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, so it’s 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 or 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 sixth edition.

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

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Chapter 1

Introduction to the ICU
Introduction

In the United States, 55,000 adult critically ill patients are cared for each day, with approximately 200,000 patients dying in intensive care units (ICUs) each year. The cost of this care is significant, with recent estimates placing the annual cost of critical care well above $100 billion. A considerable amount of this expense is unnecessary, and related to a failure to utilize evidence-based best practices and

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, reducing inefficient work flow, medical errors, and the cost of care.
- A robust quality improvement program is necessary to continually improve patient satisfaction and outcomes

Patient Case:

A 73 year-old 120 kg male patient undergoes an emergency exploratory laparotomy for a perforated gastric ulcer. The patient has a history of chronic kidney disease, diabetes mellitus, hypertension, heart failure, and obesity. The surgery is technically difficult and lengthy (>3 hours), with estimated blood loss (EBL) of 1200 mL. Following surgery, the patient remains intubated and is transferred to the intensive care unit (ICU). Initial orders by the surgeon include IV fluids, basic ventilator settings, sedation, and antibiotics. The postoperative course in the ICU is complicated by refractory hypotension (SBP 82/60), low urine output, sinus tachycardia (HR 125/min), and persistent hypoxemia (PaO2 58 mm Hg). The surgeon places the patient on dopamine at 10 mcg/kg/min and raises the FiO2 to 70%. After the strong urging of the nursing staff, an intensivist consultation is requested.
to a lack of care coordination. Such management 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 resource utilization and performance, the achievement of optimal patient outcomes, and 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 impacts 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, 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 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 EEG. Support equipment includes: 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. ICUs should also have 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 typically 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) Most recently, in hospitals without on-site intensivists, the use of telemedicine (e-ICU) is gaining in popularity (see chapter 1.9). In the e-ICU model, real-time monitoring of critically ill patient data is connected via high-speed electronic systems to intensivists and staff located in a remote telemedicine hub. The e-ICU connects the bedside nurse with an intensivist-led team. In select healthcare organizations, the e-ICU has resulted in better outcomes and a reduced ICU length of stay (LOS). (5)

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. (6) 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)

**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 either 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). To date, the benefit of one coverage model over the other has not been conclusively demonstrated. (7-9) 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:

<table>
<thead>
<tr>
<th>Bundle</th>
<th>Interventions</th>
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</table>
| **Ventilator Bundle** | 1. Elevation of the head of the bed 30-45 degrees  
2. Daily "sedation vacations" and assessment of readiness to extubate  
3. Peptic ulcer disease (PUD) prophylaxis  
4. Deep venous thrombosis (DVT) prophylaxis  
5. Daily oral care with chlorhexidine |
| **Central Line Bundle** | 1. Hand hygiene  
2. Maximal barrier precautions  
3. Chlorhexidine skin antisepsis  
4. Optimal catheter site selection, with avoidance of using the femoral vein for central venous access in adult patients  
5. Daily review of line necessity, with prompt removal of unnecessary lines |
| **Severe Sepsis Resuscitation Bundle (initial resuscitation)** | 1. Administer 30 mL/kg crystalloid for hypoperfusion  
2. Target MAP of 65 mmHg in patients requiring vasopressors  
3. Additional fluids should be guided by clinical examination and available physiologic variables or dynamic measures of fluid responsiveness  
4. Guide resuscitation to normalize lactate |
| **Severe Sepsis Resuscitation Bundle (other management strategies)** | 1. IV antimicrobials should be initiated within 1 hour of sepsis and septic shock  
2. Any required source control intervention should be implemented as soon as possible  
3. Crystalloids are recommended for fluid resuscitation over albumin, hydroxyethyl starches or gelatins  
4. Norepinephrine is recommended as the first-choice vasopressor |
| **Indwelling Urinary Catheter Bundle (CAUTI Prevention Bundle)** | 1. Avoid unnecessary urinary catheters  
2. Insert urinary catheters using aseptic techniques  
3. Maintain urinary catheters based upon current evidence-based recommendations  
4. Review urinary catheter necessity daily and remove promptly |
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. (10)

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. (11)

The critical care 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 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 Quality (AHRQ), National Quality Forum (NQF), the Institute for Healthcare Improvement (IHI), and the Leapfrog Group have strongly supported efforts to study and evaluate EBBP, the reduction of medical errors, and the development of safety indicators. The Leapfrog Group is a quality-focused consortium of large corporations, companies, and health care purchasers that provide health benefits to more than 34 million Americans and obtain health care services from hospitals that demonstrate safety, affordability, and quality, including intensivist-directed ICUs.
### Table 1.1.2 ICU Professional Support Staff

<table>
<thead>
<tr>
<th>Staff Member</th>
<th>Duties</th>
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<tbody>
<tr>
<td>Respiratory Therapist</td>
<td>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</td>
</tr>
<tr>
<td>Physical Therapist</td>
<td>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</td>
</tr>
<tr>
<td>Occupational Therapist</td>
<td>Works 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.</td>
</tr>
<tr>
<td>Clinical Dietitian</td>
<td>Collaborates 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.</td>
</tr>
<tr>
<td>Speech Therapist</td>
<td>Works with a full range of communication disorders, including the evaluation and diagnosis of speech, language, cognitive-communication and swallowing disorders. Often works as part of a “team” within various clinical settings, including the ICU.</td>
</tr>
<tr>
<td>Social Worker</td>
<td>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.</td>
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Implementing a quality improvement (QI) and safety culture within the ICU is essential for reducing medical errors, controlling practice variation, and for improving outcomes. (12) The components of a successful QI program include: strong leadership and vision, selecting 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 physicians, NPs, 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 reduce the cost of
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. The automated gathering 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 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.

<table>
<thead>
<tr>
<th>Table 1.1.3 Common ICU Quality Indicators of Performance</th>
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<tbody>
<tr>
<td>ICU mortality rate</td>
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<tr>
<td>Length of ICU stay (days)</td>
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<tr>
<td>Duration of mechanical ventilation</td>
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<tr>
<td>Incidence of unplanned extubations</td>
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<tr>
<td>Incidence of ICU readmissions</td>
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<tr>
<td>Infection rates</td>
</tr>
<tr>
<td>Ventilator-associated pneumonias (VAP)</td>
</tr>
<tr>
<td>Central line-associated blood stream infections (CLABSI)</td>
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<tr>
<td>Catheter-associated urinary tract infections (CAUTI)</td>
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<tr>
<td>Rate of compliance with hand hygiene guideline</td>
</tr>
<tr>
<td>Rate of compliance with care bundles</td>
</tr>
<tr>
<td>Sepsis bundle</td>
</tr>
<tr>
<td>Central line bundle</td>
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<tr>
<td>Ventilator bundle</td>
</tr>
<tr>
<td>Urinary catheter bundle</td>
</tr>
<tr>
<td>Incidence of decubitus ulcers</td>
</tr>
<tr>
<td>Rate of appropriate peptic ulcer disease prophylaxis</td>
</tr>
<tr>
<td>Rate of appropriate DVT prophylaxis</td>
</tr>
<tr>
<td>Medical error rates</td>
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<tr>
<td>Incidence of adverse drug reactions</td>
</tr>
<tr>
<td>Incidence of suboptimal management of pain</td>
</tr>
<tr>
<td>Patient/family satisfaction scores</td>
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<tr>
<td>Nurse turnover rate</td>
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</tbody>
</table>
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. (see also Chapter 1.2)

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.

References:


**Review Questions:**

1. Which of the following statements regarding a closed ICU model is FALSE?
   a. The incidence of medical errors is reduced in comparison to an “open unit”
   b. Studies indicate better patient outcomes
   c. Patient care is shared between the admitting physician and the intensivist-led ICU team
   d. Studies show that cost of care is less compared with an open ICU model

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 of care bundles have not conclusively demonstrated improved patient outcomes
   d. A care bundle exists for the placement and care of an indwelling urinary catheter

3. All of the following statements regarding the institution of an ICU quality improvement program are true EXCEPT?
   a. Staff motivation is essential
   b. Requires steady leadership and vision
   c. Utilizes standardized quality improvement methods
   d. Has not been demonstrated to appreciably reduce the incidence of medical errors

4. Effective communication among ICU staff results in all of the following EXCEPT
   a. Increased use of medical consultations
   b. Improved efficiency of care
   c. Reduced cost of care
   d. Improved transitions of care
“Errors in judgement must occur in the practice of an art which consists largely in balancing probabilities.” – Sir William Osler

In 1999 and 2001, the Institute of Medicine (IOM) published two landmark reports highlighting the immense morbidity and mortality due to routine medical care in the United States. (1,2) “To err is human” was a call to action, sparking a national patient safety movement. (1) “Crossing the Quality Chasm” highlighted the gap between health care that patients should receive and health care that is actually delivered. The quality movement undoubtedly contributed to safer practices in hospitals; however, recent studies quote 200,000 to 400,000 deaths still caused by medical error every year, (3) a far cry from the oft cited 98,000 deaths per year in IOM’s 1999 report. (1,4) Given the recent advancements in health care technology and research, quality improvement efforts represent a major opportunity for progress in the ICU.

