PLUS
• Meropenem 1 gm IV q8 hours
• If previous colonization or concerns for highly-resistant gram-negative organism such as acinetobacter, pseudomonas, or ESBL, consider adding ciprofloxacin 400 mg IV q12 hours OR tobramycin 7 mg/kg IV x 1
• Typical duration: 14 days

• Vancomycin, meropenem, ciprofloxacin, and tobramycin need dose and/or interval adjustment for renal insufficiency
• In case of a severe penicillin allergy: Replace meropenem with ciprofloxacin 400 mg IV q8 hours (PLUS/MINUS aztreonam 2gm IV q8 hours)

Meningitis

I. Non-Surgical Meningitis
Diagnosis: Immediate initiation of antimicrobial therapy. Lumbar puncture for opening pressure, gram stain and culture, herpes simplex virus (HSV) PCR, cell count, glucose, and protein. Add cryptococcal antigen for HIV patients.
• Consider Streptococcus pneumonia, Neisseria menigitidis, and Haemophilus influenza (rare in adults, and now rare in children since the onset of the vaccine), consider Listeria monocytogenes and HSV in younger and/or immunocompromised patients
• Ceftriaxone 2 gm IV q12 hours PLUS
• Vancomycin 2 gm IV x 1 if > 70 kg, 1.5 gm IV x 1 if < 70 kg (loading dose), then 15 mg/kg IV q8 hours (maintenance)
• If suspected listeria infection, add ampicillin 2 gm IV q4 hours
• If suspected HSV infection, add acyclovir 10 mg/kg IV q8 hours
• Typical duration: 14 days

II. Post-Surgical Meningitis
• Consider Staphylococcus epidermidis, Staphylococcus aureus, gram-negative rods
• Cefepime 2 gm IV q8 hours PLUS
• Metronidazole 500 mg IV q8 hours PLUS
• Vancomycin 2 gm IV x 1 if > 70 kg, 1.5 gm IV x 1 if < 70 kg (loading dose), then 15 mg/kg IV q8 hours (maintenance)
• Typical duration: variable

III. Other Considerations
• Ceftriaxone, vancomycin, ampicillin, acyclovir, and cefepime need dose and/or interval adjustment for renal insufficiency
• In case of a severe penicillin allergy: Replace ceftriaxone and ampicillin, with trimethoprim/sulfamethoxazole 5 mg/kg IV q8 hours PLUS aztreonam 2gm IV q8 hours PLUS vancomycin 2 gm IV x 1 if > 70 kg, 1.5 gm IV x 1 if < 70 kg (loading dose), then 15 mg/kg IV q8 hours (maintenance)

Multi-Drug Resistant Organisms

I. General Principles
As mentioned above, multi-drug

Table 37.4 Treatment Options for Multi-Drug Resistant Gram Positives		
Antibiotic	**MRSA**	**VRE**
Vancomycin	++	0
Linezolid	++	++
Fosfamycin	++	0
Rifampicin	++*	+*
Tigecycline	++	++
Daptomycin	++	?
++ = Good effect, + = Fair effect, 0 = No effect, * = Combination therapy only		

resistant organisms are an increasing problem in the ICU and therapeutic options are limited. One important principle is early detection of a multi-drug resistant bacterium and subsequent placement of the patient in isolation to avoid spread of the organism.

II. Multi-drug Resistant Gram Positive Bacteria

MRSA is now a common cause for nosocomial and healthcare-acquired infections. The reservoir for the organism is often the nose, throat, or skin of personnel or visitors. Patients are usually colonized and not ill. When transferred to a critically ill patient, the organism often causes infection. Spread of the organism can only be avoided if the patient is then properly isolated and personnel are compliant with hand hygiene measures. Antibiotic therapy for MRSA is only indicated if there is proven infection.[6] In the ICU, these are most commonly pneumonia and wound infections. Colonized individuals are treated with topical antibiotics and decontaminants.

Enterococci are enteric pathogens that have a natural resistance against many common antibiotics. More recently, some Enterococcus faecium species have developed resistance against vancomycin, which was traditionally an antibiotic for the most severe infections in the ICU. An important factor for the rise of VRE is the uncritical use of vancomycin. VRE infections are usually endogenous infections, most commonly urinary tract infections (UTI) and peritonitis. (Table 37.4)

III. Multi-Drug Resistant Enterobacteriaceae

Many enterobacteria species have the ability to produce beta-lactamases that can inactivate some of the beta-lactam antibiotics. More recently, ESBL producing enterobacteria have been found to be resistant to all available penicillins including piperacillin-tazobactam and fourth-generation cephalosporins such as cefepime. The only effective beta-lactam remaining are the carbapenems. Similar to MRSA or VRE, patients with proven ESBL enterobacterial infections must be isolated and strict hygienic measures must be applied. Most recently, there have been reports about carbapenem-resistant enterobateria, particularly klebsiella, which is another significant threat with very few therapeutic options left.

IV. Multi-Resistant Non-Lactose Fermenting Gram-Negative Rods

Table 37.5 Antibiotic Drugs and Risk of causing C.difficile associated Diarrhea		
High Risk	**Medium Risk**	**Low Risk**
Clindamycin	Cotrimoxazole	Tetracyclines
Aminopenicillins	Carbapenems	Macrolides
Cephalosporins	Fluoroquinolones	Aminoglycosides

These are relevant nosocomial organism that often reside in wet areas in the hospital. The best-known bacterium is Pseudomonas aeruginosa. Pseudomonas and similar bacteria tend to develop secondary resistance under antibiotic therapy. A combination therapy is usually indicated, and at times the only option are potentially toxic antibiotic drugs such as colistin.

Selection and "Collateral Damage"

I. Background

Antibiotic drugs do not only attack pathogenic organisms, but frequently also affect physiological flora, i.e. in the colon. If antibiotic therapy is unidirectional and not frequently changed or rotated, there will be selection of certain organisms, i.e. enterobacteria when cephalosporins are used. These can then colonize the patient in other areas of the body and potentially cause infection. Strategies to address this phenomenon include antibiotic combination and antibiotic cycling or rotation.[7]

II. Antibiotic Drug Induced Diarrhea

Diarrhea during antibiotic therapy is multifactorial, but in about 30% of the cases this is due to Clostridium difficile. Some individuals have Clostridium difficile in their gut, but when undergoing antibiotic therapy, subsequent alteration of the physiological flora of the gut can cause this microorganism to grow in an uncontrollable fashion. Depending on the severity, this can cause Clostridium difficile-associated diarrhea or Clostridium difficile colitis. Some antibiotic drugs are more prone to causing diarrhea. (Table 37.5) Clostridium difficile colitis can cause very severe disease in the ICU and often goes along with high fevers and a substantial increase in white blood cell count. Therapy should be metronidazole IV or PO for mild to moderate C.difficile colitis and vancomycin PO for severe infection.[8]

III. Strategies to Optimize Antibiotic Therapy

Interdisciplinary workgroups, guideline-driven therapy, and antibiotic stewardship programs are more recent developments to address the increasing complexity around antibiotic therapy in the hospital. Inadequate diagnosis may lead to poor antibiotic drug choices, which subsequently impairs therapeutic success and patient outcomes. This is most impactful in the intensive care unit (ICU) where we treat the most severe infections.[9,10]

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Questions

37.1 Therapy for MRSA infections can be challenging. Which of the following antibiotics is generally NOT effective against MRSA?
   A. Vancomycin
   B. Daptomycin
   C. Linezolid
   D. Vancomycin PLUS fosfomycin
   E. Amoxicillin

37.2 Clostridium difficile-associated diarrhea is not uncommon in the ICU and a potentially life-threatening condition. Which of the following is NOT considered an effective treatment for this disease?
   A. PO metronidazole
   B. IV metronidazole
   C. IV vancomycin
   D. PO vancomycin
   E. IV metronidazole PLUS PO vancomycin

37.3 When making a choice for one antibiotic drug over another, some factors should be taken into consideration. Which of the following is NOT considered important when making this clinical decision?
   A. The spectrum of microorganisms this drug is effective against
   B. The patient's clinical condition
   C. A patient's comorbidities and history of antibiotic intake
   D. Gender
   E. Local patterns of antibiotic drug resistance

37.4 What statement regarding empiric antibiotic therapy is correct?
   A. Once culture results are available, antibiotic therapy should be deescalated dependent on speciation and sensitivity
   B. When started on a specific combination of antibiotics, this treatment should be continued for a full course of 7-14 days
   C. For suspected pneumonia, empiric therapy should always be with a combination of at least two antibiotics
   D. Cultures do not necessarily have to be obtained, it is more important to start antibiotics without delay
   E. Even if the cultures do not grow out any pathogenic microorganisms, the antibiotics should always be continued for a full course of 7-14 days to avoid development of drug resistance

38. Management of the Immunocompromised Patient

Mark Caridi-Scheible MD, Christopher Paciullo PharmD and Joel Zivot MD

Key Points

• The management of an immunosuppressed critically ill patient requires a multidisciplinary team.

• Empiric broad-spectrum antibiotics should be started and administered immediately for all immunocompromised patients with severe sepsis/septic shock.

• An infection in an immunocompromised patient may not present in the usual manor as for an immunocompetent patient.

• Antimicrobial guidelines are available for organ transplant patients on immunosuppressive therapy.

A 50 year-old man with a history of a thoracoabdominal aortic aneurysm was admitted to the ICU from the operating room immediately following an open repair. Intraoperatively, he received 1000 mg methylprednisolone for spinal protection. His post-operative course was complicated by transfusion-related acute lung injury (TRALI) and hypovolemic shock that has partially improved. Today, post-operative day #3, he is intermittently diaphoretic, but is afebrile. His thrombocytopenia is worse and his white blood cell count is decreased from 15×10^9/L to 0.9×10^9/L. His vasopressor needs is also on the rise. He is currently not on antibiotics as they were discontinued after the first 24 hours following his surgery.

It is common to encounter patients in the ICU who are therapeutically immunosuppressed as well as those that are immunosuppressed as the result of a disease process or side effect of other therapy. Management of the immunosuppressed patient by the intensivist centers on:

- recognition of the immunocompromised state.
- acutely managing immunosuppressive agents until the appropriate specialists can be engaged.
- recognizing the altered presentation of an infection and sepsis, and choosing appropriate initial antibiotics.

A multidisciplinary approach is important and relevant consults should be obtained earlier rather than later, However, at times, the intensivist may need to make decisions quickly and should, therefore, be familiar with immunosuppressive pathophysiology and pharmacology.

Organ Transplant Patients

Management of the organ transplant patient can be complex and varies by organ transplanted as well as the time since transplant. Detailed guidelines are available from the American Society of Transplantation and the American Society of Transplant Surgeons (see references).

Immunosuppression is induced just before or during transplant with multiple agents. Induction agents gener-

ally include high-dose steroids and/or antibody therapy. High-dose steroids are tapered to low-dose and maintenance therapy and then continued for life. Maintenance therapy usually includes a calcineurin inhibitor (tacrolimus or cyclosporine – inhibits secretion of IL-2) or a mTor (mammalian target of rapamycin) pathway inhibitor (sirolimus – inhibits response to IL-2) and an anti-proliferative agent [azathioprine, mycophenylate (MMF)]. Polyclonal antibody therapy (antithymocyte globulin) carries the risk of serum sickness as well as very broad immunosuppressive effects. For the most part, it has been replaced with monoclonal antibodies (basiliximab) that target IL-2 receptors. Antibody therapy are more specific to organ rejection.

While assessment of organ rejection and adjustment of immunosuppressive regimens should be left to the appropriate specialists, often the intensivist will have to make adjustments based on acute illness that may affect drug clearance, toxicity or delivery. Maintenance therapy should not be interrupted if at all possible unless toxicity is present. Conversion to IV formulations is warranted when gut absorption is suspect. Serum levels need to be monitored daily and frequent consultation with the hospital pharmacist is needed to adjust doses in the presence of renal or liver dysfunction

Infection patterns in organ transplant patients are well studied and can guide empiric antibiotics. These are divided into 3 groups based on the time since transplant:

   - Day 0 - 30: Usually pre-existing (in donor or recipient) or surgically related (e.g. wound infections). Gram negative enterics, gram positives, fungal, HSV, and nosocomial respiratory viruses are most common.
   - Month 2 - 6: Viral causes tend to be CMV, EBV, and VZV. Opportunistic infections from PCP, toxoplasma, and Listeria. Gram negative enterics for small bowel recipients. Pseudomonas and Burkholderia in cystic fibrosis lung transplant patients.
   - > 6 months: Viral causes tend to be EBV, VZV, and community acquired viral infections. Listeria and Cryptococcus. Lung recipients (especially with chronic rejection) can have pseudomonas, burkholderia, and aspergillus. Gram negative bacteremia for small bowel recipients.

Common nosocomial infections can also occur at any time and are related to the presence of foreign bodies (catheters, lines) or to other procedures performed incidentally.

Empiric therapy should be according to likely organisms as above and the hospital's antibiogram for nosocomial organisms. It is NOT recommended that organ transplant patients be treated presumptively for multi-drug resistant organisms (MDRO's) unless evidence exists that one might be present (see antibiotic section below).

The need for prophylactic antibiotics varies by degree of immunosuppression, patient clinical acuity, and donor infectious disease status. Common prophylaxis may include sulfamethoxazole/trimethoprim for PCP, ganciclovir/acyclovir for HSV, CMV or EBV, and voriconazole for aspergillus. These should be continued if the patient had been on them, but should not be initiated empirically in the ICU unless indicated by the transplant team. Broad-spectrum antibiotics should not be initiated in these patients prophylactically without suspicion or evidence of active infection.

Bone Marrow Transplant (BMT)
Complications of BMT are similarly divided into 3 time-frames:

   - 0 - 30 days: ablative therapy related side-effects, graft failure or neutropenia with susceptibility to gram negative bacteremia, gram positive bacteremia, fungal infections, HSV viremia and respiratory viruses.
   - 60 - 90 days: acute graft-versus-host disease, T-cell dysfunction and hypogammaglobulinemia with susceptibility to Aspergillus, Candida, PCP and CMV infections.
   - > 90 days: chronic GVHD, functional asplenia with susceptibility to S. pneumonia, H. influenza, and viral infections (CMV and VZV).

Otherwise, the overall approach to the management of an infection is similar to organ transplant patients. See cancer section below for definition and management of neutropenia.

HIV
CD4 counts > 200/μL generally indicate immunocompetency and the patient may be treated in the normal fashion. Counts less than 200/μL may require prophylactic therapy for opportunistic infections. Opportunistic infections such as PCP, toxoplasmosis, and cryptosporidia should be considered in patients with sepsis. An altered mental status or presence of CNS abnormalities should prompt an immediate head CT followed by a lumbar puncture. Empiric coverage of serious infections should include antifungal and antiviral (for HSV/CMV) medications. Malignancy should be considered in the differential diagnosis for this population.

Patients on antiretroviral therapy (HAART) who are critically ill may have therapy suspended if unable to take oral medications or where significant renal or liver dysfunction alters drug kinetics and increases toxicity. Component HAART medications should not be continued individually as monotherapy. If in doubt, it is better to temporarily discontinue all HAART medications. For patients who have not been on HAART but are critically ill,, therapy should NOT be initiated until the critical phase of illness has resolved due to risk of immune reconstitution inflammatory syndrome.

Autoimmune Disorders
Patients with autoimmune disorders such as lupus, rheumatoid arthritis, ANCA vasculitis, Crohn's, ulcerative colitis, or psoriasis are often on immunosuppressive agents that generally include steroid therapy (with its concomitant adverse effects), anti-proliferative agent (azathioprine) and/or folate antagonist (methotrexate). Cytotoxic agents such as cyclophosphamide are generally used for acute flares. These agents can induce significant pancytopenia. For many autoimmune disorders, specific monoclonal antibody therapy is used. These all carry some degree of general immunosuppression as well. In contrast to anti-rejection medications in transplant patients, if the patient's autoimmune process is not the presenting illness, it is acceptable to hold immunosuppressive agents. The exception is chronic steroids which should not be abruptly discontinued.

Signs and symptoms of an autoimmune flare (fever, increased WBC's, constitutional symptoms) may be difficult to separate from an acute infection. Trending ESR and CRP can often help in making this differentiation. ESR will be elevated in both, but an

elevated CRP (especially >100 mg/L) is more indicative of an active infection.

Cancer patients

Cancer patients can be immunosuppressed by several mechanisms. With significant enough disease, they often have marrow suppression and dysfunction. Chemotherapy and radiation are cytotoxic and induce marrow suppression leading to leukopenia and neutropenia. Lymphoproliferative cancers do not produce functional immune cells and other cell lines will be competitively suppressed.

Chronic inflammation from tumor may also mask more acute inflammation secondary to infection. Constitutional symptoms, especially fever, may also be caused by the cancer itself and be chronic. New metastases should be part of the differential when evaluating symptoms such as an altered mental status.

Neutropenic patients as the result of ablative, chemo- or radiation therapy may have fever as the sole presentation of serious infection. Neutropenia is defined by an absolute neutrophil count (ANC) < 1.5×10^9/L, but the risk of infection generally does not increase markedly until the ANC falls below 1×10^9/L Severely neutropenic patients should be placed on neutropenic precautions. Plants or flowers in the patient's room as well as certain foods should be disallowed. Treatment guidelines are based on complex risk-stratification as defined by the Infectious Diseases Society of America (see references). Broad-spectrum antibiotics should be initiated immediately in any febrile neutropenic patient.

Congenital Immune Disorders

There are many specific congenital disorders, but they are rare and unlikely to present de novo outside of the pediatric ICU. A careful history should elicit a diagnosis and the appropriate specialist consulted. Meanwhile, use general guidelines for diagnosis and therapy below.

Other immunocompromised states

Following are other common causes of immunosuppression seen in the ICU. The significance of these varies and should be considered in the clinical context:
- Blood transfusion
- Drug therapy (e.g. typical antipsychotics, procainamide, steroids, NSAIDs, anti-thyroid medications)
- Chronic alcohol and drug abuse
- Extracorporeal circulation (ECMO, CRRT, VAD) – prevent fever and alter volume of distribution
- End stage renal disease
- Liver failure
- Critical illness in general, including trauma, burns and major surgery
- Splenectomy (notably against encapsulated organisms, vaccinations should be administered before leaving the ICU)
- Neonates
- Advanced age

Presentation of infection and sepsis

By definition, the immunosuppressed patient is unable to mount an appropriate response to an infection. White blood cell count may be unchanged or decrease instead of rise. Fever may be absent. It is important to include infection in the differential diagnosis when there is any worsening of a patient's clinical condition. Antibiotic therapy is not always warranted, but unexplainable changes that include isolated signs of sepsis should at least prompt the acquisition of cultures and close monitoring. In addition to the more recognizable signs of fever, tachycardia, tachypnea and/or hypotension, the following may also indicate infection:
- Decreasing white count
- Hypothermia
- Thrombocytopenia
- New arrhythmias
- Altered mental status
- Acidosis
- Supranormal SvO_2
- Hyperglycemia

Adherence to sepsis guidelines and initiation of goal-directed therapy remain crucial in these patients.

Lab values that may support the case for an infection include elevated lactate, SvO_2 and/or CRP. However, these may not be sensitive or specific enough. Pro-calcitonin may be more sensitive and specific, however it is not sensitive in severe neutropenia.