**General Principles in ICU Quality and Safety**

While quality and safety are often used interchangeably when discussing healthcare improvement, they are not the same. The National Patient Safety Foundation defines safety as “avoidance, prevention, and amelioration of adverse outcomes or injuries stemming from the processes of health care.” (5) The IOM states more plainly that patient safety is “freedom from accidental injury.” (1) Either
way, this critical component of health care quality is receiving increased attention from patients, providers, and regulators alike. The IOM describes quality as “the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge.” (1,5,8,9) High-quality care aims to be safe, effective, equitable, timely, patient-centered, and efficient. (2,5,8,10)

One important consideration in quality improvement is increasing reliability and efficiency during routine operating conditions. Patient safety emphasizes harm prevention by creating resilient systems that work in non-routine operating conditions. (11) The challenge with safety is the focus on preventing rare events, making evidence-based guidelines difficult to develop. Quality improvement, on the other hand, is often framed in terms of its success, which explains the abundance of information on quality initiatives relative to that of safety data. (5,11)

**Tools for Quality Analysis Adopted from Non-Healthcare Industries**

Root Cause Analysis (RCA), borrowed from NASA, is used to evaluate sentinel events and identify the fundamental reasons that allowed an error to occur. (8) This is a reactive approach, however, that focuses only on the most serious incidents, resulting in lost opportunities to review near-misses or absorbed events. Difficulties encountered with this technique are similar to those seen with traditional assessments, such as morbidity and mortality conferences and incident reports – findings are reported locally, often after a significant amount of time has passed, and do not necessarily result in concrete suggestions for risk reduction in care. (8,12)

“Lean” is a management philosophy based on the Toyota Production System. (13) Key principles include elimination of waste, problem solving at the source, worker involvement and empowerment, and the pursuit of perfection. (14) Six Sigma is another strategy (developed at Motorola), which defines quality in terms of defect rates. The main focus is reducing variability to an error rate of < 3.4 defects per million opportunities, or six standard deviations from the process mean. (15) While both tools aim to streamline operational processes, Lean is geared towards “doing the right things,” whereas Six Sigma concentrates on “doing things right (with no errors).” (15) Some evidence has demonstrated time-savings and cost reduction using these approaches, (13) though Six Sigma and Lean require system level changes to be effective. A few health care systems have successfully adopted these strategies, while other attempts have been unsuccessful, generating controversy over their usefulness.

High hazard industries, such as commercial air travel, nuclear power, and naval aviation, are another area from which safety concepts have been adopted. Many of these organizations are able to deliver consistently high performance in situations that have a low tolerance for error. (16) These high reliability
organizations (HRO) operate under five key principles to maintain and achieve nearly error-free operations (Table 1). First and foremost, HROs are preoccupied with failure – never content to revel in accident-free periods, they are constantly looking for possible weaknesses in the system. (16,17) Secondly, HRO leaders are reluctant to simplify. (5) Safety and quality issues are complex, and HROs take care to avoid minimizing or writing off any potential threats. (17) The third principle is sensitivity to operations: staying connected to the way in which work gets done. Workers on the ‘frontline’ are first to notice deviations in standard operating procedures, and they play an integral role in alerting the organization to possible safety and quality threats early on. (5,17) The fourth principle is a commitment to resilience. (5) Not unlike safer systems designed to mitigate human error, organizational resilience involves the ability to quickly recognize and contain errors and respond to unexpected events. (16,17) Finally, the fifth principle involves deference to expertise – cultivation of a culture where all members feel empowered to speak up when a credible risk has been identified. (8,17)

### Barriers and Next Steps

While the ICU is certainly a high-risk, high-hazard setting that can benefit from high reliability principles, adaptation to specific challenges in the ICU is necessary. Leape and Berwick posited that the culture of medicine is one of the biggest impediments to patient safety progress. (4) The emphasis on high standards of

<table>
<thead>
<tr>
<th>Principle</th>
<th>Example in ICU</th>
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<tbody>
<tr>
<td>Preoccupation with failure</td>
<td>• Utilize checklists and time-outs prior to procedures</td>
</tr>
<tr>
<td></td>
<td>• Establish standards for reporting complications and evaluating incidents for quality improvement</td>
</tr>
<tr>
<td></td>
<td>• Two provider verification for high risk medications (i.e., insulin, heparin)</td>
</tr>
<tr>
<td>Reluctance to simplify</td>
<td>• Consider alternatives to treatment and maintain broad differential diagnoses</td>
</tr>
<tr>
<td></td>
<td>• Be willing to challenge current beliefs of why problems exist</td>
</tr>
<tr>
<td>Sensitivity to operations</td>
<td>• Maintain clear and transparent communication with all parties</td>
</tr>
<tr>
<td></td>
<td>• Be aware of hospital wide issues including bed availability/staffing</td>
</tr>
<tr>
<td>Resilience</td>
<td>• Emphasize the importance of quality, team building, and leadership</td>
</tr>
<tr>
<td></td>
<td>• Organize debriefing sessions after challenging cases/events</td>
</tr>
<tr>
<td>Deferece to expertise</td>
<td>• Institute multidisciplinary rounds</td>
</tr>
<tr>
<td></td>
<td>• Value consultants and specialists</td>
</tr>
<tr>
<td></td>
<td>• Ask about prior experiences to guide improvements in patient care</td>
</tr>
</tbody>
</table>

individual performance and a commitment to research contributed to significant advances in modern medicine. However, these developments have increased health care complexity to levels much greater than those in other industries – the more complex the system, the more opportunities it has to fail. (4)

Strategies proposed for systemic change generally focus on decreasing complexity, (18) reducing unwanted variation, (19) and fostering a culture of safety. (1,12) W. Edwards Deming, an engineer and physicist who contributed to Japan’s post-WWII manufacturing rebirth, emphasized that reduction of unwanted variation will make random errors less likely, leading to decreased errors overall. (20) Clinical pathways are an ideal example, and minimizing variability by standardizing care (i.e. Surviving Sepsis Campaign) has improved efficiency, reduced costs, and decreased complications. (21,22)

Health information technology (HIT) has also facilitated safer systems by standardizing electronic order sets, computerizing decision-support algorithms for point of care treatment guidance, and providing alerts to notify practitioners of patient clinical status changes. Technological advances do not always result in enhanced quality, though additional HIT tactics include automation and information processing optimization where appropriate. (18) For instance, patients vary greatly in their response to opiates and may proceed to respiratory depression or apnea if not monitored appropriately. If there existed a method to prevent narcotics overdose – linking end-tidal respiration monitoring to patient controlled analgesia (PCA), for instance – this could prevent over sedation or other PCA-related adverse events. In fact, this technology is already present. Enacting a comparable policy would cost little, place minimal burden on nursing staff, and potentially save countless lives. Thus, the key to improved outcomes will involve better integration of the current technology. (23)

One missing component in HIT integration is communication between various health networks in the hospital, which would operate under rules connecting patient clinical health states, provider responses, and appropriate actions for those observed clinical circumstances. (23) Indeed, this can serve as a metaphor for quality improvement in medicine today. Incremental biomedical advancement pales in comparison to the conceivable harm reduction buoyed by a culture supporting multidisciplinary communication and quality improvement at every level. This impacts a health system’s resilience to medical errors, but requires dedicated support from leadership, trust from healthcare workers, and a shared sense of accountability in resolving issues. (24) Process improvement in medicine has come a long way since IOM’s 1999 report focused the public eye on medical errors. Progress is slow, but cultivating a highly collaborative working environment with safety and quality as the top priority will bring us closer to the ultimate goal of zero patient harm.
References:


Review Questions:

1. How can ICU patient safety be improved?
   a. Design systems that help prevent errors, or make errors visible so they can be intercepted
   b. Reduce complexity of care processes
   c. Decrease unwanted variation (i.e. different packaging for the same medications) to minimize opportunities for error
   d. All of the above

2. What is one example of a systemic process change to improve patient safety?
   a. Time-out prior to any invasive procedure
   b. Standardizing patient rooms such that the same equipment is found in the same spot
   c. Daily patient care and rounding checklists
   d. All of the above

3. What is the most common cause of errors in the ICU?
   a. Confluence of multiple factors
   b. Drug administration error
   c. Erroneous communication
   d. Failure of faulty equipment
Critical Care Analgesia

Pain is described as an “unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.” The prevalence of pain in the ICU is high and likely under treated in both medical and surgical ICUs, with 50-80% of patients reporting pain during their ICU admission. While pain is a subjective experience, there are significant physiological and psychological consequences of untreated pain. The physiologic response to pain may increase the amount of circulating catecholamines, which can lead to vasoconstriction-mediated end organ dysfunction, hyperglycemia, muscle catabolism, and reduced immune function. Psychological sequelae in

Patient Case:
A 64-year-old male with a past medical history significant for HTN and DM is admitted to the ICU after falling 10 feet from a ladder to the ground. He did not hit his head, but does have multiple rib fractures with a flail chest segment and requires intubation for respiratory failure. You place him on a propofol infusion for sedation and a fentanyl infusion for analgesia. On day 2 of admission, he is agitated and fighting the ventilator, which leads to hypertension, tachycardia and hypoxia. What is your best strategy for controlling his pain, treating his delirium, and weaning him from ventilator support?
patients who recalled painful experiences in the ICU include an increased incidence of PTSD, chronic pain, and a lower health-related quality of life. (1) Clinicians must prioritize the treatment of pain to optimize short- and long-term outcomes as well as to provide patient-centered, compassionate care.