Antibiotic therapy

Unless otherwise indicated by specific guidelines, the decision to initiate antibiotics should be done in response to a suspected or confirmed infection with signs of shock (hypotension non-responsive to fluids) or unexplained end-organ dysfunction. Pre-emptive use of antibiotics without specific indication places the patient at risk for super-infections and development of multi-drug resistant organisms (MDRO's). When indicated, rapid administration of broad-spectrum antibiotics remains critical.

Selection of antibiotics should be as narrow as possible and reflect the likely sources. Considerations for the patient's history, local microbe prevalence, likely site of infection, mechanism and timing of immunosuppression (see guidelines), local resistance patterns and patient intolerances should be taken into account. As culture data become available, therapy should be narrowed or discontinued. In severely immunosuppressed patients, it is reasonable to include fungal coverage as well. In specific populations (see above), viral coverage should also be considered.

Immunosuppressed patients are more likely to develop MDRO's over the long-term. However, it is not as a result of immunosuppression, per se, but rather the recurrent exposure to antibiotics. Routine use of second-line agents such as carbapenems accelerate this process. Indications for initial use of second-line agents include recent cultures of resistant organisms, development of severe sepsis/septic shock while already on first-line agents, or local prevalence of specific MDRO's. If there is reasonable doubt about the correct course of action and the patient is decompensating, it is acceptable to provide single doses of second or third line agents until a more definitive decision is

made. However, this practice should not become routine.

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Questions

38.1 A 45 year-old woman with metastatic disease undergoing chemotherapy has an absolute neutrophil count of 1.7 x 10^9/L and an oral temperature of 38.1°C. The next best course of action is:
   A. Continue to monitor
   B. Pan-culture and monitor
   C. Begin broad-spectrum antibiotics
   D. Begin sulfamethoxazole/trimethoprim prophylaxis

38.2 A 25 year-old man with HIV on HAART with a CD4 count of 379/μL presents with small bowel obstruction and is strict NPO. The next best course of action is:
   A. Begin broad-spectrum antibiotics
   B. Discontinue all HAART medications
   C. Begin AZT intravenously
   D. Begin sulfamethoxazole/trimethoprim prophylaxis

38.3 An 86 year-old woman with a history of renal transplantion and recent failure to thrive presents with an an altered mental status, poor urine output, oral temperature of 35.2 C, and white blood cell count 5.2 x 10^9/L. The next best course of action is:
   A. Bolus fluid and continue to monitor
   B. Pan-culture and monitor
   C. Pan-culture and begin broad-spectrum antibiotics within one hour
   D. Obtain infectious disease consult

Section 10: Miscellaneous Topics

Push Button
To Open Door

Critical Care Units

Rooms 2326-2336

PUSH
TO
OPERATE
DOOR

Cover Cough

39. Managing Endocrine Emergencies

Daniel Rubin MD

Key Points

• Tight glucose control has an increased rate of hypoglycemic events and mortality. A more liberal strategy with goal glucose levels below 180mg/dL better balances glucose control and avoids dangerous hypoglycemia.

• Evaluating the HPA axis in critically ill patients can be diagnostically challenging and stress dose steroids are more commonly administered secondary to refractory shock than a random cortisol level or response to corticotropin.

• The most common thyroid related illness in critically ill patients is non-thyroidal illness syndrome (NTIS) with low thyroid hormone levels and a euthyroid state.

A 65 year old man with a past medical history of hypertension, diabetes mellitus type II and chronic kidney disease is admitted to the ICU after emergent exploratory laparotomy for perforated viscus. The patient arrives to the ICU intubated and sedated in septic shock. He is hypotensive (90/40 mmHg), tachycardic (115 bpm), and febrile (39°C), and has decreased urine output and hyperglycemia (352 mg/dL). He is given a large volume of crystalloid (>10L) without improvement. An insulin infusion with bolus is started for treatment of hyperglycemia with a goal of keeping the serum glucose <180 mg/dL. He is also started on infusions of norepinephrine, vasopressin and phenylephrine without improvement of his vasoplegic shock. Given the clinical condition, the patient is started on hydrocortisone 100mg IV every 8 hrs for refractory septic shock.

Hyperglycemia

The presence of hyperglycemia in the critically ill is not limited to those patients with a history of either type I or type II diabetes. Serum glucose can be profoundly elevated in patients suffering from strokes, MI or post-cardiac surgery. Hyperglycemia in the critically ill may predispose patients to infection, hypovolemia from glucosuria, and worse neurological outcomes in the setting of stroke. In 2001, a study by van den Berghe suggested that tight glycemic control (80-110 mg/dL) was ideal to decrease wound infections and improve mortality. However, subsequent studies (VISEP, GLUCONTROL, and NICE-Sugar) have not only failed to validate those findings, but have suggested that tight glycemic control can increase patient mortality. This is possibly related to the increased frequency of hypoglycemic events leading to an increased sympathetic response.[1,2] A less intensive blood glucose lowering strategy, with targeted blood glucose levels below 180 mg/dL, appears to be a more moderate approach to controlling hyperglycemia and significantly decreases the episodes of hypoglycemia.

DKA

Diabetic ketoacidosis (DKA) occurs in the setting of type I diabetes mellitus. A combination of hyperglycemia, inadequate insulin supply and lipolysis results in the production of ketones and a metabolic anion gap acidosis. DKA is usually precipitated by poor patient compliance and a physiologic stressor (such as surgery, infection, MI or PE), which increases glycogenolysis and gluconeogenesis. In the setting of decreased exogenous insulin, this causes an increase in blood glucose levels. Inadequate amounts of insulin prevent the body from utilizing the glucose stores and lipolysis results with an increase in blood ketones. DKA is diagnosed

by the presence of hyperglycemia, ketones and an anion gap metabolic acidosis. Large fluid deficits are present secondary to glucosuria and an osmotic diuresis. The goals of treatment are to decrease glucose levels with insulin (infusion), replace the volume deficit with crystalloid solutions (5-10L), and correct electrolyte abnormalities (potassium). Potassium should be corrected before the initiation of an insulin infusion to avoid severe hypokalemia. Volume administration should be closely monitored to avoid over resuscitation since these patients commonly have comorbidities such as COPD, chronic renal insufficiency and CHF. The administration of sodium bicarbonate is usually unnecessary to correct the low pH since the anion gap metabolic acidosis will resolve with the administration of insulin as the body metabolizes the ketones and creates bicarbonate.[3]

HHS

Non-ketotic hyperosmolar hyperglycemia state (HHS) is the presence of hyperglycemia that results in the shift of intracellular water to the intravascular space due to increased plasma osmolality without the presence of a metabolic acidosis. A stressor such as infection, surgery, GI bleeding, MI, or CVA along with poor compliance usually precipitates HHS. HHS results in significant dehydration due to glucosuria and an osmotic diuresis, in addition to the shifting of water into the intravascular space. Plasma osmolality is typically >350 mOsm/L and can be as high as 400 mOsm/L from marked hyperglycemia. As fluid shifts to the extracellular space, serum Na concentration falls, declining 1.6 mEq/ L for every 100 mg/dL (5.55 mmol/L) increment in the plasma glucose level above normal. Patients with profound hypovolemia may develop a lactic acidosis secondary to tissue hypoperfusion and this may confuse the diagnosis with DKA due to the presence of an anion gap metabolic acidosis. Treatment is similar to DKA and includes starting an insulin bolus/infusion to decrease blood glucose levels, volume replacement (5-10L) with crystalloid, electrolyte repletion and identifying the precipitating cause.[3]

Hyperthyroidism/Thyrotoxicosis

Thyrotoxicosis occurs when the supply of thyroid hormone is significantly greater than the metabolic needs of the body resulting in clinical manifestations of hyperthyroidism. It is most commonly caused by Graves' disease, toxic nodular goiter, paraneoplastic syndromes or excessive exogenous intake of thyroid hormone. Clinical symptoms are the direct result of increased metabolism caused by the excessive amount of thyroid hormone and include pyrexia, delirium, seizures, arrhythmias (sinus tachycardia and atrial fibrillation most commonly), myocardial ischemia, congestive heart failure, respiratory failure, hypoxemia and hypovolemia. Symptoms of thyrotoxicosis are non-specific in patients with critical illness, but the evaluation of thyroid function should always be considered in patients with a pre-existing history of thyroid illness. Thyrotoxicosis should also be considered in the post-operative patient, since exacerbations are usually associated with a precipitating event such as surgery or infection. Patients with thyrotoxicosis have severely elevated T4 and T3 levels and either high or low TSH levels depending on the etiology of the hyperthyroidism.

In patients who are clinically unstable, empiric therapy should be started before confirmation of the disease if there is a strong suspicion of thyrotoxicosis. Treatment is focused on decreasing the amount of circulating thyroid hormone, antagonizing its effects on the body, supporting hemodynamic stability (anti-pyretics, volume administration, beta-blockers) and treating the precipitating event. The first medication to be administered should be an anti-thyroid medication, such as propylthiouracil or methimazole, to decrease hormone production and conversion of T4 to T3. Saturated solution of iodine should only be given after an anti-thyroid medication has been given since iodine can cause a release of pre-formed thyroid hormone and worsen the disease. Non-specific beta-blockers also decrease conversion of T4 to T3 and help mediate the cardiovascular manifestations of hyperthyroidism such as arrhythmias. Relative adrenal insufficiency may be present in patients with severe thyrotoxicosis/thyroid storm and may warrant administration of hydrocortisone 100mg IV every 8 hrs. [4]

Hypothyroidism

Nonthyroidal illness syndrome (NTIS): The most commonly encountered thyroid illness in the ICU is NTIS (also known as euthyroid sick syndrome). It is characterized in critically ill patients with low T3, low/normal T4, high/normal rT3, and low/normal TSH, but the patient is still euthyroid, despite the low thyroid hormone levels. The mechanism for this decrease in thyroid hormone is unclear but may be mediated by inflammatory markers or from baseline chronic illness (renal or hepatic disease). It is important to ensure that despite the decrease hormone levels, the patient remains euthyroid at the cellular level. Patients with a significantly decreased rT3 should be suspected of having clinical hypothyroidism and may benefit from treatment with levothyroxine. Patients who present with NTIS (decreased T4 levels without a concurrent increase in TSH) have a higher mortality than those who do not have thyroid abnormalities. One hypothesis for the physiologic mechanism of this disease is that the body decreases thyroid hormone production as a way of conserving energy during a critical illness. Treatment of NTIS with T3 or TSH is controversial as it may increase metabolic demand during critical illness and may worsen outcomes.[5]

Adrenal Insufficiency

Cortisol is a glucocorticoid that mediates many important functions that pertain to the critically ill such as immunity (cellular and cytokines), cardiovascular sensitivity to inotropes (norepinephrine, epinephrine, and angiotensin) and increasing blood glucose levels (gluconeogenesis). In non-critically ill patients, there is a steady secretion of cortisol with a normal diurnal variation that peaks in the morning and evening. During critical illness, this diurnal variation disappears. The normal physiologic response to stress results in an increase in production of corticotropin-releasing hormone (CRH) from the hypothalamus, which causes an increase in production of corticotropin (ACTH) from the pituitary, which in turn causes a sustained increase in production and secretion of cortisol by the adrenal cortex. Clinical signs of adrenal insufficiency include: shock that is refractory to intravenous fluids and vasoconstrictors, low diastolic blood pressure, mental status changes, hypoglycemia, hyponatremia, and hyperkalemia. Despite the vasoplegic shock, the overall cardiac output in these patients may be elevated, normal or lower than normal.

Identifying patients with adrenal insufficiency can be difficult since no direct test can measure whether there is a sufficient amount of cortisol for the patient's physiologic needs. The two most common tests performed to determine adrenal insufficiency are: random cortisol level and the corticotropin stimulation test. A random cortisol level, drawn at any time of day, should be greater than 15μg/dL, since diurnal variation is abolished in the critically ill. Cortisol levels below this threshold with clinical signs of adrenal insufficiency are highly suggestive of adrenal insufficiency. Levels between 15-25μg/dL for patients without septic shock and 15-34μg/dL for patients in septic shock may be seen in patients that have adrenal insufficiency and should be further evaluated by a corticotropin stimulation test. Patients not in septic shock with levels greater than >25μg/dL and patients in septic shock with levels >34μg/dL usually do not have adrenal

insufficiency and are unlikely to benefit from supplemental steroids.

The corticotropin stimulation test is used to assess adrenal reserve. It can either be given as a high-dose ACTH test or a low-dose ACTH test. Both are performed by drawing a baseline serum cortisol level and then giving a dose of corticotropin. In the high-dose ACTH test, 250mcg of corticotropin is given and in the low-dose ACTH test, only 1mcg of corticotripin is given. Low-dose ACTH appears to be more sensitive in finding patients with inadequate adrenal reserve. Cortisol levels are measured at 30 and 60 minutes after giving the corticotropin and the increase in serum cortisol should be >9µg/dL or final level >18µg/dL. Failure of the cortisol level to reach these levels is suggestive that the patient may benefit from supplemental steroids.

Cortisol levels in patients with septic shock are normally lower than patients with similar degrees of shock precipitated by other causes. The mechanism for this is unclear but may be mediated by cytokines that are released secondary to the infection. This led to studies that suggest treating patients in septic shock with hydrocortisone and fludrocortisone decreased mortality and had a faster reversal of shock.[6] However, the subsequent CORTICUS trial in 2007 suggested that there was no improvement in mortality despite a faster reversal of shock in the steroid group.[7] Even in patients that were thought to be adrenally insufficient based on random cortisol and corticotropin stimulation testing, there was no improvement in mortality with steroids. After the CORTICUS trial, treatment of septic shock with hydrocortisone has fallen out of favor and the Surviving Sepsis Campaign limits its recommendations to those patients that have shock refractory to intravascular volume repletion and vasopressors.[8] Common stress dose steroid dosing regimen is hydrocortisone 50-100mg IV q6-8hrs or a bolus of 100mgIV and then an infusion of 9mg/h for a total dose between 200mg-300mg/day. When steroids are used they should be tapered as soon as there is clinical improvement.

Certain medications can decrease cortisol production, most notably etomidate. Etomidate suppresses the function of 11-β-hydroxylase which is involved in cortisol production. Long term infusions of etomidate have been associated with increased mortality, but while single induction doses appear to decrease cortisol levels, the clinical consequences are still uncertain. Large scale retrospective reviews of etomidate use suggest that there is no increase in mortality in patients who receive a single induction dose of etomidate.[9]

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Questions

39.1 First line therapy for both DKA and HHS include all of the following except?
   A.   Intravascular volume repletion
   B.   Insulin bolus and infusion
   C.   Repletion of electrolytes
   D.   Sodium bicarbonate
   E.   Identifying the precipitating cause

39.2 A patient is admitted to the ICU with ARDS/sepsis, acute kidney injury and refractory hypotension on a low dose of norepinephrine with low T3, normal T4 and low TSH. He should be treated with what drug?
   A.   Levothyroxine
   B.   Activated T3
   C.   Nothing
   D.   Methimazole

39.3 A patient in refractory septic shock was started on hydrocortisone 100mg IV every 8hrs two days ago. He has been weaned off of vasopressin but is still mechanically ventilated. How should his dose of hydrocortisone be managed?
   A.   Continue stress dose steroids for at least 7 days
   B.   Taper the steroids
   C.   Perform a corticotropin stimulation test
   D.   Change the hydrocortisone to a continuous infusion

40. Toxicology and Support of Patients with Drug Overdoses

Matthew D Koff MD MS

Key Points

• Initial management for all toxicological emergencies is basic life support: airway, breathing, and circulation.

• Although there are some specific treatment medications ("antidotes") available for specific ingestions/exposures, the majority is managed by supportive care, including enhancement of elimination/metabolism.

• Poison control, if available, should be immediately contacted for all toxicological emergencies.

A 26-year-old man was found unconscious at home by his girlfriend after they had an argument over the phone. EMS was called and transported the patient to a local emergency department. Currently, he is spontaneously breathing with a non-rebreather mask over his face, collapsing the reservoir bag, and breathing at a rate of 40 breaths/min. His heart rate is 120 bpm and blood pressure is 138/82 mmHg. He has an altered level of consciousness. A bedside point-of-care glucose is 186 mg/dL. An ECG shows sinus tachycardia, normal intervals, and a normal axis. The results of an ABG are: pH of 6.9, $PaCO_2$ 21 mmHg, PaO_2 420 mmHg, and bicarbonate 5 mmol/L. A serum osmolality, aspirin level and acetaminophen level are pending. How should this patient be immediately managed?

Introduction:

Critically ill patients who are admitted to the intensive care unit with drug-related events test the understanding and application of pharmacology and pathophysiology. Patients can present with drug toxicity secondary to side-effects, allergic reactions, or overdoses. Additionally, toxic reactions to commonly encountered plants and animals can produce life-threatening reactions. Occasionally, some patients in the ICU, and even the OR, will develop an adverse reaction as a consequence to administered medications.

The initial step in management, irrespective of initiating factors, is supportive care, which includes control of airway patency, oxygenation/ventilation, and maintenance of circulation. Following initial assessment, these patients may require monitoring and physiologic support in the ICU. The following is an outline of important topics in the management of a patient suffering from a toxicological emergency. Use of internet-based resources such as Micromedex and Clinical Pharmacology are helpful to guide current treatment and management. There are many smartphone and tablet specific applications available (for free and for purchase) that allow for a bedside or "curbside" resource. Contact with the local poison control center can also offer immediate assistance and should be readily utilized.