The ability to assess a patient’s pain can be challenging in the ICU. It is important to note that monitoring a patient’s vital signs is not recommended for monitoring a patient’s level of pain, and at best, should be used only as an adjunct. The gold standard for pain assessment is a self-reported pain scale, such as a visual analog scale (VAS) or a numerical ranking scale (NMS). These scales consist of a horizontal line on which the patient can mark a current pain level, or a numeric rating scale from 0-10. However, many patients in the ICU are unable to reliably report their pain for a variety of reasons, such as sedation, weakness, or altered mental state. In these situations, utilizing a validated behavioral pain assessment scale such as the Behavioral Pain Score (BPS) or Critical Care Pain Observation Tool (CPOT) has been shown to improve clinical outcomes. The BPS (Table 1) monitors facial expression, flexion of limbs, and ventilator synchrony to rate pain on a scale from 3 (no pain) to 12 (maximum pain).

Opioids are the first line medications for the treatment of non-neuropathic pain in the ICU (2) and are often nurse administered, but may also be patient-administered with the use of a patient-controlled analgesia (PCA) device. In patients with intact

<table>
<thead>
<tr>
<th>Table 1.3.1 Behavioral Pain Scale</th>
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<tbody>
<tr>
<td><strong>Item</strong></td>
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<tr>
<td>----------------------------------</td>
</tr>
<tr>
<td><strong>Facial Expression</strong></td>
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<td></td>
</tr>
<tr>
<td><strong>Upper Limb Movements</strong></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Compliance with Mechanical Ventilation</strong></td>
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<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td><strong>Minimum Score (no pain)</strong></td>
</tr>
<tr>
<td><strong>Maximum score (maximum pain)</strong></td>
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</tbody>
</table>

mentation, the use of PCA for inpatient pain control may result in improved pain scores when compared to nurse administered analgesia. All opioids are equally effective when used at equipotent doses. The choice of which opioid to utilize will depend upon several factors including desired onset and duration of action, metabolism of the drug, and metabolites. Opioids do
have negative side effects that must be taken into consideration before administration and may be of particular importance in a critically-ill patient who already has altered and labile physiology. These include sedation, respiratory depression, hypotension, nausea/vomiting, and constipation. Table 2 shows commonly used opioids, recommended dosing, and common side effects that can occur.

Non-opioid adjuncts may be used in conjunction with opioids to reduce the total opioid requirement as well as offer improved pain control. Adjunct classes include acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs), which antagonize prostaglandin receptors. The use of perioperative acetaminophen has been shown to improve postoperative analgesia. A recent meta-analysis has shown that preoperative and intraoperative use of IV acetaminophen reduced post-operative nausea and vomiting and resulted in improved pain scores. (3) Postoperatively, the continued use of acetaminophen and meperidine was associated with improved postoperative analgesia, less PONV, and earlier times to extubation in the ICU setting. (4) Acetaminophen dosing must be modified in patients with liver insufficiency. In addition, NSAIDs such as ketorolac and ibuprofen may be effective adjuncts but must be used cautiously in patients with decreased renal clearance, concern for GI ulcers, or increased bleeding risk due to their nonselective COX inhibition

### Table 1.3.2 Opioids

<table>
<thead>
<tr>
<th>Agent</th>
<th>Equi-analgesic IV dose</th>
<th>Equi-analgesic PO dose</th>
<th>Onset (IV)</th>
<th>Half-life</th>
<th>Metabolism</th>
<th>Active Metabolites</th>
<th>Dosing (Intermittent)</th>
<th>Dosing (Infusion)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>0.1</td>
<td>N/A</td>
<td>1-2 min</td>
<td>2-4 hrs; context-sensitive: 200 min (6 hr infusion) 300 min (12 hr infusion)</td>
<td>N-dealkylation (CYP3A4/5 substrate)</td>
<td>None</td>
<td>0.35-0.5 mcg/kg IV q 0.5-1 hr</td>
<td>0.7-10 mcg/kg/hr</td>
<td>Less hypotension, accumulates in hepatic impairment, context-sensitive half life variable in end-organ dysfunction</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1.5</td>
<td>7.5</td>
<td>5-15 min</td>
<td>2-3 hr</td>
<td>Glucuronidation</td>
<td>None</td>
<td>0.2-0.6 mg IV q 1-2 hr</td>
<td>0.5-3 mg/hr</td>
<td>Accumulation in hepatic, renal impairment</td>
</tr>
<tr>
<td>Morphine</td>
<td>10</td>
<td>30</td>
<td>5-10 min</td>
<td>3-4 hr</td>
<td>Glucuronidation</td>
<td>6- and 3-glucuronide metabolite</td>
<td>2-4 mg IV q 1-2 hr</td>
<td>2-30 mg/hr</td>
<td>Histamine release may lead to hypotension, accumulation in hepatic, renal impairment</td>
</tr>
<tr>
<td>Methadone</td>
<td>N/A</td>
<td>N/A</td>
<td>1-3 days</td>
<td>15-60 hr</td>
<td>N-demethylation (CYP3A4/5, 2D6, 2B6, 1A2)</td>
<td>N-demethylated derivative</td>
<td>2.5-10 mg IV q 8-12 hr</td>
<td>Not recommended</td>
<td>May be used to slow the development of tolerance.</td>
</tr>
</tbody>
</table>
of prostaglandin and platelet synthesis.

Other non-opioid adjuncts include ketamine, as well as alpha-2 adrenergic agonists (clonidine and dexmedetomidine), tramadol, antidepressants, and topical lidocaine. In addition, epidural analgesia should be considered in the management of patients who have undergone thoraco-abdominal surgeries or who have traumatic rib fractures. The major disadvantage of epidural analgesia is hypotension due to a sympatholytic-mediated decrease in systemic vascular resistance.

The treatment of neuropathic pain conditions such as diabetic neuropathy, post-herpetic neuralgia, spinal cord injury, and post-stroke thalamic pain does not use opioids as a first line. Neuropathic pain commonly is described as burning, “pins and needles”, or “electrical” sensations. The use of anticonvulsants, such as gabapentin and carbamazepine, is indicated for neuropathic pain. (2) Both medications need to be monitored and doses adjusted for patients with renal disease.

Agitation and Sedation in the ICU

Sedation is the process of producing a state of calm and relieving anxiety. There are many indications for the use of sedation in the critically-ill patient, including general anxiolysis, ensuring the safety of life-sustaining lines and tubes, facilitation of bedside procedures, maintaining synchrony with the ventilator, and ensuring amnesia when neuromuscular blockade is required. The same agents may also be utilized as therapy for intracranial hypertension or for seizures/status epilepticus. Good communication with the patient and their family, ensuring that the patient is well nourished and hydrated, and providing physiotherapy to reduce pain and discomfort are all non-pharmacological interventions that can be utilized to achieve adequate sedation. Table 3 summarizes commonly available sedation agents in critically ill patients.