   I. General management
    A. Basic life support with careful and continuous evaluation of airway
      1. Neurologic evaluation

2. Glasgow coma scale
3. Antagonist administration for decreased level of consciousness
   a. Glucose 25 g IV
   b. Naloxone 0.04 mg IV every 2-3 minutes up to 10 mg
   c. Thiamine 100 mg IV
   d. Flumazenil (use with extreme caution)
B. Laboratory evaluation
   1. Acid-Base Disorders/Anion gap (Table 40.1)
   2. Co-oximetry
   3. Osmolar Gap (Table 40.2)
   4. Toxicology screens
C. Electrocardiogram
D. Prevention of further absorption
   1. Gastric lavage rarely used unless performed immediately after life threatening ingestion
   2. Activated charcoal with cathartics (single or multidose for specific ingestions)
   3. Emetics rarely indicated and used.
   4. Whole bowel irrigation for extended-release medications
E. Enhanced elimination
   1. Solute diuresis
   2. Alkaline diuresis
   3. Hemodialysis
   4. Charcoal/resin hemoperfusion

Table 40.1 Agents Associated with Elevated Ion Gap Acidosis	
Anion Gap = [Na] - [Cl] - [HCO3]	
Alcoholic ketoacidosis	Ibuprofen
Benzyl alcohol	Lactate
Diabetic ketoacidosis	Metaldehyde
Ethylene glycol	Methanol
Exogenous organic/ mineral acids	Salicylate
Formaldehyde	Valproic acid

II. Pharmacokinetics
A. Absorption
   1. Enteric-coated
   2. Sustained-release
   3. Heavy metals
B. Metabolism
   1. Liver
   2. Kidney
C. Distribution

1. Water-soluble
2. Protein-bound
3. Molecular weight
D. Excretion
   1. Renal
   2. Biliary (caution: enterohepatic circulation)

III. Alcohol-Glycols
A. Ethanol
   1. Acute
   2. Chronic/Acute-on-chronic
      a. Wernicke's encephalopathy
      b. Korsakoff's psychosis
      c. Alcoholic Ketoacidosis
   3. Treatment is supportive: glucose, thiamine, fluids
   4. Withdrawal/Delirium Tremens: benzodiazepines
B. Methanol
   1. Clinical presentation
      a. First few hours: inebriation and gastritis; osmolar gap
      b. Latent period of up to 30 hours: severe metabolic acidosis, visual disturbances, blindness, seizures, coma, death
   2. Treatment
      a. Supportive care
      b. Fomepizole or ethanol
      c. Folic or folinic acid
      d. Hemodialysis
C. Ethylene Glycol
   1. Clinical presentation
      a. First few hours: inebriation and gastritis; osmolar gap
      b. Latent period of up to 12 hours: severe metabolic acidosis, hyperventilation, seizures, coma, arrhythmias (urine oxalate crystals)
   2. Treatment
      a. Supportive care
      b. Fomepizole or ethanol
      c. Pyridoxine, folate, thiamine
      d. Calcium for hypocalcemia
      e. Hemodialysis
D. Propylene Glycol/Polyethylene glycol
   1. Clinical presentation: seizures, CNS depression, coma, lactic acidosis
   2. Treatment is supportive; hemodialysis is effective
E. Isopropanol
   1. Clinical presentation: inebriation, gastritis, coma, mild metabolic acidosis, osmolar gap, acetone (fruity breath)

2. Treatment is supportive care

IV. Sedative-hypnotics
A. Barbiturates
  1. Clinical presentation: lethargy and slurred speech to coma
  2. Treatment is supportive
B. Gamma hydroxybutyrate (GHB)
  1. Clinical presentation
    a. 15 minutes: soporific effects and euphoria
    b. 30-40 minutes: coma
    c. Delirium and agitation are common; seizures are rare
    d. Bradycardia is common; tachycardia and hypertension are rare
    e. Withdrawal syndrome has been reported with chronic use
  2. Treatment
    a. Supportive care
    b. For withdrawal: benzodiazepines (not uncommon to be refractory and may need barbiturates)

V. Benzodiazepines
A. Ultra-short acting vs. short-acting vs. long-acting
B. Clinical presentation: lethargy to coma to respiratory arrest
C. Treatment
  1. Supportive care
  2. Flumazenil: 0.1-0.2 mg up to 3 mg (not recommended in routine management)
    a. May induce seizures
    b. May induce acute withdrawal
    c. Re-sedation is common and repeat dosing is frequently required

VI. Tricyclic Antidepressants
A. Clinical presentation
  1. Seizures
  2. Anticholinergic effects: sedation, delirium, coma, dilated pupils, dry skin, diminished sweating, diminished or absent bowel sounds, urinary retention, and myoclonus
  3. Cardiovascular effects: hypotension, sinus tachycardia with prolongation of all intervals (especially QRS complex), various degrees of AV block, ventricular tachycardia, and ventricular fibrillation
B. Treatment
  1. Supportive care
  2. Sodium bicarbonate to maintain pH 7.45-7.55
  3. Avoid procainamide or other type 1a or 1c antiarrhythmics as these drugs can aggravate cardiotoxicity

VII. Opioids
A. Agonist versus mixed

B. Clinical presentation
  1. Mild to moderate: lethargy, bradycardia, bradypnea, diminished bowel sounds, miosis (pinpoint pupils)
  2. Severe: coma, apnea
  3. Seizures with meperidine, dextromethorphan, propoxyphene, tramadol
C. Treatment
  1. Supportive care
  2. Naloxone
    a. Can induce acute withdrawal syndrome (pain, anxiety, tachycardia, pulmonary edema, diarrhea, vomiting)
    b. May need to re-dose as half-life is much shorter than most opioids

VIII. Salicylates
A. Clinical presentation
  1. Acute ingestion: vomiting, tachypnea, tinnitus, lethargy, coma, seizures, hypoglycemia, hyperthermia, pulmonary edema, and death; respiratory alkalosis and metabolic acidosis
  2. Chronic ingestion: confusion, dehydration; metabolic acidosis
B. Treatment
  1. Supportive care
  2. Whole bowel irrigation
  3. Urinary alkalinization with sodium bicarbonate to keep urine pH $\geq$ 7.5
  4. Hemodialysis
  5. Do not intubate unless absolutely necessary as most patients are able to maintain the necessary minute ventilation to compensate for the metabolic acidosis
IX. Acetaminophen

Table 40.2 Agents Associated with an Elevated Osmolar Gap

Osmolality = 2[Na] + [glucose]/18 + [BUN]/2.8

Acetone	Mannitol
Diabetic ketoacidosis	Metaldehyde
Dimethyl sulfoxide (DMSO)	Methanol
Ethanol	Osmotic contrast dyes
Ethyl ether	Propylene glycol
Ethylene glycol	Renal failure without dialysis
Isopropyl alcohol	Severe alcoholic ketoacidosis
Lactic acidosis	

A. Hepatotoxicity
  1. NAPQI is formed from metabolism of acetaminophen (toxic)
  2. Glutathione is added to render it non-toxic
B. Clinical presentation
  1. Depends on the amount of liver injury

2. Rumack-Matthew normogram

C. Treatment:
1. Supportive care
2. N-acetylcysteine infusion(to allow more production of glutathione)
3. Liver transplant (King's College criteria)

X. Sympathomimetic

A. Examples
1. Amphetamine
2. MDMA
3. Cocaine
4. Methamphetamine
5. Pseudoephedrine
6. Methylphenidate
7. Cathinone (bath salts)

B. Clinical presentation
1. Central nervous system effects: euphoria, anxiety, agitation, seizures, sweating, tremor, rigidity, hyperthermia, coma, intracranial hemorrhage
2. Cardiovascular effects: tachycardia, hypertension, myocardial infarction, pulmonary hypertension (chronic use)
3. Respiratory effects: tachypnea, pulmonary edema
4. Gastrointestinal effects: abdominal pain, diarrhea
5. Serotonin syndrome

C. Treatment
1. Benzodiazepines
2. Beta and alpha blockade
   a. Labetalol
   b. Esmolol
   c. Phentolamine

XI. Cyanide

A. Sources
1. Common combustion by-product of burning plastics, wool and synthetic materials
2. Metabolic/degradation product of nitroprusside

B. Mechanism of action: binds to mitochondrial cytochrome oxidase

C. Metabolized to thiocyanate which is excreted in urine

D. Clinical presentation
1. Abrupt onset (immediately after exposure) of headache, nausea, dyspnea, confusion, seizures, coma, cardiovascular collapse
2. Severe lactic acidosis
3. Elevated mixed venous saturation

E. Treatment
1. Hydroxocobalamin
2. Sodium nitrite

3. Sodium thiosulfate
4. Supportive care

XII. Beta-blockers

A. Clinical presentation
1. Time to presentation varies depending on exact drug (selective versus non-selective), formulation (ER, XL, etc.), and quantity ingested
2. Neurologic: confusion, seizures, coma, respiratory arrest
3. Cardiovascular: hypotension, sinus bradycardia, AV block, intraventricular conduction abnormalities, interval conduction delays, ventricular tachycardia, asystole
4. Hypoglycemia

B. Treatment
1. Supportive care
2. Atropine up to 0.01-0.03 mg/kg IV
3. Epinephrine
4. Glucagon
5. Insulin/Glucose
6. Intralipid infusion (only if recommended by Poison Control)

XIII. Calcium-channel blockers

A. Clinical presentation
1. Time to presentation varies depending on exact drug (selective versus non-selective), formulation (ER, XL, etc.), and quantity ingested
2. Neurologic: stupor, confusion, nausea, coma
3. Cardiovascular: hypotension, bradycardia, AV block (usually no intraventricular conduction abnormalities)
4. Hyperglycemia

B. Treatment
1. Supportive care
2. Calcium
3. Epinephrine
4. Glucagon
5. Insulin/Glucose
6. Intralipid infusion (only if recommended by Poison Control)

XIV. Other poisons/ingestions (compound: antidote/reversal)

A. Mushrooms (amatoxin-type): N-acetylcysteine
B. Carbon monoxide: oxygen/hyperbaric oxygen
C. Cardiac glycosides (i.e., digoxin, oleander): digoxin-specific antibodies
D. Iron: deferoxamine
E. Isoniazid: pyridoxine
F. Methemoglobinemia: methylene blue
G. Organophosphates: atropine and pralidoxime

XV. Pediatric (One pill or mouthful can kill a 10 kg child)

A. Iron

B. Chloroquine, quinine, quinidine and hydroxychloroquine

C. Clonidine

D. Sulfonylureas

E. Tricyclic antidepressants

F. Lindane

G. Diphenoxylate/atropine

H. Beta-blockers

I. Theophylline

J. Calcium channel blockers

K. Camphor

L. Oil of wintergreen/salicylates

M. Ethylene glycol

N. Nose sprays and eye drops

O. Benzocaine

P. Opioids

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Questions

40.1 Which of the following is NOT consistent with cyanide toxicity?
    A. Metabolic acidosis
    B. Tachycardia
    C. Seizures
    D. Decreased mixed venous saturation

40.2 A 31 year-old patient is brought to the emergency department after being found at home, unconscious, lying next to an empty bottle containing acetaminophen/oxycodone tablets. Upon arrival to the ED, she is given naloxone and glucose and promptly awakens. No other abnormalities are noted. What other drug should be most likely administered to this patient?
    A. Flumazenil
    B. Pyridostigmine
    C. N-Acetylcysteine
    D. Ipecac

40.3 Methanol ingestion leads to a non-anion gap metabolic acidosis.
    A. True
    B. False

40.4 A comatose patient is admitted to the ICU and responds to sternal rub with withdrawal. Neurologic evaluation shows increased deep tendon reflexes. An ECG is interpreted as sinus tachycardia with first-degree heart block and prolonged QRS and QTc intervals with frequent ventricular ectopic beats. The most likely cause of her symptoms is:
    A. Aspirin
    B. Heroin
    C. Diazepam
    D. Acetaminophen
    E. Nortriptyline

40.5 Prior to administering glucose to a patient with alcohol intoxication, what drug should be administered?
    A. Folate
    B. Magnesium
    C. Multivitamins
    D. Thiamine
    E. Clonidine

40.6 The most common symptom associated with an aspirin overdose in pediatric patients is:
    A. Headache
    B. Respiratory acidosis
    C. Fever
    D. Respiratory alkalosis

40.7 The benzodiazepine receptor is an integral part of the serotonin receptor complex.
    A. True
    B. False

41. Solid Organ Transplantation

Eleanor Anne Vega MD and Darren Malinoski MD

Key Points

• **Outcomes after solid organ transplantation have increased over recent years but patients continue to suffer from transplantation-specific complications related to their underlying disease, the transplantation surgery, or immunotherapy. Prevention, early recognition, and appropriate treatment of these complications can reduce morbidity and mortality in these patients.**

• **Major complications after heart transplant include right ventricular failure, arrhythmias, primary graft dysfunction, and cardiac allograft vasculopathy.**

• **Lung transplant recipients commonly suffer from airway complications, infection, primary graft dysfunction, and bronchiolitis obliterans.**

• **Following liver transplantation, patients are at risk for arterial and biliary surgical complications, infection, and primary graft dysfunction.**

A 56-year old man is in the ICU after orthotopic heart transplant for non-ischemic cardiomyopathy. The operative course was notable for transfusion of 8 units packed red blood cells (PRBC), 8 units fresh frozen plasma (FFP), and 2 units of platelets. The patient received another 2 units PRBC, 2 units FFP, and 1 unit of platelets in the first several post-operative hours for significant chest tube output associated with hypotension. Thereafter, hemodynamics stabilized and chest tube output slowed. Infusions included epinephrine, milrinone and norepinephrine. The following day (post-operative day one), the patient again became hypotensive with a decrease in MAP from 65 to 50 mmHg. CVP increased from 10 to 20 mmHg and cardiac index decreased from 3.5 to 2.5 L/min/m². No changes had been made to pressor and inotrope infusion rates. The patient was being paced synchronously at 115 bpm. Transthoracic echocardiogram revealed a dilated right ventricle with poor right ventricular global function and no evidence of pericardial effusion.

INTRODUCTION

In recent years, patients receiving solid organ transplantation have experienced both improved survival and graft function. Despite these advances, survival remains compromised by a variety of transplantation-specific complications. Proper treatment of these complications is essential to optimizing patient outcomes. The overriding goal of care for any transplantation candidate in the pre-operative period is to create a "window of opportunity" where the patient is stable enough to qualify for and undergo transplantation.[1] Management of patients with heart disease, respiratory failure, and liver failure (i.e. pre-operative transplantation candidates) has been discussed in previous chapters and will not be revisited here. Likewise, post-operative complications common to both transplantation and non-transplantation surgeries, such as renal failure, respiratory failure, and transfusion reactions, are discussed elsewhere. This chapter will focus on the diagnosis and management of post-operative complications specific to heart, lung, and liver transplantation, including issues related to the underlying disease process, the transplantation surgery itself, acute and chronic rejection, and immunosuppression therapy.

HEART TRANSPLANTATION

Demographics and Outcome

Approximately 2000 heart transplantations are performed in the United States each year. The most common indications for heart transplantation are cardiomyopathy (54%) and coronary artery disease (38%), with a much smaller proportion of transplantation being performed for congenital heart disease and valvular disease. Outcomes following heart transplantation are generally quite good. Patient survival five years after trans-

plantation is approximately 77%. Predicted transplant half-life, conditional on 1-year survival, is 14 years. The most common cause of death remains underlying cardiovascular disease.[2]

Post-operative Intensive Care Unit (ICU) Management

I. General Post-operative Management

A. Monitoring

1. Patients arrive from the operating room (OR) with a variety of monitors in place. In addition to standard monitors and a Foley catheter, patients will have an arterial line, a pulmonary artery (PA) catheter, 1-2 sets of epicardial pacing wires, and several mediastinal drains.

B. Infusions

1. Patients may arrive on a multitude of vasoactive infusions, including a variety inotropes and vasopressors.

2. Vasopressors can be titrated according to systemic vascular resistance (SVR) and mean arterial pressure (MAP), but inotropes should be weaned slowly over the course of several days (see below).

3. In addition, patients may be on continuous inhaled nitric oxide or intermittent inhaled prostacyclins.

C. Ventilator Management

1. Ventilator settings can often be weaned and patients can be extubated within the first 1-2 post-operative days.

2. When assessing readiness for extubation, consideration must be given to hemodynamic status and right ventricular (RV) function as continued mechanical ventilation may be beneficial in the management of hypercarbia and hypoxia.

D. Hemodynamic instability

1. The differential diagnosis for hemodynamic instability in the post-operative heart transplant recipient includes the following: tamponade, hypovolemic shock due to hemorrhage, primary graft dysfunction, post-cardiopulmonary bypass inflammatory response, elevated pulmonary vascular resistance (PVR), right or left ventricular dysfunction, and hyperacute rejection.[3]

2. Values obtained or calculated from PA catheter measurements, including pulmonary vascular resistance (PVR), systolic and diastolic PA pressures, pulmonary capillary wedge pressure (PCWP), SVR, cardiac output (CO), central venous pressure (CVP), and mixed venous oxygen saturation (SvO_2), can be useful in determining the etiology of instability.

a. A combination of high CVP, low CO, and hypotension can be caused by either tamponade or RV failure; emergent echocardiogram may be helpful in differentiating between these two conditions.[4]

i. Tamponade should prompt an immediate return to the OR for re-exploration.

ii. Management of RV failure is discussed below.

3. Diagnosis of left ventricular (LV) failure can be made by echocardiogram and is supported by hypotension and low CO.

a. LV failure can be precipitated by primary graft dysfunction and hyperacute rejection.

b. Intra-aortic balloon pump (IABP) or left ventricular assist device (LVAD) should be considered as bridge-to-recovery or bridge-to-re-transplantation when

LV dysfunction does not improve with inotropic therapy.[4]

II. Right Ventricular Failure

Right ventricular failure is one of the most common and serious complications following heart transplantation, occurring in greater than 50% patients and accounting for more than 20% of early deaths.[4]

A. The etiology of RV failure in the early post-operative period is multifactorial.

1. The donor heart is exposed to multiple stressors, including ischemia, cardioplegia, and surgical manipulation, all of which contribute to myocardial stunning and decreased contractility.

2. The donor RV, previously naïve to high pressures, is exposed to elevated PVR in the recipient, which is due to a combination of longstanding pulmonary hypertension, increased levels of catecholamines secondary to inotrope and vasopressor infusions, and complications from cardiopulmonary bypass.

3. The thin walled RV is unable to generate enough pressure to overcome this resistance and subsequently dilates.

4. Excess volume from crystalloid, colloid or blood transfusions exacerbates the problem. This combination of volume overload, decreased contractility and increased afterload leads to RV failure.[3,4]

B. Severe RV dilation can cause shifting of the interventricular septum into the LV, which interferes with LV filling and leads to LV failure and decreased cardiac output.

1. Multisystem organ failure can result, including liver failure from hepatic congestion and acute kidney injury.[4]

C. Due to the critical nature of this complication, a multimodal approach is used to prevent and treat elevated PVR and RV failure.

1. Optimization of Preload

a. Some patients arrive to the ICU in a hypovolemic state and require volume resuscitation for hemodynamic instability in the early post-operative period.

b. Once the patient is no longer hypovolemic, aggressive diuresis is needed to avoid volume overload, often as early as the first post-operative day.

i. Infusions of loop diuretics are first-line therapy. Patients on long-term loop diuretic therapy pre-operatively may demonstrate resistance to the drug post-operatively.

ii. Boluses of thiazide diuretics are added if loop diuretics are insufficient.

iii. Renal replacement therapy (RRT) may be necessary to remove volume if pharmacologic therapy is inadequate.

c. Heart rate should be maintained at rates between 100-120 beats per minute (bpm) to minimize time for RV filling.

i. Atrial-ventricular synchrony should be maintained.

ii. Heart rate can be gradually decreased over time to intrinsic rate.

d. Volume status can be assessed by measurements from PA catheter (CVP, diastolic PA pressure) and by images from bedside echocardiogram.

2. Optimization of Contractility

a. Inotropes are used to maintain adequate cardiac output.

i. Popular agents that increase contractility include epinephrine, dobutamine, and milrinone, or a combination thereof.

ii. Milrinone, a phosphodiesterase type-5 inhibitor, is a frequent choice due to

its action as an inotrope and a vasodilator.

    a) Vasodilation of the pulmonary vasculature leads to decreased PVR.

    b) Vasopressors, such as norepinephrine or vasopressin, may be needed to treat systemic hypotension.

    iii. Inotropes should be weaned slowly over the course of several days, even if cardiac index is normal or supranormal, as a quick wean can lead to acute RV failure.

3. Minimizing Afterload

    a. Pulmonary vasodilation may be necessary to reduce an elevated PVR.

    i. Inhaled prostacyclins, such as iloprost, can be administered intermittently to both intubated and non-intubated patients to selectively dilate the pulmonary vasculature in well-ventilated areas of lung and subsequently reduce PVR.

    ii. Inhaled nitric oxide also causes rapid decrease in PVR, but is complicated by the need for continuous delivery, high cost, and risk of methemoglobinemia.[3]

    iii. Inhaled and intravenous pulmonary vasodilators should be weaned slowly to avoid acute rebound pulmonary hypertension.

    a) Oral sildenafil, an oral phosphodiesterase type-5 inhibitor that results in relaxation of pulmonary vascular smooth muscle, has been used to allow successful weaning of these agents.[5]

    b. Avoid hypercarbia, hypoxia and acidosis with proper ventilator management.

4. Rescue Therapies

    a. If conservative measures fail and RV dysfunction persists, a right ventricular assist device (RVAD) or extracorporeal membrane oxygenation (ECMO) may be required until RV function recovers.

III. Electrophysiology

A. The donor heart has been denervated from its autonomic nerve supply which alters both its intrinsic activity as well as its response to physiologic and pharmacologic triggers.

  1. Lack of parasympathetic tone results in a resting heart rate of 90-110 bpm.

  2. No change in heart rate is seen in response to carotid massage or Valsalva maneuver. Exercise or hypovolemia leads to a delayed and/or blunted increase in heart rate.[6]

  3. The denervated heart will have a decreased or no response to indirect acting medications such as atropine. Phenylephrine fails to cause reflex bradycardia.

  4. The allograft responds appropriately to direct beta-agonists such as isoproterenol, epinephrine, and dobutamine.

  5. Adenosine may cause an exaggerated response of prolonged asystole.[4]

B. Sinus node dysfunction occurs often in the postoperative period, due to surgical manipulation or ischemia.

  1. First degree atrioventricular (AV) block and right bundle branch block are common.[6]

  2. Atropine is ineffective treatment for bradycardia.

  3. Epicardial pacing or isoproterenol infusion may be necessary to maintain adequate heart rate.

    a. AAIR or DDDR modes are preferable.[7]

4. Sinus node dysfunction is usually temporary but 2-5% of cases require a permanent implanted pacemaker.[6]

C. Tachycardias

  1. Atrial fibrillation and flutter occur much less frequently after heart transplantation compared with other cardiac surgeries.[4]

  2. Both atrial and ventricular tachycardias may be signs of acute cardiac allograft rejection.

    a. These arrhythmias should trigger investigation of rejection with an endomyocardial biopsy (EMB). [7]

    b. Class III anti-arrhythmics, sotalol and amiodarone, can be safely used in heart transplant patients. [7]

D. Of note, the EKG tracing may demonstrate two p waves, one from the residual native right atrium and the second from the donor heart.

IV. Primary Graft Failure

Primary graft failure (PGF) occurs in the first 24 hours after heart transplantation and manifests as left, right, or biventricular dysfunction.[8]

A. The etiology of PGF is thought to be ischemia-reperfusion injury.

B. Diagnosis is made by echocardiographic evidence of ventricular failure in the setting of hypotension, low cardiac output and adequate filling pressures. Hyperacute rejection and tamponade must be ruled out as potential causes of graft failure.

C. Treatment is supportive, and includes increase in inotropic support, ECMO, and VAD placement.

D. Despite therapy, PGF remains a leading cause of early death in heart transplant recipients.

Rejection

I. Hyperacute Rejection

Hyperacute rejection to any transplanted organ is due to preformed recipient antibodies against the donor organ and occurs in the OR within minutes of reperfusion. In heart transplantation, the result is often profound biventricular failure and hemodynamic instability requiring therapies such as ECMO, plasmapharesis, and potentially re-transplantation.[3,4]

II. Acute Rejection

Acute rejection occurs quite frequently in heart transplantation recipients. Approximately 25% patients have experienced an episode by the end of the first year; by five years, 50% of patients have experienced acute rejection.[2]

A. Acute cellular rejection (ACR) is T-cell mediated and can occur at any time, but is most common in the first 3-6 months following transplantation.[9]

  1. ACR may present with fatigue, shortness of breath, RV dysfunction, or LV dysfunction.[10]

  2. Diagnosis is made with EMB and is treated with either steroids or anti-lymphocyte agents such as thymoglobulin.

B. Acute vascular or humoral rejection is caused by recipient antibodies against mismatched human leukocyte antigens (HLAs) present within the allograft.[3]

  1. Acute vascular rejection can present with severe ventricular dysfunction and

diffuse ischemia.

    2. Like with ACR, diagnosis is made with EMB. However, acute vascular rejection can be treated by intensifying the immunosuppressive regimen or plasmapheresis to modulate antibody production.

III. Chronic Rejection

Chronic rejection after heart transplantation manifests as cardiac allograft vasculopathy (CAV), a progressive narrowing of the coronary arteries. CAV occurs frequently, in approximately one-half of patients by 5 years post-transplant, and is the leading cause of late death in heart transplant patients.[4]

  A. CAV is diagnosed on routine coronary angiography.

  B. Angioplasty and stenting can be used to treat focal, isolated coronary artery stenoses but CAV often leads to widespread disease not amenable to percutaneous coronary intervention (PCI).[6]

  C. While CAV can progress to myocardial infarction, and ultimately, graft failure, patients rarely experience classical anginal pain due to cardiac denervation.

LUNG TRANSPLANTATION

Demographics and Outcomes

The number of lung transplantations performed yearly in the United States has steadily risen over the last decade, with 1830 performed in 2011. The majority of these patients received a transplant for either restrictive lung disease (45%) or obstructive lung disease (33%), with a smaller proportion for cystic fibrosis (15%). Outcomes after lung transplantation are among the worst for solid organ transplantation. Only 53% of patients are alive five-years post-transplant and median survival is 7.7 years in patients who survived the first year.[2] Leading causes of death include non-CMV infections, graft failure, and bronchiolitis obliterans syndrome (BOS).

Post-operative ICU Management

I. General Post-operative Management

  A. Monitoring

    1. Patients will arrive from the OR with standard monitors, arterial line, and possibly a PA line. Other lines will include a Foley catheter, chest tubes, and possibly an epidural. If a double-lumen endotracheal tube (ETT) is used intra-operatively, it is usually changed out for a single-lumen ETT prior to arrival to the ICU.

  B. Ventilator Management

    1. Ventilator management will depend on the underlying disease process.[11]

      a. In general, a low PEEP strategy is employed.

      b. Patients with emphysema who underwent single lung transplantation require zero PEEP and prolonged expiratory time to prevent air trapping in the native lung.

    2. Patients can usually be weaned from mechanical ventilation and extubated within the first 1-2 post-operative days.[11]

      a. Bronchoscopy is often performed prior to extubation to evaluate the bronchial anastomosis and clear any secretions.

    3. Aggressive pulmonary toilet is imperative after extubation to reduce the risk of mucous plugging.[4]

  C. Fluid Management4

    1. The allograft is at risk of pulmonary edema due to increased vascular permeability and disruption of lymphatic drainage.

    2. Judicious fluid administration is essential and filling pressures (CVP and PCWP) should be maintained as low as tolerated.

    3. Vasopressors may be necessary to treat hypotension.

    4. Diuretics and inotropes minimize the risk of cardiogenic pulmonary edema.

  D. Hemodynamic instability

    1. Patients who are hemodynamically unstable post-operatively should be evaluated for hypovolemia, hemorrhage, tension pneumothorax, tension pneumocardium, and tamponade physiology.

II. Airway Complications

Airway complications are prevalent following lung transplantation, occurring in up to 20% of patients in the first 3-6 months, and have high rates of recurrence after treatment.[12]

  A. Ischemia of the bronchial wall is a major contributor to many airway complications.

    1. In the native lung, the bronchus receives blood flow from the bronchial arteries, which are routinely interrupted during transplantation; therefore the recipient lung must depend on collateral flow from the pulmonary circulation to perfuse the bronchus until revascularization is achieved several weeks after transplantation.[12]

    2. Ischemia can be exacerbated by hypotension, hypovolemia and low cardiac output in the intra- and post-operative periods.

    3. The resulting airway complications are often compounded by airway infections, surgical technique, ischemia-reperfusion injury, and prolonged mechanical ventilation.

      a. Ischemia-reperfusion injury contributes to airway complications by increasing interstitial edema and compromising pulmonary blood flow.[13]

      b. Prolonged mechanical ventilation and PEEP put continuous stress on the bronchial wall and anastomosis and may interfere with graft perfusion and collateralization.[13]

  B. Surprisingly, while airway complications result in significant morbidity, overall survival is unaffected.[13]

  C. Airway complications include bronchial stenosis, bronchial dehiscence, exophytic granulation tissue, tracheo-bronchomalacia, and bronchial fistulae.

    1. Many of these complications will not require ICU-level care.

    2. Bronchial dehiscence and bronchial fistulae often lead to significant morbidity.

III. Bronchial Dehiscence

  A. Bronchial dehiscence is a serious complication that occurs in 1-10% of patients, typically within the first 1-5 weeks after transplantation.

  B. Patients present with dyspnea, prolonged mechanical ventilatory requirements, lung collapse, persistent air leak, pneumothorax, pneumomediastinum or subcutaneous emphysema.[13]

  C. Dehiscence increases the risk of developing an airway infection or abscess, which can progress to sepsis.[13]

D. Diagnosis is suggested with chest CT and confirmed with flexible bronchoscopy.

E. Mild or moderate dehiscence can often be treated with antibiotics and surveillance, whereas more severe dehiscence requires stent placement or surgical repair.

   1. Severe dehiscence can be life-threatening and prognosis is generally poor.

IV. Bronchial Fistulae

A. Fistulae can form in various places along the bronchial tree; lung transplantation recipients have suffered from bronchopleural, bronchomediastinal, and bronchovascular fistulae.[13]

   1. While these complications are rare, they result in significant morbidity and mortality.

B. Bronchopleural fistulae may present with dyspnea, subcutaneous emphysema, tension pneumothorax, or persistent air leak.

   1. Management ranges from chest tube placement to surgical intervention.

C. Bronchomediastinal fistulae can occur at any location in the airway and present as bacteremia, mediastinal abscess, or cavitation.

   1. Treatment includes appropriate antimicrobial therapy, percutaneous drainage of any abscesses, and potentially surgical debridement.

D. Bronchovascular fistulae can also form between the bronchus and the aorta, pulmonary artery or left atrium.

   1. Presenting symptoms include hemoptysis, air embolus, and sepsis.

   2. Patients have been treated with bi-lobectomy or pneumonectomy.

V. Airway Infections

A. Infections are a frequent source of morbidity in the post-transplantation period.

   1. The allograft is exposed to not only the flora of both the donor and the recipient airways, but also that of the external environment.

   2. Immunotherapy increases risk of opportunistic infection.

   3. Allograft ischemia and prolonged mechanical ventilation impair cough and swallow strength and reduce mucociliary clearance which subsequently encourage microorganism growth.[12]

B. Airway infections increase the risk of other airway complications, including dehiscence, stenosis, malacia and fistulae.[13]

C. Pseudomonas and Staphylococcus aureus are the most prevalent bacterial infections, whereas Aspergillus is the most common fungus encountered.[13]

D. Infection can arise anywhere along the respiratory track, resulting in tracheitis, bronchitis, pneumonia or anastomotic infection.

E. Antimicrobial prophylaxis, source control, and appropriate antimicrobial treatment are all indicated in the management of airway infections.

VI. Primary Graft Dysfunction

Primary graft dysfunction (PGD) is seen in up to 25% lung transplant recipients[4], and is usually diagnosed within the first three post-operative days.[14]

A. PGD is a form of acute lung injury (ALI), indistinguishable from acute respiratory distress syndrome (ARDS), caused by ischemia-reperfusion injury and the subsequent inflammatory response.

   1. Increased vascular permeability and subsequent noncardiogenic pulmonary edema result.[12]

B. PGD significantly increases mortality, duration of mechanical ventilation, hospital length of stay, as well as the risk of developing subsequent BOS.[14]

   1. Patients with moderate to severe PGD suffer from an all-cause 30-day mortality of 63% compared to 9% of patients without PGD.

C. Patients experience progressive hypoxemia; chest radiograph demonstrates new bilateral infiltrates.[12]

D. Unfortunately, the only treatment for PGD is supportive, with lung protective ventilation, judicious fluid management, and temporary ECMO in cases refractory to more conservative approaches.[14]

Rejection

I. Hyperacute Rejection

A. Hyperacute rejection after lung transplantation manifests as pulmonary edema and allograft dysfunction.[15]

B. Described treatments include plasmapheresis, rituximab, and IVIG, but this condition is often fatal.[4]

II. Acute Rejection

Acute rejection affects greater than 50% of lung transplantation patients and it is most common within the first year.[2] Patients may present with dyspnea, cough, fevers, pleural effusions and increasing hypoxia or decreasing forced expiratory volume in one second (FEV1) on pulmonary function tests.[12]

   A. Acute cellular rejection is diagnosed by transbronchial lung biopsy.

      1. Treatment usually consists of optimization of immunotherapy regimen and a pulse of high dose steroids.[15]

      2. ACR puts the patient at significantly increased risk of developing BOS.[15]

   B. Humoral rejection is diagnosed by detecting circulating donor-specific anti-HLA antibodies.

      1. Treatment options include IVIG, plasmapheresis, or anti-CD20 monoclonal antibodies (ex. rituximab).[12]

III. Chronic Rejection

Chronic lung allograft rejection manifests as bronchiolitis obliterans syndrome (BOS), a progressive and irreversible airflow obstruction, which is the biggest obstacle to graft and patient survival.

   A. Approximately half of lung transplantation recipients have been diagnosed with BOS by five years post-transplantation; survival in these patients is 20-40% lower than in patients without BOS.[16] Median survival ranges from 1.5 to 2.5 years after diagnosis.[12]

   B. Diagnosis and staging is based on the degree of FEV1 decrease from baseline.

      1. CT often shows air trapping and bronchiectasis.[12]

   C. Most treatments are focused on optimizing immunosuppressive therapy[15] and palliative measures.[12]

LIVER TRANSPLANTATION

Demographics and Outcomes

Liver transplant recipients are the most common solid organ transplantation patients encountered in the ICU, with almost 6000 liver transplantations being performed each year in the United States. Hepatitis C virus is the leading indication for liver transplantation, with approximately one-quarter performed for this reason. Other indications are malignancy (19%) and alcoholic cirrhosis (17%). Outcomes after liver transplantation are quite good, with 68% of patients alive after five years. Transplant half-life, conditional on one-year survival, is 15 years.[2] The most common causes of death in liver transplant recipients are disease recurrence, infection, new malignancies, and cardiovascular disease.[17]

Post-operative ICU Management

General Post-operative Management

A. Monitoring

  1. In addition to standard monitors, patients will arrive to the ICU with an arterial line, possible PA line, Foley catheter, nasogastric tube, and multiple abdominal drains in place. Depending on the surgical technique used, a T-tube may be present in the bile duct, allowing for monitoring of bilious drainage.

B. Ventilator Management

  1. Ventilator settings can be weaned and patients can be extubated relatively quickly, sometimes as early as intra-operatively. Patients with significant deconditioning prior to transplantation may require more prolonged mechanical ventilation.[18]

C. Fluid management

  1. Patients often receive massive transfusions and large volume fluid resuscitation in the OR that can lead to post-operative pulmonary edema and allograft congestion. Once the patient is adequately volume resuscitated and hemodynamically stable in the ICU, diuresis should begin, as early as the first post-operative day. A daily negative fluid balance may help mitigate complications arising from volume overload.[19]

D. Hemodynamic instability

  1. Patients may require infusions of one or more vasopressors, as the pre-operative hemodynamic profile of liver failure, which includes vasoplegia and hyperdynamic cardiac output, often persists into the post-operative period.

    a. Hypotension may be exacerbated by metabolic acidosis and allograft ischemia.

    b. Increasing pressor requirement or inability to wean from pressors is concerning for a more serious complication.

  2. Other causes of hemodynamic instability in the early post-operative period include hemorrhage, portopulmonary hypertension, ischemia-reperfusion injury, primary graft dysfunction, hepatic artery thrombosis, portal vein thrombosis, preexisting cardiomyopathy, intra-operative myocardial infarct, and hypocalcemia related to massive blood transfusions. Workup may include assessment of laboratory values and drain output, duplex Doppler ultrasound, and echocardiogram.

E. Laboratory abnormalities

  1. Laboratory values should be checked frequently in the post-operative period, including markers of acid-base status, liver function, coagulation function, and renal function.[20] Quantity and quality of abdominal drain and t-tube output should also be monitored closely.

    a. Electrolyte abnormalities may persist from the pre-operative period, including hyponatremia. It is important to correct hyponatremia slowly, as a rapid increase in serum sodium could result in central pontine myelinosis.[18]

    b. Liver function tests (LFTs) will be grossly elevated post-operatively, but should begin to trend towards normal in the first several days.

  2. Persistently elevated or rising LFTs should raise concern for graft dysfunction or arterial thrombosis.[18]

  3. Hypoglycemia is another marker for poor liver function.[19]

    a. INR can act as an indirect measure of graft function. Transfusions of fresh frozen plasma may be necessary to counteract clinical bleeding in the setting of initial poor allograft function.[20] Thrombocytopenia is common in the post-operative period and can also contribute to clinical bleeding.[19]

Surgical Complications

Liver transplantations are complex surgical procedures involving multiple anastomoses; complications arising from the surgery itself are some of the most frequently seen after transplantation.

A. Surgical complications can be divided into three categories: vascular, biliary, and other complications. Vascular complications include both arterial and venous problems.

B. Arterial complications, which can be very serious, occur in 2-25% of patients, and include anastomotic bleeding, anastomotic stenosis secondary to thrombosis, steal syndrome or aneurysm. Approximately half of these patients will require re-transplantation.[21]

  1. Hepatic artery thrombosis (HAT)

    a. HAT occurs in approximately 3% of patients and can manifest as fulminant liver failure.

    b. Diagnosis may be made in multiple ways, including duplex Doppler ultrasound, celiac angiography, computerized tomography (CT) angiography and magnetic resonance angiography (MRA), with the gold standard being surgical exploration.

    c. Treatment options include catheter-directed thrombolysis and surgical arterial reconstruction, but re-transplantation is frequently necessary.[22]

C. Venous problems are rare and can include occlusion of the portal vein or inferior vena cava.

  1. Portal vein thrombosis (PVT) occurs in 0.5-1.5% of patients and can be diagnosed by duplex Doppler ultrasound.

    a. Symptoms include transaminitis, ascites, intestinal congestion, and GI bleeding.

    b. Immediate operative thrombectomy is indicated, although emergent re-transplantation may be required.

    c. Without treatment, PVT is almost universally fatal.[22]

D. Biliary complications occur in 10-20% of patients and include biliary leak and biliary stricture, among others.[21]

  1. The majority of biliary complications occur early, within the first six months after transplant.[21]

2. Patients present with pain, fever, ascites and persistent drain output.

3. Diagnosis is made by a variety of modalities, including abdominal ultrasound, CT, CT cholangiography, magnetic resonance cholangiopancreatography (MRCP), and endoscopic ultrasound (EUS).[23]

4. Treatment options include endoscopic retrograde cholangiopancreatography (ERCP) and stenting, percutaneous transhepatic cholangiography (PTC) with percutaneous transhepatic biliary drainage (PTBD), or surgical exploration.[23]

E. Other surgical complications include early internal bleeding (from non-anastomotic sites), evisceration, wound infection, and incisional hernia.

Infection

Infectious complications develop frequently in liver transplantation recipients, occurring in more than one-half of patients in the first post-operative year.[22]

A. Infections are the leading cause of early death in these patients.

B. Most early causes of infection are similar to non-transplantation surgeries, and include surgical wound infections, bloodstream infections, pneumonia, and Clostridium difficile-associated diarrhea.[22]

1. Opportunistic infections (OI) tend to arise during the first several months after transplant at the height of immunosuppression.[22]

   a. The most prevalent OI are cytomegalovirus (CMV) in previously CMV-seronegative recipients and fungal infections caused by aspergillosis and endemic fungi.