The routine use of sedation scales to monitor a patient’s level of sedation is important for achieving and maintaining effective sedation. (2) One of the most commonly used and reliable scales is the Richmond Agitation-Sedation Scale (RASS). The RASS has the advantage of enabling providers to conduct a series of evaluations over time and monitor response to titrated therapy. It describes a patient’s behavior on a continuum from unarousable (-5) through a midpoint of 0 (alert and calm, cooperative) to combative (+4). (2) Maintaining minimum safe (“light”) levels of sedation is clearly linked with improved patient outcomes, including decreases in ICU/hospital length of stay and duration of mechanical ventilation, (5,6) improved participation with physical therapy, and a reduced incidence of ICU-acquired weakness, without having any adverse mental health effects such as PTSD. (7) The implementation of pain, agitation, and delirium (PAD) protocols is intended to provide an integrated, evidence-based method of pharmacologically treating these common problems in the ICU. Studies have shown that implementation of PAD...
protocols has improved patient outcomes by decreasing the amount of time spent requiring mechanical ventilation, decreasing ICU length of stay, and improving mortality. (8)

Long acting benzodiazepines (lorazepam, diazepam), or infusions of shorter-acting agents (lorazepam, midazolam) are still used in the ICU, but they have fallen out of favor given the association with longer lengths of stay and onset of delirium. These drugs bind GABA receptors and increase the conductance of chloride ions across the cell membrane. The choice of which drug to use in this class must be made carefully as their onset times, duration of action, and active metabolites can differ significantly. While benzodiazepines have many indications such as the treatment of seizures, prophylaxis and treatment of alcohol/drug withdrawal, and production of amnesia, the use of high doses for long durations may have negative patient outcomes. It has been clearly described that continuous infusions of benzodiazepines without appropriate titration results in longer length of stay in the ICU and a longer duration of mechanical ventilation. (6,7) All benzodiazepines are metabolized in the liver, so special dosing considerations should be made for patients with liver dysfunction.

Propofol is a potentiator of the GABA receptor and is commonly used in the ICU as an infusion for sedation. Because of its side

<table>
<thead>
<tr>
<th>Table 1.3.3 Sedation Agents</th>
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<tbody>
<tr>
<td>Agent</td>
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<tr>
<td>----------------</td>
</tr>
<tr>
<td>Midazolam</td>
</tr>
<tr>
<td>Lorazepam</td>
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<td></td>
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<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Propofol</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
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</table>
effect of respiratory depression, this agent should only be used in mechanically-ventilated patients, or in conjunction with vigilant respiratory monitoring by practitioners capable of providing respiratory support. It is important to remember that propofol has sedative effects but does not have any analgesic effects, and so treatment of pain needs to be accomplished with additional medications. One important hazard of propofol is the development of Propofol-Related Infusion Syndrome (PRIS). PRIS is most commonly seen with high dose infusions of greater than 4-6 mg/kg/hr for longer than 24-48 hours, and manifests as metabolic acidosis usually from elevated blood lactate levels, rhabdomyolysis, acute renal failure, bradycardia, and when severe, sudden cardiac collapse. Propofol usage is also associated with increased triglyceride levels due to the lipid emulsion carrier, so daily triglyceride measurements are often recommended. The clinical significance of elevated triglyceride levels, however, is controversial.

Dexmedetomidine is an alpha-2-receptor agonist that has properties of sedation, amnesia, and analgesia without significant respiratory or neurologic depression. EEG changes under dexmedetomidine sedation are similar to those seen during natural sleep. (9) When compared to midazolam for sedation in the ICU, patients receiving dexmedetomidine had fewer days on the ventilator, less hypertension and tachycardia, and less delirium. (10) This favorable side effect profile has made dexmedetomidine the preferred agent for sedation in many ICUs. Adverse effects of dexmedetomidine include dose dependent decreases in heart rate and blood pressure due to sympatholytic actions of the medication, which may be of particular concern in patients with cardiac conduction defects and heart failure who may be more susceptible to these side effects.

References:


Review Questions:

1. The behavioral pain score (BPS) takes into account which of the following variables:

   a. Delirium, lower body movements, and reported pain score
   b. Facial expression, upper limb movements, and synchrony with the ventilator
   c. Blood pressure, heart rate, and respiratory rate
   d. Pain that the patient feels across a continuum

2. Propofol-related infusion syndrome is characterized by all of the following EXCEPT:

   a. Non-anion gap metabolic acidosis
   b. Renal failure
   c. Bradycardia
   d. Rhabdomyolysis

3. Dexmedetomidine is associated with all of the following EXCEPT:

   a. EEG that is similar to normal sleep cycle
   b. Maintained respiratory drive
   c. Tachycardia
   d. Decrease in ventilator dependent days
Before we begin to discuss neuromuscular blocking agents (NMBs) use in the ICU, a basic understanding of how this class of drug works is needed. NMBs (also called paralytics) act primarily on nicotinic acetylcholine (ACh) receptors located on the postsynaptic motor end plate of the neuromuscular junction to cause

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**Key Points:**

- There are 2 main classes of NMBs, depolarizing and nondepolarizing.
- Succinylcholine should be used with caution in patients with ESRD, and is contraindicated in patients that have had burns or crush injuries over 24 hours, neuromuscular disease, or significant immobility for over 3-5 days, secondary to risk of hyperkalemia.
- Continuous NMB has only been shown to improve mortality in early ARDS.
- Monitoring of not only the neuromuscular blockade itself with TOF testing, but for awareness is recommended.

**Patient Case:**

A 45 year old obese man with ESRD and history of a difficult airway presents to the surgical ICU after Graham patch for a perforated gastric ulcer. He was extubated in the operating room, although he was noted to have a Grade IV view with video laryngoscope. Initially, the patient does well, but over the next 48 hours, he begins to have increasing oxygen demands and bilateral infiltrates are noted on chest X-ray. The decision is made to re-intubate the patient and an awake fiberoptic intubation is attempted. The patient does not tolerate the attempts at intubation and begins to desaturate. Succinylcholine is then used for intubation, and the patient is successfully intubated. Peaked T-waves are noted on EKG after intubation. Calcium chloride is immediately given, and the patient is started on hemodialysis. The patient is asynchronous on the ventilator and the decision is made to start the patient on a continuous cisatracurium infusion. Two days later, the patient’s clinical exam is greatly improved and he is able to be extubated without event and is eventually transferred to the floor.
skeletal muscle paralysis. Since NMBs do not act on muscarinic receptors, they do not have any effect on cardiac or smooth muscle. NMBs do not have any sedating properties.

Since NMBs act on the neuromuscular junction, it is important to understand the physiology of the neuromuscular junction. The neuromuscular junction contains a prejunctional motor nerve ending and the postsynaptic membrane on the skeletal muscle fiber. An action potential causes the release of ACh from synaptic vesicles in the prejunctional nerve ending that then diffuses across the synaptic cleft to nicotinic cholinergic receptors. When two ACh molecules bind to the nicotinic receptor within the motor end plate, a depolarization occurs leading to a release of calcium from the sarcoplasmic reticulum of the skeletal muscle cell causing muscle contraction. ACh is then rapidly hydrolyzed by acetylcholinesterase at the motor end plate. Alternatively, ACh may diffuse away from the cleft. Both mechanisms terminate depolarization, which ultimately results in muscle relaxation.

NMBs can be broken into two main categories: depolarizing and nondepolarizing agents. The only clinically available depolarizing agent is succinylcholine (SCh). Nondepolarizing agents are further subdivided by their structural composition into two groups, benzylisoquinoliniums, which includes agents such as cisatracurium, and the aminosteroids, which includes agents such as vecuronium and rocuronium.

Because succinylcholine is the only depolarizing neuromuscular blocker, there are some special considerations that must be taken into account with its use. SCh has a chemical structure similar to ACh, therefore, it acts as a nicotinic agonist at the postsynaptic membrane of the neuromuscular junction. SCh’s tight binding to the receptor initially causes muscle contraction with the release of calcium, then because it is still bound to the receptor, calcium is not shuttled back to the sarcoplasmic reticulum which leads to continued muscle relaxation. SCh is then hydrolyzed by plasma cholinesterase, which is outside the neuromuscular junction. Subsequently, SCh’s duration of effect is dependent on its diffusion away from the neuromuscular junction. The act of muscle contraction and depolarization causes an increase in serum potassium. In normal healthy patients, without renal failure, the serum potassium rises about 0.5 mEq/L with SCh use. (1) Potassium rise can be exaggerated in patients with extrajunctional ACh receptors present in certain conditions. Burns, crush injuries over 24 hours, neuromuscular diseases such as Duchenne muscular dystrophy or Guillain-Barre, and strokes can cause a higher release of potassium than in patients without these disease states. The hyperkalemia can cause cardiac arrhythmias, even cardiac arrest. SCh also causes an increase in intraocular pressure and intracranial pressure. Its use should be balanced with the concern for aspiration when used for rapid sequence intubation in patients with open globe injuries and severe intracranial pathology with mass effect. (2,3)
Nondepolarizing NMBs are competitive antagonists of the nicotinic cholinergic receptors. There are multiple nondepolarizing NMBs and their onset, duration of action, and elimination are presented in Table 1. Older benzylisoquinolininiums were known to cause histamine release resulting in hypotension and bronchoconstriction. This effect is minimal with atracurium use and negligible with cisatracurium use. Cisatracurium and atracurium undergo Hofmann elimination, an organ independent process leading to metabolism of the drug. Hofmann elimination is prolonged by hypothermia and acidosis, resulting in prolongation of the effect of benzylisoquinolininium compounds.