C. Late infections (more than six months after transplant) include community-acquired pneumonias, hepatic abscesses, and recurrent chronic infection with hepatitis B or C virus.[21]

D. As with any infection, management should include prophylaxis, source control and appropriate antimicrobial therapy.

Early Graft Dysfunction

Primary non-function (PNF) and initial poor function (IPF) are a spectrum of graft dysfunction defined by timing of onset after liver transplantation and severity of disease. Ischemia-reperfusion injury is thought to be the underlying mechanism of action.[24] Graft dysfunction is accompanied by elevated transaminases, elevated INR, decreased bile production, and elevated lactate. Multi-organ system failure may develop, characterized by coma, oliguria, clinically significant bleeding, and hypoglycemia.[19]

A. Primary non-function (PNF):

1. This serious complication is seen in 4-6% of patients.[21]

2. PNF is universally fatal without re-transplantation.[21,22]

B. Initial poor function (IPF) does not have a standard definition. Some have defined IPF as graft dysfunction 15-30 days after transplantation.[21]

1. Some patients with IPF recover liver function while others go on to require re-transplantation.[22]

Rejection

I. Hyperacute Rejection

Hyperacute rejection after liver transplantation presents as thrombosis and hemorrhagic graft necrosis.[22]

A. Treatment options include plasma exchange, IVIG, B-cell depleting therapy, or splenectomy.

B. Without therapy, acute liver failure ensues.

II. Acute Rejection

Acute rejection is seen less frequently after liver transplantation than after heart or lung transplantation, with an incidence of 16% at one year and 24% five years post-transplantation.[2]

A. ACR occurs in 25-60% of patients within the first six months after liver transplantation.[22]

1. Suspicion is raised by rising aminotransferase and bilirubin levels, and diagnosis is confirmed by liver biopsy.[22]

2. Treatment is based on severity of rejection; options include optimizing immunosuppression, steroids pulses, T-cell depleting therapy, and re-transplantation.[22]

III. Chronic Rejection

Chronic rejection after liver transplant is much less prevalent than acute rejection, occurring in 4% of patients.[25]

A. Chronic rejection is characterized as immunologic injury to the bile ducts, arteries and veins of the allograft resulting in ductopenia and perivascular fibrosis.[26]

B. Chronic rejection is usually seen in patients who have experienced prior episodes of acute rejection that were resistant to standard steroid treatment.[25]

C. Diagnosis is made by liver biopsy.

IMMUNOSUPPRESSIVE THERAPY

Types of Immunosuppression

There are three main types of immunosuppression: induction therapy, maintenance therapy, and treatment of rejection. Immunosuppression regimens are not standardized among transplant type or across transplantation centers.

I. Induction Immunosuppression

Induction immunosuppression is given peri-operatively, with the intent to induce immunologic tolerance to the graft.[9]

A. The majority of heart (55%), lung (55%) and liver (70%) transplant recipients do not receive any induction therapy.[2]

B. When induction therapy is administered, interleukin-2 receptor (IL-2R) antagonists and T-cell depleting therapies are the most frequently used agents.[2]

II. Maintenance Immunotherapy

Maintenance immunotherapy begins in the early post-operative period, and continues for the life of the transplant.

A. Initial maintenance therapy includes a combination of an antimetabolite, a calcineurin inhibitor and steroids.

1. The most common regimen in heart, lung, and liver transplant recipients contains a steroid, mycophenolate mofetil, and tacrolimus.[2]

B. Steroids are frequently reduced over time and often eliminated altogether.

III. Treatment of Rejection

Treatment of rejection will involve drugs specific to the type of rejection, either cellular or humoral.

  A. As described above, approaches may include optimization of current medications, addition of pulse-dose steroids or anti-lymphocyte agents, or methods such as plasmapheresis.

Immunosuppressive Drugs

There are several different categories of immunosuppressive agents in use today (see Table 41.1). While they act with differing mechanisms of action, most agents will ultimately result in the interference of lymphocyte production, proliferation, or activation. Each of these drugs has its own group of adverse effects. Using several different types of drugs simultaneously allows for a dose reduction of individual drugs while maintaining adequate levels of immunosuppression; the goal of multidrug therapy is to reduce the overall quantity or severity of side effects.

I. Polyclonal anti-lymphocyte antibodies (ATGAM, Thymoglobulin)

  A. Thymoglobulin is a polyclonal rabbit antibody preparation containing antibodies against human surface B- and T-cell antigens.[9]

    1. Binding of antibody to antigen leads to complement-dependent opsonization and ultimately, cell lysis or apoptosis of B- and T-cells.

    2. An acute hypersensitivity allergic reaction can occur in response to thymoglobulin, with symptoms of urticaria, fever, chills, and rash.

    3. Other side effects include cytokine release syndrome, serum sickness, leukopenia, and thrombocytopenia.

    4. In heart transplant recipients, thymoglobulin is used for induction therapy and for treatment of steroid-resistant rejection.

  B. ATGAM is a similar preparation made from horse-derived antibodies.

II. IL-2R antagonists (daclizumab, basiliximab)

  A. These drugs are monoclonal antibody preparations that bind to the IL-2R on activated T-cells, resulting in the inhibition of T-cell proliferation.

  B. Hypersensitivity reactions can occur but these drugs are generally well tolerated.[9]

  C. IL-2R antagonists are used for induction therapy after heart, lung, and liver transplantation.

III. Antiproliferative agents (azathioprine, mycophenolate mofetil)

  A. Azathioprine (AZA) is a prodrug which is converted into a purine analog that is incorporated into DNA. DNA synthesis and subsequently, proliferation of B- and T-lymphocytes, are inhibited.[10]

    1. AZA can cause a dose-dependent, reversible myelosuppression resulting in anemia, leukopenia, and thrombocytopenia.

  B. Mycophenolate mofetil (MMF) is a non-competitive inhibitor of an important enzyme in the de novo synthesis pathway for guanine nucleotides.[10]

    1. Inhibition of proliferating lymphocytes results due to these cells' reliance on the de novo pathway for purine synthesis. Unlike other cells, they are unable to utilize the salvage pathway.

    2. MMF can also result in anemia, and thrombocytopenia, as well as GI distress.

  C. Antiproliferative agents are used for prophylaxis against acute rejection after heart, lung, and liver transplantation.

IV. Calcineurin inhibitors (cyclosporine, tacrolimus)

  A. Cyclosporine and tacrolimus achieve immunosuppression by binding to cyclophilin and FK-binding protein, respectively; these drug complexes then block calcineurin, a calcium-dependent phosphatase, leading to inhibition of IL-2 transcription and ultimately, T-cell activation.[10]

  B. Nephrotoxicity is the most prevalent side effect of both drugs, which can result in end stage renal failure.

    1. One major goal of a multimodal approach to maintenance immunotherapy is to minimize the necessary dose of calcineurin inhibitors, and in turn, mitigate the associated nephrotoxicity.

  C. Other side effects include diabetes mellitus, hypertension, hyperlipidemia, and neurotoxicity, which can present as seizures or altered mental status.

  D. Both cyclosporine and tacrolimus are used to prevent rejection in heart, lung, and liver transplant recipients.

V. Inhibitors of mammalian rapamycin (sirolimus, everolimus)

  A. Sirolimus and everolimus bind to FK-binding protein, and the resulting complex inhibits the mammalian target of rapamycin (mTOR), an enzyme involved in the regulation of the cell cycle.[10]

    1. The cell cycle is arrested and proliferation of B- and T-lymphocytes is inhibited.

  B. Side effects of these medications include hyperlipidemia, thrombocytopenia, anemia, and neutropenia.

    1. Sirolimus has been associated with excess mortality, increased graft loss, and hepatic artery thrombosis in liver transplant recipients, and bronchial anastomotic dehiscence in lung transplant recipients.

  C. Sirolimus has been used in place of calcineurin inhibitors to treat rejection in heart transplant patients.

  D. Everolimus was approved earlier this year for prophylaxis of acute rejection in liver transplant recipients but has also been used after heart and lung transplantation as well.

VI. Steroids (prednisone, methylprednisolone)

  A. The mechanism of action of steroids is not completely understood, but it involves alteration of the transcriptional regulation of genes involved in immune function and inflammation.

  B. Steroids have a wide range of adverse effects, including chronic adrenal suppression, hypertension, diabetes, and obesity.

  C. These drugs are used in all aspects of immunotherapy, from induction and maintenance to treatment of rejection.

Table 41.1 Immunosuppressive therapy agents, their mechanisms of action, and side effects

Category of Drug	Drug	Mechanism of Action	Side Effects
Polyclonal anti-lymphocyte antibodies	ATGAM Thymoglobulin	Antibodies bind B- and T-cell antigens, leading to death of B- and T-lymphocytes	Acute hypersensitivity allergic reaction, serum sickness, leukopenia, thrombocytopenia
IL-2 receptor antagonists	Basiliximab Daclizumab	Monoclonal antibody preparation binds to the IL-2 receptor on activated T-cells, inhibiting proliferation	Minimal
Antimetabolites	Mycophenolate Azathioprine	Interferes with purine synthesis and DNA synthesis, inhibiting lymphocyte prolipheration	Anemia, leukopenia, thrombocytopenia, GI distress
Calcineurin inhibitors	Tacrolimus Cyclosporine	Drug complexes bind to calcineurin which leads to inhibition of T-cell activation	Nephrotoxicity, neurotoxicity, diabetes mellitus, hypertension, hyperlipidemia
Corticosteroids	Methylprednisolone Prednisone	Alteration of transcriptional activity of genes involved in immune function and inflamation	Chronic adrenal suppression, hypertension, diabetes, obesity
Inhibitors of mammalian target of rapamycin (mTOR)	Sirolimus Everolimus	Drug complexes bind mTOR, interrupting the cell cycle and inhibiting B- and T-cell proliferation	Anemia, neutropenia, thrombocytopenia, hyperlipidemia

CONCLUSION

Recipients of solid-organ transplants are living longer and healthier lives, due to advances in immunotherapy and pre- and post-operative care. Caring for these patients post-operatively in the ICU presents a specific set of challenges. In addition to common post-surgical complications, these patients suffer from transplantation-specific complications that can lead to significant morbidity and mortality. Quick recognition and proper management of these complications is essential to maximizing graft and patient survival.

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Questions

41.1 Referring to the case above, which of the following would be an inappropriate action to treat patient's failing right ventricle?

    A. Increase rate of epinephrine infusion.
    B. Diuresis with infusion of a loop diuretic.
    C. Decrease epicardial pacing rate.
    D. Add inhaled iloprost.

41.2 Which of the following would NOT increase heart rate in the heart transplant recipient?

    A. Isoproterenol
    B. Epinephrine
    C. Atropine
    D. Epicardial pacing

41.3 Which of the following laboratory abnormalities are common after liver transplantation?

    A. Hypoglycemia
    B. Hyponatremia
    C. Elevated transaminases
    D. Elevated INR
    E. All of the above

41.4 What 3 types of drugs comprise the most commonly prescribed maintenance regimen for solid organ transplant recipients?

    A. Antimetabolite, IL-2R antagonist, and polyclonal anti-lymphocyte antibodies
    B. Steroid, calcineurin inhibitor, and IL-2R antagonist
    C. IL-2R antagonist, antimetabolite, and calcineurin inhibitor
    D. Steroid, antimetabolite, and calcineurin inhibitor

42. Trauma Management in the ICU

Mark J Baskerville MD and T Miko Enomoto MD

Key Points

• **A systematic trauma survey algorithm is essential to effectively perform a simultaneous evaluation and resuscitation of the trauma patient.**

• **Hemorrhage is the most preventable cause of mortality in trauma. Injured patients with signs of shock are bleeding until proven otherwise.**

• **Common pitfalls in the management of the trauma patient include missed injuries and delayed complications.**

• **Serial reassessment, vigilant monitoring and targeted diagnostic studies are paramount to the timely recognition of all injuries and complications.**

A 42 year old man involved in a motor vehicle crash is admitted to the ICU directly from the operating room after a splenectomy. He is intubated and sedated. His vital signs are: T 34.9 HR 119 BP 100/80 SaO$_2$ 99% He is placed on volume control ventilation at 16 breaths/minute with FiO$_2$ 0.5. He has two 16 gauge peripheral IVs and a radial arterial catheter. Despite receiving five liters of crystalloid and three units of type-specific blood, his blood pressure continued to decline over the next hour. Bedside labs demonstrate anemia (Hgb 6.1) and acidosis (HCO$_3$ 15). What are your concerns? How would you evaluate and manage the patient? What immediate and delayed complications is he at risk for?

INTRODUCTION

Effective trauma care mandates a dynamic, systematic focus on evaluation, resuscitation and re-assessment. The Advanced Trauma Life Support (ATLS) course developed by the Committee on Trauma of the American College of Surgeons helps physicians maximize resuscitative efforts and avoid missing life-threatening injuries through an organized approach to trauma care.[1] In the ICU, serial assessment and targeted monitoring are essential to managing severely injured patients – particularly those that have undergone damage control surgery and those admitted for nonoperative management of solid organ injuries. Critical care management of the trauma patient centers on goal-directed resuscitation to prevent the "second hits" (i.e., SIRS, ALI, DIC, AKI, MSOF) arising out of the fatal triad of hypothermia, acidosis and coagulopathy.

ICU Evaluation and Resuscitation

Trauma patients will be admitted to the ICU at various stages of resuscitation and stabilization. It is imperative to repeat the trauma survey early and often. Treatment and diagnosis must occur simultaneously with management prioritized to the greatest threat to life or limb. Critical questions that should be continually entertained are: what can kill this patient and what are we missing?

Primary Survey

The primary survey focuses on the rapid evaluation and correction of physiological functions crucial to survival. Assessment and intervention occur contemporaneously following the strict ABCDE algorithm:
Airway → Breathing → Circulation → Disability → Exposure.

Establishing and maintaining a protected **airway** is the first priority. Interventions to ensure a patent airway can range from simply speaking to the patient to a rapid sequence intubation to a surgical cricothyroidotomy. It is mandatory to maintain cervical spine stabilization during this process until an underlying injury has been ruled-out. Figure 42.1 illustrates a typical emergency airway algorithm for trauma patients.

Figure 42.1 Trauma Airway Algotirhm
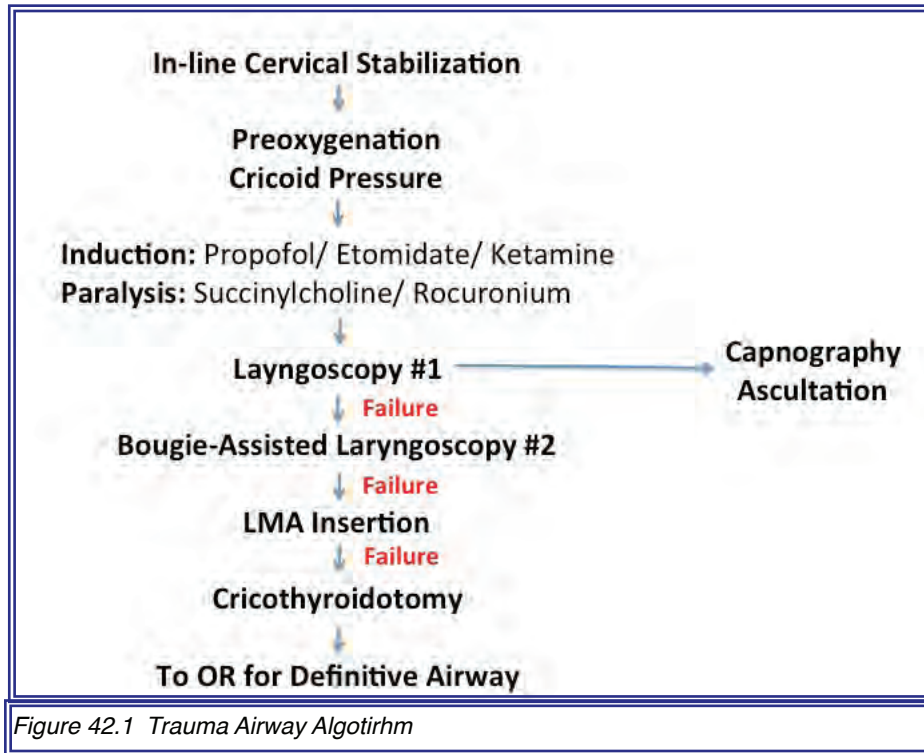
After a patent and protected airway is confirmed, **breathing** is the second priority demanding rapid assessment to ensure adequate oxygenation and ventilation. The respiratory rate and effort are observed, pulse oximeter monitored, and oxygen administered. The thorax is inspected, palpated and auscultated. Potentially lethal injuries that must be excluded include tension pneumothorax, simple pneumothorax, hemothorax, pulmonary contusion and flail chest. Immediate interventions range from simply the application of supplemental oxygen to needle decompression and multiple chest tube thoracostomies.

The rapid assessment and restoration of **circulation** comprises the third priority in the primary survey. Heart rate and rhythm are monitored while a blood pressure is measured, peripheral pulses palpated in all four extremities, and intravenous access secured optimally both above and below the diaphragm. Signs of shock include pale, cool, clammy extremities, delayed capillary refill, tachycardia, hypotension, narrow pulse pressure, oliguria and obtundation. Life and limb threatening injuries that must be ruled-out at this stage include pericardial tamponade, blunt cardiac injury, vascular disruption and hemorrhagic shock. Resuscitation is typically accomplished with the rapid infusion of crystalloid fluids and/or blood products. Additional interventions range from the insertion of invasive monitoring and resuscitation catheters to immediate fracture reduction to restore pulses to a bedside thoracotomy to prevent exsanguination.

The fourth priority is a focused neurological exam. **Disability** is assessed by determining the level of consciousness, pupillary size and reactivity, and any focal sensory or motor deficits. The Glasgow Coma Scale (GCS) is helpful in characterizing and communicating the neurological status of the trauma patient. The scale consists of three best responses – eye, verbal and motor – with scores ranging from 3 (dead or deep coma) to 15 (alert and responsive).[2] See Table 42.1.

Finally, the patient is fully **exposed** and thoroughly examined, while preventing or reversing hypothermia. The clothes are removed and the patient is log-rolled with axial cervical stabilization to assess the integrity of the spine and to search for occult injuries. Deformities are identified and fractures reduced.

Table 42.1 Standard Glasgow Coma Scale

Eye Opening		Best Verbal Response		Best Motor Response	
				6	Obeys Commands
		5	Oriented	5	Localizes
4	Spontaneous	4	Confused	4	Withdraws
3	To Speech	3	Inappropriate Words	3	Abnormal Flexion
2	To Pain	2	Incomprehensible Sounds	2	Extension
1	None	1	None	1	None

Secondary and Tertiary Surveys

The secondary survey involves a head-to-toe examination while continuously reevaluating the progress of resuscitation. A more thorough history is sought, serial labs obtained, diagnostic images reviewed and monitoring upgraded. This stage represents a valuable opportunity to identify missed injuries and early complications.

For example, undetected hemorrhage is a common oversight during the initial evaluation of the trauma patient. Typical sites where blood can accumulate and remain unaccounted for include the thorax, the abdomen, the retroperitoneum, the pelvis, the thigh and the street (i.e., the scene of the injury).