The aminosteroids include agents such as vecuronium, rocuronium, and pancuronium. Rocuronium has been shown to cause anaphylaxis in some patients. Pancuronium can cause a vagolytic effect, resulting in increased heart rate, cardiac output, and blood pressure, while vecuronium and rocuronium have minimal cardiovascular effects.

When the decision is made to use a NMB in the ICU, monitoring is required, not only of the neuromuscular blockade, but also of the depth of sedation. Peripheral nerve stimulation is the preferred method to monitor the depth of neuromuscular blockade. Nerve stimulation can be performed on the ulnar nerve, facial nerve, or peroneal nerve, but generally the ulnar nerve is preferred by observing the amount of contraction of the adductor pollicis muscle. Train of Four (TOF) and double-burst stimulation (DBS) are common methods for assessing depth of neuromuscular blockade. TOF is performed by applying current to the muscle as four stimuli over a 2 second period. The qualitative measurement is usually reported as the number of palpated muscle twitches out of four. Newer methods, such as quantitative acceleromyography, give TOF as a ratio, and have been shown to decrease residual neuromuscular blockade in the operating room. (4)

Nondepolarizing agents produce a fade with TOF testing, while

<table>
<thead>
<tr>
<th>Table 1.4.1 Onset, Duration of Action and Elimination of NMBA</th>
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<tbody>
<tr>
<td>ED95 (mg/kg)</td>
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<tr>
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</tr>
<tr>
<td><strong>Depolarizing Neuromuscular Blockers</strong></td>
</tr>
<tr>
<td>Succinylcholine</td>
</tr>
<tr>
<td><strong>Aminosteroidal Agents</strong></td>
</tr>
<tr>
<td>Rocuronium</td>
</tr>
<tr>
<td>Vecuronium</td>
</tr>
<tr>
<td><strong>Benzylisoquinolinium</strong></td>
</tr>
<tr>
<td>Cisatracurium</td>
</tr>
</tbody>
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**ED95**: Dose required to produce 85% reduction in twitch height
succinylcholine use results in a consistent decreased amplitude, unless a phase II blockade has occurred. For the nondepolarizing agents, the number of twitches determines the amount of neuromuscular blockade, with 1, 2, 3, and 4 twitches representing 90-95%, 80-90%, 70-80%, and 65-75% blockade remaining, respectively. If no twitches are present, it is difficult to determine the degree of blockade. Maintaining 1-2 twitches should provide a clinically effective neuromuscular blockade when using a continuous infusion of a NMB in the ICU.

NMBs have no amnestic properties, therefore monitoring sedation levels should be considered when using these agents as a continuous infusion. There are several methods to monitor depth of sedation including continuous EEG and processed EEG. Processed EEG monitoring provides a numerical score that purportedly represents depth of awareness. It has been shown that this value is not accurate when neuromuscular blockade is present. (5) Careful monitoring of sedation in patients with neuromuscular blockade is, therefore, recommended to help minimize awareness.

Neuromuscular blockade is either delivered as a one-time dose, usually for intubation, or as a continuous infusion for a specific indication. With one-time dosing, succinylcholine may be preferred due to its short duration of action. SCh has also been shown to provide superior intubating conditions when compared to rocuronium. (6) It is also useful for rapid sequence intubations, but if SCh is contraindicated, rocuronium is an appropriate replacement with adequate relaxation within 2 minutes.

There are few indications for continuous neuromuscular blockade in the intensive care unit, and fewer still where it has been definitively proven to decrease morbidity and mortality. The Society of Critical Care Medicine recently updated their clinical practice guidelines for sustained neuromuscular blockade in 2016. The updated guidelines reviewed all relevant current evidence, then graded it, and made one strong recommendation, ten weak recommendations, found not enough evidence on nine subjects, and made six good practice statements based on expert consensus (Table 2). (7) One recommendation, administering NMB to patients with ARDS with an PaO2/FiO2 less than 150, is based on a study of a 48-hour infusion of cisatracurium that showed a reduced risk of mortality at 28 days, but did not affect the duration of mechanical ventilation or risk of ICU-acquired weakness. (8)

Nondepolarizing NMBs are also affected by different commonly used drugs in the ICU that can either potentiate or antagonize their effect (Table 3). Hypothermia, hypophosphatemia, hypokalemia and hypermagnesemia can increase the duration of neuromuscular blockade. Hypercalcemia, however, decreases the amount of time needed to recover from neuromuscular blockade.

Certain nondepolarizing NMBs also have active metabolites that should be taken into consideration with their use. Vecuronium has
a potent metabolite, 3-deacetylvecuronium, which has slower plasma clearance. Therefore, vecuronium should not be used in patients with hepatic and renal dysfunction. Atracurium also has an active metabolite, laudanosine, whose elimination is dependent on renal and hepatic function. Laudanosine can theoretically have CNS (seizures) and cardiovascular (hypotension) side effects, limiting its use in continuous blockade. Cisatracurium, a more potent isomer of atracurium, is thought to produce clinically insignificant amounts of laudanosine, making

<table>
<thead>
<tr>
<th>Table 1.4.2 SCCM Recommendations for Sustained Neuromuscular Blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strong Recommendation:</strong></td>
</tr>
<tr>
<td>1. Scheduled eye care with lubricating drops and eyelid closure</td>
</tr>
<tr>
<td><strong>Weak Recommendations:</strong></td>
</tr>
<tr>
<td>1. Use of NMB infusion early in course of ARDS in patients with P/F ratio &lt; 150</td>
</tr>
<tr>
<td>3. NMBA can be used to manage shivering in therapeutic hypothermia</td>
</tr>
<tr>
<td>5. Use structured physical therapy regimen for patients on NMBA</td>
</tr>
<tr>
<td><strong>Good Practice Statements (evidence lacking, but expert consensus):</strong></td>
</tr>
<tr>
<td>1. Use a protocol to guide NMBA use in therapeutic hypothermia</td>
</tr>
<tr>
<td>3. Reduce dose of NMBA in patients with myasthenia gravis</td>
</tr>
</tbody>
</table>

### Table 1.4.3 Drugs that Antagonize and Potentiate Neuromuscular Blocking Drugs

<table>
<thead>
<tr>
<th>Drugs that antagonize the actions of nondepolarizing NMBs (Decrease duration)</th>
<th>Drugs that potentiate the action of nondepolarizing NMBs (Increase duration)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phenytoin</strong></td>
<td><strong>Local anesthetics</strong></td>
</tr>
<tr>
<td><strong>Carbamazepine</strong></td>
<td><strong>Antimicrobials</strong> (aminoglycosides, polymyxin G, clindamycin, tetracycline)</td>
</tr>
<tr>
<td><strong>Valproate</strong></td>
<td><strong>Antiarrhythmics</strong> (procainamide, quinidine)</td>
</tr>
<tr>
<td><strong>Ranitidine</strong></td>
<td><strong>Magnesium</strong></td>
</tr>
<tr>
<td><strong>Steroids</strong></td>
<td><strong>Calcium channel blockers</strong></td>
</tr>
<tr>
<td><strong>Azathioprine</strong></td>
<td><strong>B adrenergic blockers</strong></td>
</tr>
<tr>
<td><strong>Ranitidine</strong></td>
<td><strong>Immunosuppressive agents</strong> (cyclophosphamide, cyclosporine)</td>
</tr>
<tr>
<td><strong>Dantrolene</strong></td>
<td><strong>Diuretics</strong></td>
</tr>
<tr>
<td><strong>Inhaled anesthetics</strong></td>
<td><strong>Lithium carbonate</strong></td>
</tr>
<tr>
<td><strong>Tamoxifen</strong></td>
<td></td>
</tr>
</tbody>
</table>
cisatracurium a good choice for prolonged neuromuscular blockade.

There are risks associated with continuous neuromuscular blockade. Awareness is the largest risk and should be closely monitored when these agents are used. Other risks include skin breakdown, corneal abrasions, generalized deconditioning and muscle atrophy, and ICU-acquired weakness. Critical illness neuromyopathy’s (CINM) main clinical sign is ICU-acquired weakness. This condition can cause structural or functional changes in the skeletal muscle, prolonging ventilator times, making ventilator weaning more difficult and increasing ICU length of stay. There are five main risk factors of which neuromuscular blockade is one. The other four are multiple organ failure, muscle immobilization, hyperglycemia, and use of corticosteroids. Diagnosis is made by electrophysiological testing, which shows a decrease muscle action potential with spontaneous electrical activity. Treatment includes early mobilization paired with aggressive sedation weaning protocol and daily physical therapy.

Pharmacologic reversal of neuromuscular blocking agents is often desired. Traditionally, cholinesterase inhibitors such as neostigmine are administered once it has been confirmed that the block has partially resolved, allowing acetylcholine to build up at the neuromuscular junction and ‘outcompete’ residual NMB. Given the non-specific action of these agents and the propensity to cause bradycardia via muscarinic receptors, an anticholinergic agent such as glycopyrrolate is often administered concurrently. Recently, sugammadex, a novel agent, which binds rocuronium rapidly and with great affinity was approved for reversal of neuromuscular blockade. The rocuronium-sugammadex complex is excreted renally so its use is contraindicated in patients with renal failure.

This chapter is a revision of the original chapter authored by Monirath Saly MD and Matthias Merkel MD PhD

References:


Weakness and Improves Quality of Recovery in the Early Postoperative Period. Anesthesiology 2011; 115(5):946-954


Review Questions:

1. Which of the following is a benzylisoquinolinium compound?
   a. Rocuronium
   b. Vecuronium
   c. Atracurium
   d. Pancuronium

2. What condition has neuromuscular blockade shown to improve mortality?
   a. Pulmonary edema
   b. Early ARDS
   c. Muscle spasms
   d. Difficult ventilation management

3. Which medicine can decrease the duration of action of neuromuscular blockade?
   a. Propofol
   b. Magnesium sulfate
   c. Calcium chloride
   d. Furosemide
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

Patient Case:
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.
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. A mechanism should be in place to track critical events as well as any other pertinent 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 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. The incidence of adverse events clearly depends on how adverse events are defined and not all events will require an intervention. However, some studies have reported an incidence of adverse events as high as 70% associated with patient transport. Several studies have reported complications related to gas exchange with manually assisted ventilation. Brain injured patients are particularly sensitive to alterations in oxygenation and ventilation that can result. Transport ventilators are increasingly employed to mitigate this risk. Recent data suggests that patients with elevated intracranial pressure may be at especially increased risk for events during transport and many of these will meet criteria for treatment. Adverse events reported across all transport domains are reviewed in Table 2. A wide range of factors have been implicated in contributing to adverse events.

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There may be many factors that are solely related to patient condition. However systems factors are often identified including 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

**Table 1.5.1 Sample Transport Checklist**

<table>
<thead>
<tr>
<th>Decision to Transport</th>
</tr>
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<tbody>
<tr>
<td>- Does the expected benefit of transport outweigh the risk?</td>
</tr>
<tr>
<td>- Staff/equipment/vehicles available?</td>
</tr>
<tr>
<td>- Receiving location prepared?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Team</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Adequately trained and experienced</td>
</tr>
<tr>
<td>- Detailed handoff to transport team</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Equipment</th>
</tr>
</thead>
<tbody>
<tr>
<td>- All equipment operational</td>
</tr>
<tr>
<td>- Portable power supply/ batteries charged</td>
</tr>
<tr>
<td>- Alarm limits checked and set</td>
</tr>
<tr>
<td>- Lines and tubes simplified, secured and labeled</td>
</tr>
<tr>
<td>- Oxygen supply with back-up</td>
</tr>
<tr>
<td>- Transport pack with emergency drugs and supplies</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Stabilized on transport stretcher</td>
</tr>
<tr>
<td>- Monitors in placed and operational/ equipment secured</td>
</tr>
<tr>
<td>- Ventilation adequate/ assessment of gas exchange if using transport ventilator</td>
</tr>
<tr>
<td>- Appropriate sedation/ neuromuscular blockade (if indicated)</td>
</tr>
<tr>
<td>- Measures to prevent heat loss</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Communication</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Transfer documents prepared</td>
</tr>
<tr>
<td>- Full physician and nursing report to receiving location</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Documentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Vital signs/ notation of events during transport</td>
</tr>
<tr>
<td>- Adverse events/ process improvement</td>
</tr>
</tbody>
</table>

**Table 1.5.2 Adverse Events Associated with Transport**

<table>
<thead>
<tr>
<th>Cardiovascular Events</th>
<th>Respiratory Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Hypotension</td>
<td>- Hypoxia</td>
</tr>
<tr>
<td>- Hypertension</td>
<td>- Hypercarbia</td>
</tr>
<tr>
<td>- Dysrhythmia</td>
<td>- Bronchospasm</td>
</tr>
<tr>
<td>- Loss of vascular access</td>
<td>- Pneumothorax</td>
</tr>
<tr>
<td>- Hemorrhage</td>
<td>- Respiratory arrest</td>
</tr>
<tr>
<td>- Cardiac arrest</td>
<td>- Inadvertent extubation</td>
</tr>
<tr>
<td>- Death</td>
<td>- Increased risk of VAP</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neurological Events</th>
<th>Staff and Administrative Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Agitation</td>
<td>- Inadequate staff</td>
</tr>
<tr>
<td>- Altered mental status</td>
<td>- Communication and liaison problems</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Equipment and Medical Supply Related Events</th>
<th>Miscellaneous Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Equipment failure</td>
<td>- Hypothermia</td>
</tr>
<tr>
<td>- Improper use of equipment</td>
<td></td>
</tr>
<tr>
<td>- Battery failure</td>
<td></td>
</tr>
<tr>
<td>- Inadequate medical supplies</td>
<td></td>
</tr>
<tr>
<td>- Oxygen failure</td>
<td></td>
</tr>
<tr>
<td>- Critical medications/supplies/ equipment unavailable</td>
<td></td>
</tr>
</tbody>
</table>
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. Many of these transfers occur from ICU to ICU. Others may take place from the emergency department of a transferring facility to an ICU in the receiving hospital. Federal regulations 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 factors 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

### Table 1.5.3 Considerations for Interhospital Transport

<table>
<thead>
<tr>
<th>Administrative</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Informed consent is obtained from the patient or a legally authorized representative.</td>
</tr>
<tr>
<td>- If consent cannot be obtained, the reason should be documented along with the indication for transport.</td>
</tr>
<tr>
<td>- A written order for transfer is recommended.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Coordination and Communication</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Referring physician communicates with accepting physician to confirm acceptance of the patient, availability of required resources and to give detailed report of patient condition.</td>
</tr>
<tr>
<td>- Designate a physician to assume responsibility for treatment during transport if no physician is on the transport</td>
</tr>
<tr>
<td>- Determine the mode of transport.</td>
</tr>
<tr>
<td>- Nursing report is performed by a nurse at the referring facility or a member of the transport team.</td>
</tr>
<tr>
<td>- Send/ deliver a copy of the medical record along with pertinent studies to the receiving facility.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Team Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Team composition is variable and often based on patient acuity.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>- 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.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Equipment</th>
</tr>
</thead>
<tbody>
<tr>
<td>- 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.</td>
</tr>
<tr>
<td>- All equipment and supplies are checked before transport including available IV fluids, drips and blood products.</td>
</tr>
</tbody>
</table>
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.

**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.

**References:**


2. Blakeman TC, Branson RD: Inter- and Intra-hospital Transport of the Critically Ill. Respir Care 2013; 58: 1008-23


7. AH: Association between helicopter vs ground emergency medical services and survival for adults with major trauma. JAMA 2012; 307: 1602-10


**Review Questions:**

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 AKI and hyperkalemia from a hospital without a hemodialysis service to a hospital with availability of RRT

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

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

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 to 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
Section 6

Cardiopulmonary Resuscitation  
Eric Ursprung MD, Andrea Tsai MD

Key Points:

- The 5 criteria defining high quality chest compressions are: adequate rate (100 - 120/min), adequate depth (2-2.4 inches), allowing for full chest recoil between compressions, minimizing interruptions and avoiding excessive ventilation.

- Vasopressin has been removed from the ACLS algorithm in favor of epinephrine.

- For lay rescuers, CPR should be conducted with a chest compressions-only approach; for trained rescuers, it is reasonable to conduct CPR incorporating chest compressions, airway and breathing.

- If a patient remains comatose after ROSC, targeted temperature management (32°C to 36°C for at least 24 hours) should be considered.

Patient Case:
An 80 year old patient with past medical history including CAD status post CABG, HTN and DM presents from a nursing home for scheduled endoscopy for epigastric discomfort. During sedation for endoscopy, the patient becomes apneic and his cardiac rhythm becomes sinus bradycardia and then PEA. CPR is initiated and the patient is emergently intubated. During CPR, the patient receives 3 doses of epinephrine. VF develops. He is successfully defibrillated with one shock at 200J. ROSC is achieved after 17 minutes. Post-ROSC ECG demonstrates ST elevations in V1-V4 with reciprocal depressions in I and III. The patient is brought emergently to cardiac catheterization, but no intervention is done due to lack of a defined culprit lesion. In the ICU following return from catheterization, the patient remains obtunded with flexion to pain, no verbal response and no eye opening. The patient is cooled to 36°C for 24 hours. Upon rewarming, the patient opens eyes spontaneously, follows commands in all four extremities, and is able to be extubated.