Unstable patients refractory to initial resuscitation efforts typically undergo immediate operative intervention, while stable patients are further evaluated via a tertiary survey:

a repeat head-to-toe examination supplemented with more advanced imaging modalities such as ultrasound, computed tomography and angiography. Many metropolitan trauma centers have protocolized imaging algorithms that provide a head-to-toe radiographic evaluation of all severely injured, polytrauma patients to minimize missing occult injuries.[3]

The FAST exam (Focused Assessment with Sonography in Trauma) is becoming increasingly utilized in the ICU setting – particularly in the unstable patient not suitable for transport to the CT scanner. Four transducer positions can quickly assess for free fluid in the pericardium, subdiaphragmatic space, hepatorenal interface, splenorenal interface and the pelvis.[4] Although helical CT remains the gold standard, the high specificity (98%), negative predictive value (98%) and accuracy (97%) make FAST an efficient, reliable screening exam to differentiate patients in need of immediate operative intervention versus further diagnostic imaging.

Finally, laboratory analysis can aid in both diagnosis and monitoring resuscitation. A comprehensive panel of labs is initially drawn from all severely injured trauma patients. In the ICU, any abnormal values should be repeated. A few parameters deserve special attention:

I. CBC and Coagulation:
Serial hemoglobin levels are useful for trending slow bleeding, but have limited utility in guiding therapy in the briskly bleeding trauma patient. Here, immediate operative intervention is mandated to find and stop the source of the bleeding.

Coagulopathy in the severely injured patient significantly influences mortality rates. Tissue disruption, hemodilution, hypothermia and acidosis all drive coagulation disturbances from dilutional thrombocytopenia to rampant DIC. Early recognition and strategic use of component transfusion therapy is essential to reduce morbidity. Although most laboratories utilize a standard coagulation panel, thrombelastography (TEG) is becoming more prevalent in leading trauma centers to provide a more rapid assessment of the dynamic coagulation status of severely injured patients.[5]

II. Renal Function:
Trauma patients are at a heightened risk for acute kidney injury: ATN from hypotension, rhabdomyolysis and nephrotoxins. Daily BUN and creatinine levels should be obtained in patients who are hypotensive, received contrast agents, or have a history of chronic kidney disease. A serum creatinine level that begins to rise within 48 hours of contrast administration may indicate contrast-induced nephropathy. It typically peaks at approximately 96 hours and then normalizes with supportive care over several weeks.

III. Creatine Kinase and Myoglobin:
Rhabdomyolysis commonly occurs with crush injuries, burns, prolonged immobilization, extremity compartment syndromes and ischemia-reperfusion physiology following repair of vascular injuries. Elevated creatine kinase and myoglobinuria signal rhabdomyolysis and should trigger aggressive hydration guided by serial CK levels and urine output. A large amount of fluid can accumulate in the muscles and can cause hypovolemia, shock and worsen renal function. Gap acidosis, hypocalcemia, and hyperkalemia all frequently occur and need to be treated aggressively. Kidney injury arises from tubular cast formation, hemoglobin cytotoxicity and vasoconstriction.

IV. Lactic Acid:
Serial lactate levels are recommended for all severely injured trauma patients. Lactate is a marker of anaerobic metabolism. Its clearance suggests adequate resuscitation and satisfactory end-organ perfusion. Lack of lactate clearance has been associated with increased mortality, and in the face of clinical euvolemia, an aggressive search for a missed injury, liver dysfunction and/or cardiac decompensation must immediately commence.[6]

Damage Control Surgery and Resuscitation

Damage control surgery has evolved as a temporizing measure to mitigate the lethal triad of hypothermia, acidosis and coagulopathy often responsible for the early mortality of severely injured trauma patients. It involves the immediate operative control of hemorrhage and bowel contamination with subsequent transfer to the ICU for intravascular volume resuscitation, component transfusion therapy and rewarming prior to returning to the OR for definitive operative repair of injuries and closure of the abdomen.

In fact, resuscitation strategies during damage control surgery may equal the importance of the operative repairs themselves. Recommendations include avoiding hypothermia, tolerating a lower blood pressure (MAP 50-60) until surgical bleeding is controlled, and supporting the coagulation system early with plasma, platelets and antifibrinolytic agents.[7] Many of these interventions are directed to promoting clot stability in order to minimize blood loss and overall transfusion requirements. The CRASH-2 (Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage) study demonstrated a mortality benefit in bleeding trauma patients, if tranexamic acid was administered within three hours of injury.[8]

Commonly Missed Injuries

The acuity and complexity of critically ill trauma patients puts them at a heightened risk for missed injuries and delayed diagnoses. Studies have demonstrated that clinically significant injuries are overlooked 15% to 22% of the time.[9] Accordingly, a high index of suspicion coupled with a sensitive diagnostic approach must be used to identify occult injuries.

I. Intraabdominal Injuries
Overlooked intraabdominal injuries carry a high mortality rate, and unfortunately, continue to be a common pitfall in the evaluation of trauma patients. A missed injury must be suspected in any trauma patient with an evolving systematic inflammatory response (SIRS), persistent tachycardia and worsening acidosis. Although advanced imaging studies (CT, ERCP, angiography) can help identify an occult injury, exploratory laparotomy remains the gold standard.

II. Diaphragm Injuries
Diaphragm injuries often go undetected upon initial evaluation. Simultaneous injuries above and below the diaphragm – particularly with penetrating trauma – should always implicate a diaphragm disruption, until proven otherwise.

III. Pulmonary Contusion

Pulmonary contusion is the most common parenchymal lung injury associated with blunt trauma. Mortality rates are estimated to be from 15 to 25% - often due to the development of a superimposed pneumonia and ARDS. This injury is easily overlooked because both clinical and radiographic findings tend to be delayed. In fact, pulmonary contusions can occur in the absence of any identifiable chest wall injury – particularly in children. At risk patients must be closely monitored for respiratory failure over the ensuing days.

IV. Vascular Injuries

Blunt injury to a vessel may not be immediately apparent depending upon its severity and location. Low-grade injuries, such as intimal tears, can dissect slowly over time to narrow the vessel lumen and potentially result in a complete occlusion. Moreover, the tissue flap can act as a nidus for clot formation, so early detection is essential so that antiplatelet and/or anticoagulant therapy can be initiated. Ankle-brachial indices (ABIs) are useful bedside metrics to evaluate the integrity of extremity perfusion. CT angiography is becoming increasingly popular over angiogram for definitive evaluation.

V. Blunt Cardiac Injuries

Blunt injury to the heart should be suspected in any trauma patient with a mechanism consistent with significant thoracic impact (e.g., steering wheel injury) – particularly if associated with fractures of the sternum or 1st and 2nd ribs. An electrocardiogram should be obtained and the patient placed on continuous telemetry. Serial cardiac enzymes have limited utility, but echocardiography can be extremely helpful in discovering valve disruptions, assessing cardiac function and identifying pericardial tamponade. Additionally, if a TEE is utilized, the proximal aorta can be easily visualized to rule-out a tear or dissection.

VI. Rib Fractures

Rib fractures are the most common injury seen with thoracic trauma. A flail chest – defined as three or more contiguous fractures in two or more places – is a potentially lethal injury. Centers that have implemented protocols to identify and aggressively treat these fractures have improved outcomes as measured by decreased ventilator and ICU days and overall mortality. Pain should be aggressively managed in order to facilitate a strong cough, mobilization, recruitment maneuvers and pulmonary toilet. Consideration should be given to regional anesthesia for pain control.

VII. Spinal Cord Injuries

Assessing for a spinal cord injury begins during the primary survey. Until an injury has been confidently excluded, at risk trauma patients must remain in a cervical collar and on a rigid backboard with strict precautions exercised throughout the trauma surveys. Nowadays, CT is the imaging modality of choice. If the scan is negative, but the patient is either clinically symptomatic or unable to give a reliable exam, then a MRI is typically required to exclude ligamentous injury.

Over the last decade, several clinical scoring systems have evolved to assist the practitioner in determining the need for imaging. The National Emergency X-Ray Utilization Study (NEXUS) is a popular validated tool owing to its simplicity and reliability. If an alert, sober patient without any significant distracting injuries and a normal neurological exam denies midline posterior cervical tenderness, then the probability of a cervical spine injury is extremely remote (NPV=99.8%).[10] See Table 42.2

Table 42.2 NEXUS Criteria

1	No midline cervical tenderness
2	No focal neurological deficit
3	Normal alertness
4	No intoxication
5	No painful distracting injury

Early consultation with a neurosurgeon is mandated for any significant spine or cord injury. High-dose methylprednisolone is no longer recommended for acute spinal cord injuries. Multiple studies have shown that it failed to offer any long-term benefit, while placing the patient at a heightened risk for complications and infections.[11]

VIII. Compartment Syndromes

Trauma patients are at risk for both extremity and abdominal compartment syndromes. Crush injuries, long bone fractures and ischemia-reperfusion scenarios place the injured patient at a heightened risk for developing a fascial compartment syndrome. Although creatine kinase levels may aid in diagnosis, a high index of suspicion coupled with a low threshold to quantitatively monitor compartment pressures remain mandatory.

Abdominal compartment syndrome is a potentially fatal complication resulting from aggressive resuscitation of critically ill trauma patients. Although the abdomen is much more distensible than extremity compartments, third-space fluid accumulation can ultimately create intraabdominal hypertension – directly compressing organs and vessels – leading to poor perfusion, oliguria, acidosis and ischemia. Serial monitoring of intraluminal bladder pressure can detect this potentially fatal complication prior to any observable clinical signs. Grading systems correlate bladder pressures with end-organ damage.[12]

Early and Delayed Complications

Trauma management and emergency surgery pose an inherently heightened risk for both early and delayed complications. As emphasized earlier, hypothermia, acidosis and coagulopathy are the most feared early complications in the severely injured trauma patient. Early interventions must be directed to preventing or reversing this lethal cascade.

Other complications are directly related to specific injuries (e.g., biliary fistula in the setting of blunt pancreatic trauma), but may also be due to inadequate prophylaxis, such as the development of thromboembolisms. Complications can also arise from lack of monitoring (abdominal compartment syndrome), prolonged ventilation (VAP), immobilization (decubiti) and even the resuscitative efforts themselves (TRALI, contrast induced nephropathy, CLABSI). Invasive catheters inserted in the trauma bay are uniformly considered contaminated and should be removed or replaced as soon as clinically feasible. Empiric antibiotics are typically indicated depending on specific injuries and procedures performed. Finally, the frequent association of intoxication and subsequent withdrawal syndromes present additional challenges to managing the trauma patient in the ICU.

I. Nutrition

Nutritional support is mandatory for trauma patients, who typically present hypermetabolic – leading to breakdown of muscle and inhibition of protein synthesis. The aim of nutritional support is to maintain lean body mass and prevent protein malnutrition. High protein enteral nutrition should be provided early to injured patients who are unable to achieve adequate caloric intake. Studies have demonstrated the superiority of enteral nutrition over TPN, including markedly reduced complications and overall mortality.[13]

II. Wound Care

Diligent wound care is essential to prevent delayed complications, infections and disability. A multidisciplinary approach and early specialty consultation are necessary for optimal outcomes and rehabilitation. Negative pressure wound dressings are becoming increasingly popular as a means to promote wound healing and minimize infectious complications.

III. Pain Management

A multimodal approach to pain management is essential to optimally control pain in the trauma patient, as well as, mitigate complications. Effective pain control promotes early mobilization, which in turn, protects against the development of atelectasis and deep venous thrombosis. Although opioids tend to be the primary modality, they should be supplemented with anti-inflammatory agents, anti-epileptics, neuroaxial analgesia and targeted nerve blocks, when clinically feasible. Multiple studies have demonstrated the efficacy of both epidural analgesia and intercostal nerve blocks in reducing the incidence of pulmonary complications associated with rib fractures.[14]

This chapter is a revision of the original chapter authored by Edgar J. Pierre M.D. and Shawn M. Cantie M.D.

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Questions

42.1 A 27 year old man is found to have an unstable C2 fracture sustained in a diving accident. He is unable to move his legs and is weak in both arms. The next appropriate action is:
   A. MRI
   B. flexion-extension views
   C. strict C-spine stabilization and neurosurgical consultation
   D. high dose methylprednisolone infusion

42.2 Several hours after an exploratory laparotomy for an abdominal GSW, a patient develops progressive oliguria, a firm distended abdomen and rising peak airway pressures. What is the most likely cause of these findings?
   A. cardiac tamponade
   B. pulmonary edema
   C. transfusion reaction
   D. abdominal compartment syndrome

42.3 The most common arrhythmia after blunt cardiac injury is:
   A. ventricular fibrillation
   B. sinus tachycardia
   C. atrial fibrillation
   D. normal sinus rhythm

42.4 The GCS of a trauma patient who opens her eyes only to pain, intermittently moans and mumbles, and grabs her left shoulder with her right hand when vigorously pinched is:
   A. 4
   B. 12
   C. 9
   D. 8

42.5 An alert 23 year old man is found to have an isolated femur fracture after falling twelve feet while painting his house. He denies any tenderness upon palpation of his posterior cervical spine and has a normal neurological exam. Using the NEXUS criteria, does he require diagnostic imaging to rule-out a significant c-spine injury?
   A. Yes
   B. No

43. Burn Management

Ronald Pauldine MD

Key Points

• The %TBSA burned, age and presence of IHI are the primary determinants of mortality in major burn injury.

• The optimal fluid resuscitation protocols, type of fluid and endpoints of resuscitation in major burn injury are not well defined.

• Overly aggressive resuscitation of the burn patient can result in serious complications including compartment syndromes of the abdomen, extremities, and orbit as well as pulmonary edema and significant pericardial and pleural effusions.

• Diagnosis of infection and sepsis is extremely difficult in burn patients.

• Burn patients often have altered pharmacokinetics leading to risk of inadequate antibiotic therapy due to an increased volume of distribution and augmented clearance. Therapeutic drug monitoring is recommended.

A 38 year-old woman is brought to the emergency department after being rescued from a burning building in a rural area. She was found unconscious inside the building on the first floor. Paramedics intubated her at the scene and initiated resuscitation with Lactated Ringers solution at 200 ml/hr via a peripheral intravenous line. Transit time to your facility was 2 hours. On initial evaluation, she is observed to have burns covering her torso, right lower extremity and bilateral upper extremities. The estimated involvement with deep partial thickness and full thickness burns is 65% total body surface area. The respiratory therapist suctions her endotracheal tube demonstrating moderate thick, black tinged secretions. Heart rate is 110 bpm. Blood pressure is 148/90 mmHg and SaO_2 is 91%.

INTRODUCTION

Major burn injury is among the most devastating injuries experienced by any patient. Management is challenging, heralded by extreme alterations in normal physiology, complex wound management, and the risk of multiple complications. Many patients require repeated surgeries after initial treatment to optimize function and cosmetic appearance. Long-term psychological and psychosocial problems often affect burn survivors. Modern management of major burn injury is best performed by dedicated centers, requires a multidisciplinary approach and demands allocation of considerable resources.

Initial Evaluation

Burn injury may be the result of flame, scald, steam, electricity and chemicals. Estimation of the burn size, depth, mechanism and area of involvement is important in differentiating triage to a burn center, calculating fluid requirements and determining prognosis. Indications for triage to a burn center are listed in Table 43.1. Initial evaluation follows the American College of Surgeons Advanced Trauma Life Support algorithm. Burn injuries can be distracting and it is important to ensure that a full exam is performed. Burn patients are seldom hypotensive on presentation. Hypotension should prompt a search for a concomitant traumatic injury. Burn depth has been classified by various terms as indicated in Table 43.2. Generally, superficial burns heal with minimal scarring and deep involvement is best treated with excision and skin grafting. Circumferential deep burns of the extremities and trunk result in a burn eschar that can cause compartment syndromes and impaired chest wall excursion. These require release via escharotomy. Many methods have been proposed for estimation of the percentage of total body surface area (%TBSA) burned. Each has relative strengths and limita-

Table 43.1 Criteria for Referral to a Burn Center

Partial-thickness burns > 10% TBSA
Burns involving the face, hands, feet, genitalia, perineum, or major joints
Full thickness burns in any age group
Electrical burns including lightning injury
Chemical burns
Inhalation injury
Patient co-morbidities that could complicate management, prolong recovery or affect mortality
Patients with burns and concomitant trauma where the burn injury poses the greatest risk of morbidity or mortality
Pediatric burns
Patients who will require special social, emotional or rehabilitative intervention

tions. The most commonly used methods include the Rule of Nines and the Lund and Browder chart. Chemical burns are often observed in industrial mishaps. Acid injuries result in coagulation necrosis of affected areas while alkali exposure causes liquefaction and tends to cause deeper injury. Initial treatment includes removal of clothing and copious irrigation. Electrical injury is classified by the magnitude of the current causing the injury, with high-voltage injuries resulting from currents greater than 1000 volts. With high-voltage injury, the current passes through the patient and can cause deep tissue destruction that can be severely underestimated by the observed skin involvement. Complications can include rhabdomyolysis, compartment syndrome and pigment nephropathy. Late effects include peripheral neuropathy and cataracts.

Injury Severity and Outcome

Mortality in the burned patient has been most closely associated with %TBSA involved, presence of full thickness injury, presence of inhalation injury, age and sex. These variables are utilized in the abbreviated burn severity index (ABSI). The Baux score is a simple index using age plus %TBSA to estimate mortality. Neither of these indices includes co-morbidities. Unsurprisingly, the presence of significant co-morbidities is associated with increased mortality.

Airway Management and Inhalational Injury

The airway should be addressed during the primary survey. Inhalation injury (IHI) may lead to respiratory compromise and the need for endotracheal intubation. During the resuscitation of major burns, edema formation should be anticipated. History suggestive of IHI includes closed-space fires, need for rescue and altered mental status. Familiar signs of possible IHI include burns to the face, carbonaceous sputum, facial erythema and facial edema. Stridor, dyspnea and increased work of breathing are late findings. Even in the absence of IHI, the airway may become compromised during the resuscitation phase leading to difficult or impossible intubation. This should be anticipated and the airway should be secured early if there is clinical concern. IHI is primarily a chemical process. Injury to the upper airway above the vocal cords occurs when air over 150°C is inhaled. Frank thermal injury to the lower respiratory tract is rare except in the scenario of inhaled steam due to the efficiency of the pharynx in dissipating heat.

Chemical injury to the more proximal airways occurs through exposure to toxic gaseous compounds. Distal damage is facilitated by toxins binding to carbon particles with distribution throughout the respiratory tract. Resulting effects include sloughing of respiratory epithelium, increased mucous secretion, inflammation, atelectasis and airway obstruction.

Carbon monoxide (CO) toxicity is an important cause of death in fires. CO leads to tissue hypoxia and cell death due to impaired oxygen delivery. The affinity of hemoglobin for CO is over 200 times greater than its affinity for oxygen leading to decreased oxygen carrying capacity. In addition carboxyhemoglobin shifts the oxyhemoglobin dissociation curve to the left and changes the shape of the curve such that there is impaired unloading of oxygen at the tissue level. Symptoms include headache, dizziness, nausea, and confusion leading to unconsciousness. Pulse oximetry will significantly overestimate arterial oxygen saturation in the setting of CO toxicity. Direct measurement of carboxyhemoglobin is required. The half-life of carboxyhemoglobin is significantly reduced by administration of 100% oxygen.