INTRODUCTION

This chapter will only cover adult cardiopulmonary resuscitation (CPR) and assumes knowledge of basic life support (BLS) and advanced cardiovascular life support (ACLS) algorithms. As of this writing, BLS and ACLS algorithms were most
CHEST COMPRESSIONS AND DEFIBRILLATION

In 2010, CPR guidelines for untrained lay rescuers were changed from ABC (Airway, Breathing, Compressions) to CAB, reflecting the importance of high quality chest compressions to the outcome of CPR. (1,2) The importance of prompt initiation of chest compressions, as well as high quality chest compressions, was again emphasized in the 2015 update. The five criteria defining high quality chest compressions are: adequate rate (100 - 120/min), adequate depth (2 - 2.4 inches), allowing for full chest recoil between compressions, minimizing interruptions in chest compressions and avoiding excessive ventilation. (1) While it is known that inadequate chest compression rate and depth may reduce survival, multivariate analysis of observational data suggest that excessive rates or depth of compression may also be associated with decreased return of spontaneous circulation (ROSC) and increased morbidity, respectively. (1,2) Upper limits on the rate of compression (120/min) and depth of compression (2.4 inches) are new 2015 recommendations.

The importance of minimizing interruptions to chest compressions is another emphasis of the 2015 recommendations. Observational studies have shown that shorter pauses in chest compressions maximize coronary perfusion and blood flow and can be associated with greater shock success, ROSC, and higher survival to hospital discharge. (1,2) The recommended goal chest compression fraction (the percentage of time spent doing chest compressions during cardiac arrest) should be as high as possible and no less than 60%, though guidelines acknowledge that the optimal chest compression fraction remains unknown. (1,2) Furthermore, in patients with witnessed outside of hospital cardiac arrest (OHCA) with a shockable rhythm, guidelines state that it may be reasonable for responding healthcare personnel to adopt a strategy of shocks and up to 3 cycles of 200 continuous compressions while relying on passive oxygenation and delaying positive pressure ventilation. (1) Data comparing immediate defibrillation to delayed defibrillation (after up to 180 seconds of CPR) show no advantage to a period of CPR prior to attempted defibrillation so it is reasonable to proceed with defibrillation, if indicated, as soon as is feasible. (2) Based on three randomized clinical trials (collectively, n = 7,060) showing non-superiority of mechanical chest compression devices compared to conventional (manual) CPR, conventional CPR remains the standard of care. (1,3) However, special circumstances may warrant the consideration of mechanical CPR (e.g., CPR that is prolonged, in a moving ambulance, or during a procedure such as cardiac catheterization). (1)

AIRWAY AND BREATHING
The 2010 revision of CPR guidelines from ABC to CAB shifts the emphasis to circulation first. Dispatchers instructing lay callers for adults with suspected OHCA will provide chest compression-only CPR instructions. (1) Prior to advanced airway insertion, cycles should consist of 30 chest compressions and 2 breaths; following advanced airway insertion, 1 breath every 6 seconds (10 breaths per minute) with continuous chest compressions is reasonable. (1,4) The highest possible FiO\textsubscript{2} should be used for ventilation during CPR, though guidelines acknowledge that data in adult humans does not yet exist to support this recommendation. (1,4)

Regarding devices and monitors in ventilation management, a high quality, randomized, controlled, double blind trial (n = 4,345) showed no benefit in the use of an impedance threshold device in CPR (an airway valve that reduces intrathoracic pressure, theoretically improving venous return). (1,3,5) Continuous waveform capnography should be used to confirm endotracheal tube placement, with ultrasound use as an additional possibility. (1,4) Furthermore, observational studies suggest that low end-tidal carbon dioxide (e.g., 10 mmHg or less) after 20 minutes of CPR in a patient with an endotracheal tube is strongly associated with resuscitation failure. (1,4,6)

**MEDICATIONS**

Epinephrine at the usual dose (1 mg every 3-5 minutes) remains the standard for CPR; higher rates of ROSC and hospital admission were seen with epinephrine use in OHCA in a randomized double-blind placebo-controlled trial. (1,4,7) For nonshockable rhythms, observational studies suggest that it may be reasonable to prioritize epinephrine administration (within 1 to 3 minutes for in-hospital cardiac arrests [IHCA] and within 10 minutes for OHCA) to increase likelihood of ROSC, whereas there is insufficient data to make a similar recommendation for shockable rhythms as defibrillation should be the priority. (1,4) Notably in several trials, vasopressin was found to be equivalent to epinephrine, but was removed from the ACLS algorithm for simplification. (1,4) In patients with VF/VT arrests that are unresponsive to CPR, defibrillation and vasopressors, amiodarone may be considered. (1,4) A blinded randomized controlled trial showed amiodarone to be better for survival to hospital admission for this subset of OHCA compared to lidocaine or placebo, though guidelines still suggest lidocaine as an alternative to amiodarone. (1,4) The use of steroids in cardiac arrest is controversial and studies of steroid use in OHCA and IHCA have yielded conflicting results; as such, no recommendation is made regarding the routine use of steroids. (1,4) For patients with known or suspected opiate ingestion presenting with respiratory arrest and a clear pulse, naloxone should be administered intramuscularly or intranasally. (1,2)

**POST-RESUSCITATIVE CARE**

Following ROSC, numerous observational studies support that emergent (as opposed to later in the hospital course) cardiac
catheterization should be performed in all patients in whom a cardiac etiology of arrest is suspected, regardless of return of mental status. (1,8) High quality randomized controlled studies show that patients who remain comatose (e.g., lack of meaningful response to verbal commands or Glasgow Coma Scale < 8) after ROSC should have targeted temperature management between 32°C and 36°C for at least 24 hours, with active prevention of fever after cooling. (1,8,9) The earliest possible time to prognosticate a poor neurologic recovery is 72 hours after ROSC if therapeutic hypothermia is not employed or 72 hours after return to normothermia if targeted temperature management was employed. (1,8) Neurologic prognosis is best done using an array of testing, including clinical exam, imaging and neurophysiologic testing (electroencephalography, somatosensory evoked potentials, etc.). (1,8)

CONCLUSION

In 2015, the American Heart Association updated guidelines for CPR. Updated guidelines further define and emphasize the importance of high quality chest compressions. The ACLS algorithm was further simplified, with epinephrine as the sole vasopressor and amiodarone as the primary antiarrhythmic. Patients that continue to be comatose after ROSC should undergo targeted temperature management with a goal temperature between 32°C and 36°C at the discretion of the provider, for at least 24 hours.

References:


**Review Questions:**

1. When performing high quality chest compressions during adult CPR, the appropriate rate of compression should be no less than 100 and no more than

   a. 110
   
   b. 120
   
   c. 140
   
   d. 150

2. A hospitalized patient sustains a VT arrest. CPR is immediately initiated and the code cart arrives. At what point is it most appropriate to defibrillate?

   a. As soon as feasibly possible
   
   b. After a full round (2 minutes) of chest compressions
   
   c. During the next pulse check
   
   d. After epinephrine has been administered

3. An intubated patient continues to be in PEA arrest. Chest compressions are ongoing and epinephrine 1 mg IV was administered 3 minutes ago. What is the most appropriate next drug to give?

   a. Amiodarone 300 mg
   
   b. Vasopressin 40 units
   
   c. Lidocaine 1.5 mg/kg
   
   d. Epinephrine 1 mg
Key Points:

- The four principles of medical ethics are autonomy, beneficence, non-maleficence, and justice.
- A major challenge in the end-of-life care of potential organ donors is the potential conflict between the primary obligation to uphold the patient’s best interests versus the need to preserve organs for transplantation.
- Informed consent is an absolute requirement for organ procurement and donation.
- The Uniform Anatomical Gift Act of 2006 (UAGA) attempts to clarify and establish a standard approach to the care for potential organ donors.

Patient Case:
A 55-year-old man collapsed at home and was brought to the emergency department. Upon his arrival, he was found to be unresponsive with a GCS of 6. He was intubated, stabilized, and underwent a CT scan which showed a massive intracerebral hemorrhage. After emergent decompression craniectomy, he was admitted to the ICU. It has been 5 days since the event with little change in his clinical picture. A family meeting occurs with physicians, nurses, and a social worker to discuss prognosis and goals of care with his wife and daughters. After being updated regarding his overall clinical picture and poor prognosis, his wife makes the difficult decision to withdraw ventilator support, stating that her husband would never have wanted to be kept alive with a ventilator if there was little chance for meaningful recovery. Prior to this, 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.