Hydrogen cyanide is a combustion byproduct of a variety of materials and elevated cyanide levels have been reported in victims of closed space fires. Cyanide-related toxicity should be suspected in patients with IHI and unexplained lactic acidosis. Treatment is usually supportive but specific therapy with hydroxycobalamine and sodium thiosulfate (contraindicated in patients with significant CO levels) is increasingly reported. Treatment of IHI is primarily supportive with mechanical ventilation and aggressive bronchopulmonary hygiene. Fiberoptic bronchoscopy is used to confirm diagnosis via visualization and quantification of hyperemia, edema and carbonaceous material in the airway.

Resuscitation

Burn shock results from a complex cascade of physiologic events leading to a mixed hypovolemic and distributive shock. It is usually seen in patients with burns involving more than 20% TBSA. A transient increase in capillary permeability results from the action of a variety of inflammatory mediators. With fluid resuscitation, significant edema occurs in both burned and unburned tissue. Various formulas for burn resuscitation have been described and generally differ in the amount of fluid recommended per %TBSA involved and the use and timing of colloids (Table 43.3). It is important to understand that resuscitation formulas serve as a starting point in resuscitation. It is necessary to monitor and adjust the administration rate based on patient response. In general, conditions such as IHI and electrical burns will increase fluid requirements greater than that predicted by % TBSA alone. Timing of fluid administration starts at the time of the injury so patients that arrive to care late without adequate fluid replacement may have a significant deficit. Endpoints and goals of resuscitation in burn are controversial. Most centers target mean arterial pressure of 60 mmHg and urine output of 0.5cc/kg/hr in adult patients. Base deficit and lactate levels at time of presentation correlate with mortality. Overzealous resuscitation of burn patients has been an emerging problem with patients frequently receiving volumes far in excess of those predicted. Excess fluid administration has been associated with an increased incidence of compartment syndromes of the abdomen, extremities, and orbit as well as pulmonary edema and significant pericardial and pleural effusions. Use of colloid in patients with a difficult resuscitation course may decrease total fluid administration and the risk of abdominal compartment syndrome. Serial bladder pressure measurement should be considered for

Table 43.2 Assessment of Burn Depth

	Terminology			Structures Affected	Clinical Features
Superficial	Superficial		"First Degree"	Epidermis	Erythema, minimal edema, mild discomfort Heal without scarring Example: Sunburn
	Partial Thickness	Superficial Partial Thickness	Superficial "Second Degree"	Epidermis + Dermis (<50%)	Wet, pink, blistered, painful. Blanches with pressure. Heal with minimal scarring within 2 weeks Example: Scald
Deep		Deep Partial Thickness	Deep "Second Degree"	Epidermis + Dermis (>50%)	White, mottled, varied appearance. may not blister. Heal by hypertrophic scarring and contracture. Best treated wiht excision and grafting
	Full Thickness		"Third Degree"	Epidermis + Dermis + Subcutaneous	Dry, leathery, insensate. Do not blanch with pressure. Require excision and Grafting

patients at risk of developing abdominal compartment syndrome.

Burn Wound Management

Early excision and grafting for full thickness and deep partial thickness burns has resulted in improved survival, decreased incidence of sepsis, attenuation of hypermetabolism, less need for repeated surgery, better functional outcome and shorter hospital length of stay. The surgical goal is to debride all dead skin and achieve coverage of the wound as soon as possible. In large %TBSA burns, donor sites for skin autograft are limited and coverage frequently requires staged operations with use of biological dressings. Ideally, this should occur immediately after hemodynamic stability is achieved and within 48 hours post-burn. Beyond this time, bacterial colonization of the wound is common leading to greater blood loss and graft failure. Burn excision can result in significant blood loss so patients are at risk for familiar transfusion related complications including coagulopathy, electrolyte imbalance, immunosuppression and acute lung injury.

Intensive Care Unit Management

Infectious Disease

Burn patients are at increased risk of infection due to loss of the barrier function of the skin and an induced state of immunosuppression. Defining and diagnosing infection can be challenging. All burn patients manifest systemic inflammatory response syndrome (SIRS) and transition to a hypermetabolic state where baseline temperature is elevated. Organ dysfunction may be evident during the resuscitation period and persist for several days with alterations in WBC, platelets and urine output as common findings. Therefore, vigilance for changes in patient condition that may suggest infection and are not easily explained by the burn injury alone are warranted. The risk for pneumonia is increased in IHI.

The burn wound is frequently a source of infection. Early colonization can be decreased with the use of topical antibiotics. Routine use of systemic antibiotics is contraindicated.

The wound should be assessed for signs of infection including conversion of partial thickness wounds to full thickness, cellulitis, rapid eschar separation and frank tissue necrosis. Swab cultures from the wound may be useful in defining colonization. Quantitative tissue culture and histologic analysis may be considered for diagnosis of wound infection. Catheter related blood stream infection appears to be more common in burn patients and practice may differ from current CDC guidelines with some centers electing to change central venous catheters at regular intervals. Pharmacokinetic changes are frequently observed in burn patients with altered volume of distribution and clearance leading to less than predicted serum levels and risk for inadequate antimicrobial therapy. Therapeutic drug monitoring should be performed for available agents.

Ventilation

Burn patients are at risk to develop ARDS related to SIRS, IHI, sepsis, pneumonia, transfusion related complications and ventilator associated lung injury. Lung protective ventilation strategies may be useful. However, this strategy may be clinically challenging due to increased CO_2 production associated with hypermetabolism. Modest decreases in tidal volume may lead to significant increases in pCO_2. The considerations for timing of tracheostomy in burn patients are similar to those for any critically ill patient requiring mechanical ventilation and are often subject to institutional bias given an overall lack of evidence.

Nutrition and Metabolism

The metabolic response to burn injury involves profound catabolism with enhanced release of corticosteroids, glucagon, and catecholamines leading to breakdown of muscle and release of amino acids. Evidence suggests that alterations in amino acid transport contribute to ongoing proteolysis and negative nitrogen balance. Hepatic function is impaired as well. Hypermetabolism and catabolism persists nine months to as long as three years post injury. Nutritional needs are high but provision of optimal nutrition does not prevent loss of lean body mass. Use of early enteral feeding may be beneficial and careful attention should be paid to minimize the interruption of nutrition for operative procedures. Overfeeding is not beneficial and may lead to complications including fatty liver. Indirect calorimetry may be used to guide nutritional support. Hyperglycemia

Table 43.3 Burn Resuscitation Formulas (Examples)

Formula	Description
Brooke	LR 1.5ml/kg/%TBSA + colloid 0.5ml/kg/%TBSA during first 24 hours LR 0.5ml/kg/%TBSA + colloid 0.25ml/kg/%TBSA + D5W 2000ml during second 24 hours
Parkland	LR 4ml/kg/%TBSA (half in first 8 hours, half in next 16 hours) D5W 2000ml + colloid 0.5ml/kg/%TBSA during second 24 hours
Modified Brooke	LR 2ml/kg/%TBSA (half in first 8 hours, half in next 16 hours) Colloid 0.3-0.5ml/kg/%TBSA + D5W to maintain urine output during second 24 hours
US Army Institute of Surgical Research "Rule of Ten"	%TBSA * 10 + (100ml/10kg over 80kg body weight) = initial fluid rate (ml/hr). Adjustments made based on clinical response.

is common and peak serum glucose concentrations and duration of hyperglycemia have been associated with increased mortality. It is prudent to prevent hyperglycemia with insulin therapy as in any other ICU population. Pharmacologic interventions to address hypermetabolism include the anabolic steroid oxandrolone and the beta blocker propranolol. Oxandrolone has been demonstrated to improve wound healing and decrease hospital length of stay. Propranolol has been reported to attenuate the inflammatory response and decrease catabolism. The use of immunonutrition remains controversial with trials reporting mixed results.

Transfusion
The currently available data suggest that restrictive transfusion strategies are beneficial in burn patients.

Thromboembolism Prophylaxis
There is little consensus regarding venous thromboembolism (VTE) prophylaxis in burn patients. Recent data suggests risk is related to %TBSA and the need for ICU admission. Routine VTE prophylaxis is beneficial and should be administered.

Conclusions
Critical care of the burn patient is challenging, resource intensive, multidisciplinary and remains an area of active research with many unanswered questions.

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Questions

43.1 Which of the following is MOST LIKELY true regarding nutrition in the patient with major burn injury?
  A. Exogenous amino acid administration reverses protein catabolism.
  B. Immunonutrition has been demonstrated to improve survival in large prospective randomized trials.
  C. Oxandrolone decreases hospital length of stay.
  D. Calorie overfeeding promotes wound healing.

43.2 Regarding pneumonia in the burn patient which of the following statements is MOST LIKELY true?
  A. Fiberoptic bronchoscopy and bronchoalveolar lavage lead to overuse of antibiotics.
  B. Risk is increased in the setting of inhalation injury.
  C. The clinical pulmonary infection score is a valid diagnostic aid.
  D. Initial doses of antibiotics should be reduced for a contracted volume of distribution.

43.3 A 70-kg patient presents immediately following a burn injury involving 50%TBSA. His initial fluid rate as estimated by the Parkland formula is
  A. 450cc/hr
  B. 575cc/hr
  C. 650cc/hr
  D. 875cc/hr

44. Obstetric Critical Care

A Jason Vaught MD and Brenda G Fahy MD

Key Points

• Cardiopulmonary physiologic changes of pregnancy include hypervolemic high cardiac output state, increased minute ventilation and decreased functional reserve capacity.

• Hypertensive diseases occur in 12% to 22% of pregnancies and account for approximately 17% of maternal mortalities in the United States.

• Postpartum hemorrhage occurs in about 4% to 6% of pregnancies, with 80% caused by uterine atony.

• Amniotic fluid embolism (AFE), although occurring only in 1:26,000 pregnancies, has a high mortality rate and high rate of permanent neurologic sequela.

A 29-year-old G1P0 at 35 weeks is being induced for severe pre-eclampsia. A magnesium sulfate infusion is begun at 2 mg/h and intermittent doses of hydralazine and labetalol are required to treat hypertension. Twelve hours later, her urine output falls and despite fluid administration by the obstetric team, it remains below 0.5 mL/kg/h for more than 6 h. You are consulted and you assess the patient, noting an altered mental status, respirations of 8 per minute, a heart rate of 60 bpm, and a blood pressure of 115/80 mmHg. The patient seizes following your assessment.

INTRODUCTION

Pregnancy is a common occurrence usually with low morbidity and mortality rates. There are approximately 4 million births per year in the United States alone. Of these 4 million births, approximately 1% to 3% require an advanced level of critical or intermediate care that may or may not be within the scope of practice for the obstetrician or physician on call[1,2].

The critical care of the pregnant patient involves special considerations due to maternal physiologic changes associated with pregnancy, the presence of a viable fetus, and the location of the patient in a specialized peripartum area of the hospital, often in a labor and delivery suite that may or may not be close to critical care services. Key knowledge areas warranting special consideration in this section include: (1) physiologic changes of pregnancy, (2) severe hypertensive disease during pregnancy, (3) postpartum hemorrhage and the coagulopathy of pregnancy, and (4) the critical illness of amniotic fluid embolism.

Physiologic Changes in Pregnancy

Obstetrical critical care requires a foundation in the cardiopulmonary physiologic changes in pregnancy. During a normal pregnancy, cardiovascular changes include a hypervolemic, high cardiac output state secondary to the increase in blood volume and heart rate. The circulating blood volume can be elevated by up to 50% above normal while the red cell mass increases at a lower rate of 25% in a single gestation. The result is a

mild dilutional anemia.

Pulmonary changes also occur with the diaphragm elevation by the enlarging uterus and ribcage circumference expansion secondary to increased levels of relaxin[3]. These changes can result in a decrease in functional residual capacity of 25%, and up to 70% in the supine position[3]. The minute ventilation increases by 30% to 50%, mostly secondary to the increase in tidal volumes, causing respiratory alkalosis with $PaCO_2$ of approximately 32 to 34 mmHg[3].

Hypertensive Diseases

Hypertensive diseases occur in 12% to 22% of pregnancies and account for approximately 17% of maternal mortalities in the United States[4]. Hypertension in pregnancy can be categorized as gestational hypertension, pre-eclampsia/eclampsia, and chronic hypertension. Gestational hypertension is hypertension after the first 20 weeks of pregnancy without proteinuria, and blood pressures usually normalize in the postpartum period[5]. Pre-eclampsia is diagnosed in a previously normotensive patient when systolic blood pressures exceed 140 mmHg or diastolic pressures exceed 90 mmHg with proteinuria. The diagnosis of proteinuria typically requires more than 0.3 g of protein in a 24-h urine specimen[5]. Classification of mild versus severe pre-eclampsia is based on signs of organ dysfunction and/or symptoms of hypertensive encephalopathy (e.g., blurred vision). Chronic hypertension is diagnosed when blood pressure is elevated before 20 weeks and/or continues 4 to 6 weeks postpartum.

The patient in this vignette has severe pre-eclampsia with multiorgan dysfunction, including acute kidney injury. Therapeutic levels of magnesium for severe preeclampsia range from 4 to 6 g/dL. A magnesium level above 8 g/dL can lead to signs of magnesium toxicity, including respiratory depression, depressed mental status, and cardiovascular collapse. Because of the decreased magnesium excretion with AKI, this patient now has magnesium toxicity with respiratory compromise. Treatment is intravenous calcium (1 g of calcium chloride or 2 g of calcium gluconate) to reverse the effects of magnesium. If the patient fails to respond to calcium administration, a seizure may follow. The differential diagnoses include new onset seizure, withdrawal seizure, and eclamptic seizure. An eclamptic seizure usually presents with tonic-clonic movements in addition to altered mental status. Regardless of the mechanism of the seizure, securing the airway in the pregnant female should be a priority if initial therapeutic measures fail.

Postpartum hemorrhage

Postpartum hemorrhage occurs in about 4% to 6% of pregnancy, with 80% caused by uterine atony[6]. An estimated blood loss of greater than 500 mL following vaginal birth, greater than 1000 mL after a cesarean section, or a decline in hematocrit of greater than 10% has been used to quantitatively define postpartum hemorrhage[7].

Amniotic Fluid Embolism

Amniotic fluid embolism (AFE), although occurring only in 1:26,000 pregnancies, has a high mortality, with reported rates from 26%[8] to 86%[9]. Although mortality has drastically decreased over the years, 85% of survivors suffer some permanent neurological deficit. First described in 1926, the pathogenesis is theorized to be caused by amniotic debris entering the maternal circulation.

The cardinal findings for AFE are hypoxia, hypotensive shock, altered mental status,

Following infant delivery, the mother complained of dyspnea, had an acute mental status change and was intubated. The placenta has been extracted and vigorous bimanual massage is being performed. The patient has already received oxytocin, multiple doses of methylergonovine and carboprost, and the obstetrician is now placing 1000 mcg of misoprostol. Although uterine tone is good, the patient continues to have uterine bleeding with bleeding noted from peripheral intravenous sites. The patient is hypotensive despite crystalloid, colloid, and blood products, and an epinephrine infusion is now begun.

and disseminated intravascular coagulation, all of which are typically present during or shortly after labor[10]. Although the index of suspicion is high for AFE in this vignette, other potential causes need to be excluded. These include HELLP syndrome, eclampsia, septic shock, hemorrhagic shock, and acute respiratory distress syndrome.

Mortality with AFE usually occurs within the first hour of presentation. Stabilization of the airway is critical, as hypoxemia occurs in 93% of patients with AFE, with hypoxic encephalopathy believed to be a major contributor to neurologic deficits in this patient population[10]. Hypoxemia is proposed to be secondary to cardiogenic edema of the alveoli, non-cardiogenic edema of the alveoli, exudative edema, and bronchospasm[10]. Therapeutic options include use of positive-end expiratory pressure, bronchodilators, and for refractory hypoxemia, nitric oxide may be of benefit.

Hypotension also occurs with AFE, and is most commonly described as cardiogenic, with 70% of patients having some degree of left ventricular failure, although there may be distributive and obstructive components as well. Amniotic debris may cause pulmonary vasospasm and pulmonary hypertension. Cardiac arrhythmias including bradycardia, pulseless electrical activity, and ventricular fibrillation may also occur[10].

Regardless of the reason for hypotension, these patients should have continuous telemetry. Although it is up to the practitioner to decide whether to use arterial access and/or central venous access, these monitoring devices can be of large benefit for the guidance of resuscitation and administration of vasopressors and/or inotropes.

Patients with AFE require intensive care admission and the treatment is largely supportive. It is imperative to prevent further hypotension and hypoxemia. To prevent hypoxemia, it may be appropriate to use lung protective ventilation or even alternative forms of ventilation with refractory hypoxemia (e.g., BILEVEL or oscillator techniques). Because hypotension can have several etiologies, monitoring of central venous pressures and cardiac function may be required. Bedside echocardiography performed by the critical care physician urgently could help guide resuscitative efforts. It is also imperative to correct disseminated intravascular coagulation to prevent any further bleeding. The prognosis and mortality of AFE have improved significantly, most likely related to early resuscitative efforts in this patient population. Mortality occurs early and thus

rapid intervention is required.

Conclusion

To provide obstetrical critical care, the intensivist must first understand the normal physiologic changes of pregnancy with special attention paid to the cardiopulmonary changes. Hypertensive disease often complicates pregnancy, with its treatment determined by its cause-gestational hypertension, pre-eclampsia/eclampsia, and chronic hypertension. Management of postpartum hemorrhage, including coagulopathy and disseminated intravascular coagulation, and recognition and therapy for AFE (a rare but serious pregnancy complication) are discussed.

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Questions

44.1 Physiologic changes of pregnancy include
 A. Decreased circulating blood volume
 B. Metabolic acidosis
 C. Decreased functional residual capacity
 D. Elevated liver enzymes

44.2 Therapeutic levels of magnesium for severe preeclampsia range from
 A. 2 – 2.5 g/dL
 B. 2.5-4 g/dL
 C. 4-6 g/dL
 D. 8-10 g/dL

44.3 Which of the follow about AFE is true
 A. Mortality from AFE usually occurs 24-48h post presentation
 B. Cardiogenic heart failure is common
 C. If patients survive, long term sequelae is rare
 D. Occurs in 1 in 2000 births

45. Management of the Critically Ill Geriatric Patient

John Adam Reich MD, Konstantin Balonov MD and Ruben J Azocar MD

Key Points

• The elderly patient has a high likelihood for using ICU resources.

• There are multiple physiologic changes that occur as the body ages. These changes should be taken into consideration when caring for an elderly patient in the ICU

• Long-term goals and goals-of-care should be addressed with the geriatric patient and the family.

A very frail 86 year-old woman with atrial fibrillation, hypertension and chronic obstructive pulmonary disease, falls and sustains a hip fracture and subdural hematoma. Her home medications include wafarin, metoprolol, tiotropium, albuterol, tramadol, simvastatin, and hydrochlorothiazide. She is admitted to the ICU for reversal of her supratherapeutic INR, serial neurologic examinations, and for operative planning for her hip fracture.

INTRODUCTION

Geriatric admissions to the ICU will become increasingly common in the coming decades. Aging itself is not pathologic per se, but there are physiologic changes associated with aging that affect critical care management. The geriatric age group has more utilization of ICU resources than other age groups, and has special considerations.

I. Demographics of Aging Population[1]
  A. Geriatric population is growing faster than the overall population (1.9% vs. 1.2% per year)
  B. Between years 2000-2030 the number of older adults will increase from 550 million to 973 million
  C. By 2050, 9% of North America will be greater than 80 years old.
  D. In the United States, about 50% of all admissions are geriatric patients and 60% of all ICU days are attributed to geriatric patients.
  E. 40% of all Medicare patients who die are admitted to the ICU during their terminal illness
  F. Data suggest higher ICU admission rate for patients > 75 years old.[2]

II. Physiologic Changes Associated with Aging
  A. Function and structural changes occur as patients age.
  B. Basal function of organ systems may remain the same or slightly decrease, but the physiologic reserve

decreases with age.[3]

C. Frailty might be the best indicator of overall physical status

D. Central Nervous System Changes [4]
1. Loss of neural tissue: 26% reduction of white matter
2. 10-20% reduction in cerebral blood flow
3. Decreased number of serotonin, acetylcholine, and dopamine receptors
4. Decline in memory, reasoning, and perception
5. Disturbed sleep-wake cycle
6. Prone to delirium and cognitive dysfunction

E. Cardiovascular Changes [4]
1. Frequently associated comorbidity
2. Diastolic dysfunction is common
3. Vascular bed (arteries-arterioles) become noncompliant
4. Less compliant heart and vascular bed results in increased sensitivity to volume changes
5. Less responsive to catecholamines
6. Frequently taken medications blunt sympathetic response
7. Autonomic tissue is replaced by fat and connective tissue
8. Prone to arrhythmias, most commonly atrial fibrillation and AV Block

F. Pulmonary Changes [4]
1. Loss of pharyngeal reflexes
2. Decrease in chest wall compliance
3. Decline in lung elasticity
4. Alteration in control of ventilation
5. Diaphragm strength is 25 % reduced in healthy elderly individuals
6. A-a (alveolar to arterial) gradient increases with age
7. Closing capacity increases with age

G. Renal Changes [4]
1. Loss of renal tubular mass
2. Decreased renal blood flow by 50%
3. Decreased glomerular filtration rate (by 80 years old, decreased by 45%)
4. Reduced ability to dilute and concentrate urine and conserve sodium
5. Decreased drug clearance

III. Management in the ICU

A. Central Nervous System Management
1. Delirium is a frequent occurrence in the geriatric population
   a. Acute onset or fluctuating in mental status
   b. Inattention is the most prominent feature
   c. May be accompanied with emotional disturbances (agitation)
   d. May be hyperactive and/or hypoactive
   e. Increases morbidity, mortality and length of stay
2. Contributing factors to delirium
   a. Metabolic derangements
   b. Pain
   c. Hypoxemia
   d. Hypercarbia
   e. Hypotension
   f. Metabolic disorders
   g. Sepsis
   h. Substance abuse
   i. Preexisting disease (depression/dementia)
   j. Delirium-causing drugs (benzodiazapines, anticholinergics)
   k. Sleep deprivation
   l. Visual/hearing impairments
3. Delirium Management & Treatment
   a. Delirium is a medical emergency
   b. Have a high index of suspicion - frequently screen (5)
   c. Correct/minimize triggers
   d. Avoid deliriogenic drugs
   e. Encourage proper sleep-wake cycle
   f. Minimize noise and interruptions to daily routine
   g. Frequently re-orient patient to date, time and place
   h. Consider antipsychotic medications for hyperactive delirium that is a danger to patient and/or staff
4. Beware of polypharmacy and possible drug-drug interactions
5. Be respectful of loss of autonomy, wishes for dignity and end of life

B. Cardiovascular Management
1. Need for tight volume control due to diastolic dysfunction
2. Consider dynamic monitoring (pulse pressure variation, stroke volume variation) to optimize cardiovascular status
3. Early diuresis may be needed to avoid pulmonary edema

C. Pulmonary Management
1. Maintain aspiration precautions
2. Consider noninvasive ventilation in selected populations (COPD exacerbation and congestive heart failure)

D. Renal Management
1. Avoid nephrotoxic agents
2. Use alternative imaging studies to avoid IV contrast
3. Remove bladder catheters as soon as possible to decrease risk of infection
4. Careful dosing of drugs cleared by kidney

E. Outcomes
1. Planned surgical admissions have better survival and quality-of-life post ICU discharge than unplanned surgical admissions and medical admissions [6,7]
2. Both morbidity and mortality after major surgery increase with age. [8]

3. Long-term mortality as a metric may be flawed in this elderly population, and rather quality-of-life and other indicators should be considered.
4. Providing guidance in establishing goals of care at the end-of-life is an important role for the Intensivist.
5. Family experience during ICU and hospitalization as well as after patient's death may be an important outcome.

Discussion

The above case is representative of the geriatric patient with multiple comorbidies having an unplanned admission to the ICU. How quickly should her supratherapeutic INR be reversed in the setting of subdural hematoma? Should we use multiple units of fresh frozen plasma, vitamin K, or recombinant factor VIIa? Administration of large volumes of plasma in a patient with no atrial kick and diastolic dysfunction from years of hypertension could quickly result in pulmonary edema and respiratory failure. Her pain should be treated with acetaminophen and opioids while monitoring to make sure her respiratory status is not compromised. She is at high risk of developing delirium with disruption of her sleep-wake cycle and addition of new medications. It is important to have a discussion with the patient and family so that her goals of care coincide with treatment plan.

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Questions

45.1 An 82 year-old woman is brought to the hospital by her family who noticed that she was confused, had lack of energy, and a cough for one week. Chest radiograph reveals right lower and middle lobe infiltrates. In the Emergency Department, she develops severe respiratory distress and cyanosis, requiring intubation and initiation of mechanical ventilation. Which of the following drug infusion regimens is best for sedation in this patient?
    A. Lorazepam
    B. Hydromorphone
    C. Dexmetomidine
    D. Etomidate
    E. Ketamine

45.2 An 86 year-old man presents to the emergency department with a COPD exacerbation. He has previously filled out a an advanced directive that stated "Do Not Intubate, Do Not Resuscitate." He is having extreme difficulty breathing and gasping for air. Which of the following is the next best step.
    A. Call his family and ask if they want everything done.
    B. Ask the patient: "Do you want me to put the breathing tube in to make your breathing easier?"
    C. Start a morphine drip and make the patient comfortable.
    D. Place the patient on bi-level non-invasive ventilation
    E. Intubate the patient and treat for COPD exacerbation-it is only for the short term so the patient will understand.

45.3 An 87 year-old man is admitted to the ICU after an exploratory laparotomy for small bowel obstruction. A 20 cm portion of proximal jejunum right at the ligament of Treitz was removed with end-to-end anastomosis. He is from overseas and was visiting family. He has no medical records or history that is readily obtainable. He received 3 liters of crystalloid preoperatively in the emergency room and 3 liters crystalloid intraoperatively during the 2-hour surgery. Through an interpreter in the recovery room, he tells his nurse that he is having shortness of breath. Physical exam reveals crackles and wheezes, bilaterally. His BP is 158/84 mmHg, HR 90 beats/minute, RR 25 breaths/minute, and SaO_2 91% on 50% face mask oxygen. Chest radiograph shows hilar congestion with cephalization of pulmonary vessels. What is the next best step?
    A. Intubate patient for respiratory distress.
    B. Place patient on noninvasive ventilation.
    C. Administer 40mg furosemide IV.
    D. Place a pulmonary artery catheter to determine loading conditions and function of heart.
    E. Administer albuterol nebulizer.

Answers

Chapter 1
1.1   A
1.2   B
1.3   C
1.4   D

Chapter 2
2.1   C
2.2   B
2.3   D
2.4   B

Chapter 3
3.1.   C. Phenytoin is associated with resistance. The other medications are associated with potentiating the effects of NMBAs.
3.2.   A. Cis-atracurium is intermediate.
3.3.   C. Hyperkalemia is a potential complication of a depolarizing muscle relaxant (succinylcholine).
3.4.   D. ICU acquired weakness is most likely multifactorial with concomitant use of steroids, drug over-dose, drug or drug metabolite accumulation, and sepsis. Propofol has not been implicated in damaging the neuromuscular junction.

Chapter 4
4.1   B
4.2   D
4.3   C

Chapter 5
5.1   D
5.2   B
5.3   B

Chapter 6
6.1   A
6.2   D
6.3   C

6.4　　D
6.5　　C

Chapter 7
7.1　　B Lowering of the arterial line transducer will increase the measurement by the pressure produced by a column of saline in the arterial line tubing between the transducer and the level of the heart. 20cm H_2O = 15mmHg
7.2　　A Lead V5 is most sensitive to ischemia
7.3　　C $ETCO_2$ is the most accurate indicator of the quality of the CPR

Chapter 8
8.1　　D
8.2　　B
8.3　　B
8.4　　A

Chapter 9
9.1　　D
9.2　　D
9.3　　E
9.4　　D

Chapter 10
10.1　　A

that test are often subject to less formal protocols, training of personnel may be less formal, and there may be little or no formal documentation process.
10.2　　C
10.3　　D

Chapter 11
11.1　　B
11.2　　C
11.3　　D

Chapter 12
12.1　　D. Initial evaluation and management of all trauma victims, including those with suspected head trauma, targets airway, breathing and circulation. This patient's SBP is < 90 mmHg that is associated with worse outcome in TBI and should be promptly corrected as per ATLS guidelines. Of the answers, only D will improve his blood pressure. A CT of the head should be obtained after initial resuscitation. Without an abnormal CT, he does not meet criteria for ICP monitoring. Therapeutic hypothermia remains controversial in TBI.
12.2　　A. Contrary to common misconception, placement of central lines in the IJ is not associated with significant ICP elevation. Lung protective ventilation, especially with higher levels of PEEP, impairs cerebral venous drainage and can raise ICP. Similarly, placing the bed in Trendelenberg hinders venous drainage from the head. Reducing

a femoral fracture is a painful procedure. Without adequate analgesia, pain can increase the $CMRO_2$ and cause Valsalva physiology. Both can result in an increase in blood pressure that can raise ICP if cerebral autoregulation is disrupted.
12.3　　D. Of the choices listed, the only indication for systemic steroids is the situation in which an intracranial mass has surrounding edema. In the case of TBI, steroids have been shown to worsen outcome. Data illustrating a benefit is lacking for both subarachnoid hemorrhage and hydrocephalus.

Chapter 13
13.1.　　B
13.2.　　C
13.3.　　E
13.4.　　E

Chapter 14
14.1　　D
14.2　　A
14.3　　C
14.4　　C
14.5　　C

Chapter 15
15.1　　E
15.2　　A
15.3　　C
15.4　　D
15.5　　A

Chapter 16
16.1　　A
16.2　　D
16.3　　C

Chapter 17
17.1　　B The patient has developed tachypnea during his SBT; therefore the SBT should be aborted and the patient should be placed back on a non-fatiguing mode of MV. A search for the underlying etiology of the patient's inability to breath spontaneously should be undertaken and reversible causes for failure should be addressed. The SBT should be repeated within 24 hours if appropriate. SIMV has not been shown to be an effective mode for weaning.
17.2　　C A low Glasgow Coma Score is not necessarily a contraindication to weaning and extubation. Coplin et al. randomized low GCS patients who had passed a SBT to either early or delayed extubation. The patients in the early extubation arm had a lower incidence of pneumonia, lower mortality, and did not incur a higher rate of weaning failure.[2] On the other hand, other studies have reported a high rate of weaning failure in neurological patients. (16) Neurologically impaired patients can be assessed for weaning and extubation on a case-by-case basis assuming they are able to meet other standard cri-

teria. Nutritional status should be optimized but is also not necessarily a contraindication to weaning. Correctable causes for weaning failure should be addressed. In this patient, draining the pleural effusion, or diuresis, could be considered.

17.3. B Non-invasive ventilation (NIV) has been shown to prevent reintubation in patients with hypercarbic respiratory failure but not in hypoxemic respiratory failure. (17) Furthermore, NIV has been shown to decrease the need for intubation and improve morbidity and mortality in three specific populations of patients with acute respiratory failure: chronic obstructive pulmonary disease (COPD) exacerbations; hydrostatic pulmonary edema; and in certain immunocompromised states. (18) In addition, patients who are neurologically impaired or have an increased risk of aspiration should not be placed on NIV; therefore, NIV was not an appropriate intervention for the case description patient presented at the beginning of the chapter.

Chapter 18
18.1   C
18.2   A
18.3   D

Chapter 19
19.1   C
19.2   B
19.3   D

Chapter 20
20.1   B
20.2   B
20.3   D

Chapter 21
21.1   C
21.2   C
21.3   D

Chapter 22
22.1.   C   Arrhythmia is the most common reason for hospital admission in patients with ACHD.
22.2.   B Modified Blalock-Taussig shunt is a shunt between the subclavian artery and pulmonary artery in patients who are otherwise cyanotic. Due to shunting from the systemic to pulmonary circulation, blood pressure in the ipsilateral arm will be decreased. Therefore, blood pressure monitoring should be contralateral to the repair.
22.3.   B Patent ductus arteriosus does not cause cyanosis. Recall the 5 Ts for cyanotic congenital heart defects: Transposition of the great vessels, tetralogy of Fallot, truncus arteriosus, tricuspid valve abnormalities, and total anomalous pulmonary venous connection. Other cyanotic lesions include hypoplastic left heart syndrome, coarctation of the aorta, Eisenmenger syndrome, and pulmonary atresia

Chapter 23
23.1   C
23.2   C
23.3   B

Chapter 24
24.1   E
24.2   D
24.3   A
24.4   D

Chapter 25
25.1   C
25.2   C
25.3   B
25.4   C

Chapter 26
26.1   C
26.2   C
26.3   D

Chapter 27
27.1   C
27.2   D
27.3   D
27.4   E
27.5   E

Chapter 28
28.1   D
28.2   D
28.3   A
28.4   D
28.5   E

Chapter 29
29.1   E
29.2   E
29.3   B

Chapter 30

30.1   C
30.2   B
30.3   E
30.4   D
30.5   A

Chapter 31
31.1   D
31.2   B
31.3   C

Chapter 32
32.1.   A
32.2.   D
32.3.   B

Chapter 33
33.1   D
33.2   E
33.3   D

Chapter 34
34.1   C
34.2   B
34.3   A
34.4   B

Chapter 35
35.1   C
35.2   C
35.3   B

Chapter 36
36.1   B
36.2   B
36.3   A
36.4   C

Chapter 37
37.1   E
37.2   C
37.3   D
37.4   A

Chapter 38
38.1   A
38.2   B
38.3   C

Chapter 39
39.1   D
39.2   C
39.3   B

Chapter 40
40.1.   D   Cyanide, by blocking cytochrome c in the electron transport chain, prevents the utilization of oxygen and consequently the mixed venous saturation increases. (Reference 1)
40.2   C   Reference 1
40.3   B   Reference 9
40.4   E   Reference 14
40.5   D   Reference 8
40.6   C   Reference 15
40.7   B   Reference 12

Chapter 41
41.1   C

The approach to preventing and treating right heart failure in the heart transplant recipient involves optimizing preload, contractility and afterload. Diuresis and a high heart rate can decrease the preload to the right ventricle. Lowering the heart rate would allow more time for the right ventricle to fill during diastole, worsening the volume overload and exacerbating the RV dilation and dysfunction. Inotropes increase contractility and help offload the right ventricle. Agents such as inhaled iloprost and nitric oxide can decrease afterload by decreasing pulmonary vascular resistance.

41.2   C

The transplanted heart has been denervated from its autonomic nervous supply and therefore does not respond to atropine, which works by opposing the parasympathetic activity of the vagus nerve. Only agents that act directly on the heart itself, such as epinephrine and isoproterenol, are effective. Epicardial pacing is also effective as it directly stimulates the cardiac muscle with electricity.

41.3   E

Hypoglycemia can be a sign of poor liver function. Of note, hyperglycemia is also common due to high doses of steroids as part of the immunosuppressive regimen. Hyponatremia can persist from the pre-operative period; sodium should be corrected slowly to avoid central pontine myelinosis. Transaminases are usually quite elevated in the post-operative period but should begin to normalize after the first few days. Persistently elevated or rising transaminases can be a sign of graft dysfunction due to various causes. The INR is also usually elevated post-op, until the allograft regains normal protein synthesis.

41.4   D

The most common initial regimen for maintenance immunotherapy after heart, lung and

liver transplantation is a steroid, an antimetabolite (usually mycophenolate) and a calcineurin inhibitor (usually tacrolimus). Many patients are able to taper steroids and often stop them all together within the first year. Lung transplant recipients are the most likely to continue taking steroids along with MMF and tacrolimus.

Chapter 42
42.1   C
42.2   D
42.3   B
42.4   C
42.5   A

Chapter 43
43.1   C
43.2   B
43.3   D

Chapter 44
44.1   C
44.2   C
44.3   B

Chapter 45
45.1   C   Drug effects can be pronounced in the elderly, and avoiding drugs associated with delirium in this high-risk patient population is important. Lorazepam is a benzodiazapine – a class of drugs known to cause delirium. Hydromorphone is a longer acting opiod that could be used, but patients may develop respiratory depression that impedes weaning from the ventilator as well as the significant side effect of constipation. Dexmetomidine is the best selection for sedation in this patient. It will allow the patient to remain awake and interactive on the ventilator. However, it can cause bradycardia and hypotension. Etomidate infusion is not practiced in any age group anymore due to the side effect of adrenal suppression and nausea. Ketamine would be a poor choice as its psychomimetic effects may worsen confusion and delirium.

45.2   D   These scenarios are not uncommon. It is best to have end-of-life discussions in a nonemergent situation, with a longitudinal primary care provider who knows the patient the best. Unfortunately, the intensivist broaches many end-of-life discussions for the first time. This patient had a chronic disease and had taken the time to fill out advanced directives. Noninvasive ventilation has been shown to be superior in COPD exacerbation to invasive ventilation and honors the patient's wishes so choice D is correct. Talking to the family and the patient are important, but always treat the patient first. Asking questions to a patient in respiratory distress is controversial because they are under extreme physiologic and psychological stress and will want their dyspnea treated. Dyspnea can be treated with invasive ventilation, noninvasive ventilation, anxiolytics and analgesics—the patient in distress may say "yes" to any and all of the above just to get relief. Choice C is wrong because DNI/DNR doesn't mean that we stop caring for the patient. COPD exacerbation is treatable with antibiotics, steroids, nebulizers, and noninvasive ventilatory support until the exacerbation subsides.

45.3   C   The patient has signs, symptoms, and imaging consistent with flash pulmonary edema. This likely is a result from the fluid replacement given before and during the operation. Choice E is incorrect as the patient's respiratory insufficiency is most likely due to diastolic dysfunction and a slightly over resuscitated patient (cardiac asthma!). Choices A-D can all be used to treat (choices A-C) or aid in the treatment (choice D) of diastolic congestive heart failure. Flash pulmonary edema can be quickly treated with positive pressure ventilation and diuresis. In a fresh postoperative patient with proximal GI surgery, noninvasive ventilation (Choice B) is somewhat controversial because some of the air can travel down the GI tract and apply pressure on the bowel anastomosis. Choice C is the best answer as patients often get relief immediately and reintubation of this patient might be avoided. If furosemide were ineffective at achieving improvement of symptoms, positive pressure ventilation and elucidation of cardiac function with an echocardiogram is warranted.