I. Ethics

Ethical issues occur frequently in the intensive care unit, and decision-making during critical illness or at the end of life may pose some of the most complex
ethical challenges encountered in medicine. There are four core principles in medical ethics that provide a framework to guide such decision-making: autonomy, beneficence, non-maleficence, and justice. *Autonomy* is the concept that the patient has the right to self-determination: to choose or refuse treatments when offered. *Beneficence* is the tenet that providers should always deliver care which is in the best interest of the patient, while *non-maleficence* refers to refraining from care that causes harm to the patient. The principle of *justice* refers to the fair and equitable allocation of resources amongst patients. (1)

In acute illness, the ability to prognosticate the course or possibility of recovery requires consideration of a multitude of variables including, but not limited to, the nature and course of illness and the patient’s co-morbidities and physiologic reserve. The concept of medical futility can be an important yet difficult premise to establish when dealing with patients having progressive disease. In such circumstances, the determination of an appropriate treatment and care plan is multifaceted. Conversations to establish goals and plans of care require delving into the patient’s quality of life, values, religious/cultural beliefs, and life goals. (2) The discussions should be approached in a multidisciplinary manner with physicians, nurses, other specialists (including social work or palliative care, when appropriate), and the patient with his/her support system and decision-makers. Such conversations should happen early in the course of the patient’s care, and should be revisited frequently.

Patients in the ICU 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 understand the outlined treatment and comprehend the risks and benefits of accepting or rejecting options.

Advance care planning may include the execution of documents that outline a patient’s pre-determined wishes when the patient is unable to voice them during a critical illness, or identify the individual(s) that should have decision-making capacity under such circumstances. These documents - such as a health care proxy, durable power of attorney for health care, and other advance care directives - may give insight to those individuals and the health care team as to what the patient would or would not have wanted. Advance directives include documents like living wills or instructional directives, which can include desire for or against certain interventions (e.g., artificial nutrition, cardiopulmonary resuscitation, ventilator support, invasive surgical measures) in the event of specific scenarios such as respiratory failure or coma.

If the patient is deemed not capable of making his or her own decisions and has not previously designated a particular individual for that role, a surrogate decision maker can be identified to be their “voice.” In these cases, relatives are used in the following order (which can vary legally from state to state):
1. Spouse (court recognized)
2. Adult child or majority of adult children available to decide
3. Parents
4. Siblings
5. Nearest living relative
6. Close friends who are aware of the patient’s wishes

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.

II. 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 concerns about patient abandonment, violation of the principle of beneficence, or the use of sedatives hastening death.

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 emotionally 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 precedents on current ethical standards in 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 decline if nutritional support is withdrawn. It should be emphasized that pain relief will be a primary consideration and a plan for narcotics or sedative/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 even longer.

Additionally, the family should be prepared emotionally for the dying process. In some facilities, a palliative care service is involved as emotional and psychological support and aids 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 of 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.

III. End-of-Life Care and Organ Donation:

An evolving area of interest involves the care for potential organ donor patients. Often these patients require aggressive interventions, which may offer no direct benefit to the patients themselves, in order to preserve organs for transplantation.

A central tenet of organ donation is the “dead donor rule.” The core principle of this rule is that it is wrong to kill (or cause the death) of one individual to save the life of another. There are currently two accepted classifications of deceased donors: heart-beating organ donation requires determination of death based on irreversible cessation of entire brain function, including the brain stem (donation after brain death), while non-heart-beating organ donation (donation after cardiac death) requires the determination of death based on irreversible cessation of circulatory and respiratory function without antecedent brain death. (3)

Non-heart-beating organ donation involves withdrawal of life-sustaining therapies in or near the operating room setting in a patient for whom the decision to withdraw such support is made independent of, and prior to, the decision to donate organs. Families may or may not elect to be present at the 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, 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 with the transplantation service has certified death. If death by cardiac criteria does not occur within that five minute window, the solid organs are not procured and the patient is returned to the ICU for comfort care at the end of life.

A challenge of end-of-life care for potential organ donors is the conflict created between the primary obligation to uphold the patient’s best interests and prevent pain and suffering versus the challenge of preserving organs for transplantation. Often the goal of organ preservation requires aggressive interventions such as mechanical ventilation, hemodynamic support, and medication administration, which may not offer any direct benefits to the dying patient. The patient and their family may view such interventions as a sharp contrast to their cultural and religious beliefs. Unfortunately, care providers may unintentionally cause pain and suffering to their patients and their families. The ultimate safeguard in protecting the patient and care providers from this potential conflict is informed consent. (4)

Consent provides protection against potential conflicts of interest in regards to deceased-donor organ donations. An ethically valid informed-consent process should consist of a balanced discussion of the available options and counseling to help patients and their families reach the choice that is best for them.

It is recommended that the conversation regarding organ donation and end-of-life care be approached early in the treatment course and with a team of care providers. Often, the local organ procurement organization (OPO) is invited to participate in this discussion, (5) and sometimes the discussions of organ donations are led by providers other than the patient’s primary care team in order to prevent the appearance of a conflict of interest.

The Revised Uniform Anatomical Gift Act of 2006 (UAGA) attempted to clarify and establish a standard approach to the care for potential organ donors. It establishes a two-step process. Step one recommends ongoing resuscitation and life support to preserve organs until procurement staff can determine the medical suitability of potential donors. The UAGA permits these efforts without consent unless there is documentation of valid contrary intent (must specifically address the use of life-sustaining efforts for potential organ donation). This rule can create conflict among critical care professionals who are forced to contend with a potential discrepancy with the donor’s advanced directives. With this in mind, the UAGA requires prompt resolution of the conflict by consulting with the patient’s surrogates as soon as possible.

Step two of the Uniform Anatomical Gift Act states that consent is required before organs may be removed. First-person consents such as document of gift, donor registry, driver’s license, or donor
card are irrevocable and do not require further assent of a surrogate. Although legally appropriate to proceed with organ procurement in the setting of first-person consent, it is strongly advised that the family be closely involved in the discussion to mitigate any potential conflicts.

If appropriate consent is obtained, critical care professionals should begin to transition the goals of care. (6) Providers must never lose sight that the patient is their primary recipient of care. Any potential organ donor has the right to comfort measures and all attempts should be made to provide this support, whether or not they may become donors. This includes appropriate use of pain medications and anxiolytics as needed. Additionally, support should be provided to the families of potential organ donors, including pastoral care, social work, and palliative care staff. A multidisciplinary approach to the end-of-life care for potential organ donors often provides the best care for all parties involved.

As medicine evolves, the opportunities for potential organ transplantation continue to increase. Organ donation can be a wonderful gift allowing those at the end of their life to extend the lives of others and can offer families the closure that something positive has come from their loss. It is important to understand that not all patients and families will share these sentiments. Critical care providers have an important role in ensuring that their patients’ wishes are always respected while fully realizing the value that organ donation offers to society.

References:


Review Questions:

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 chemotherapy 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

2. A 68-year-old man has suffered a massive heart attack and is now intubated and on full support including an intra-aortic balloon pump. On exam, he has positive corneal and gag reflexes, but his imaging studies reveal devastating neurological injury. He had previously expressed to his wife that he would not want to be “on a breathing machine.” His driver’s license notes that he is an organ donor. Should he qualify for organ donation, he will be considered a:

a. Heart-beating organ donation  
b. Non-heart-beating organ donation

3. This law was enacted to facilitate the process of organ procurement for donation:

a. Health Insurance Portability and Accountability Act  
b. Patient Self-Directive Act  
c. Uniform Anatomical Gift Act  
d. Uniform Determination of Death Act

4. A critical care physician’s primary obligation is to the:

a. Hospital  
b. Patient  
c. Family  
d. Potential organ recipient
ICU Triage: Triage strategies (developed from healthcare management experience in natural disasters, infectious disease outbreaks, mass casualty incidents, and military conflict) aim to allocate limited resources and prioritize quality care to those that will benefit the most. (1) The tenets that underlie all models are equity, ethics, and transparency. (2) Intensive Care Unit (ICU) physicians frequently rely on triage principles to make ICU admission decisions. These decisions may be difficult, particularly when they involve end-of-life discussions or the rationing of medical care. (3) In an international multicenter cohort study, critically ill patients refused ICU admission for any reason had a 20% increased 90-day mortality compared to those admitted. The benefit of ICU admission increased for patients with higher

**Patient Case:**
A young 35 year-old nurse presents to the emergency room with persistent fever, cough and myalgias. In the last 24 hours, he has had worsening diarrhea and abdominal pain. You learn he has recently returned from a medical mission in Sierra Leone. He is admitted to the ICU where he is diagnosed with Ebola. The next day, 2 more healthcare workers present with similar symptoms. As you discuss the possibility of an Ebola outbreak with your colleagues, you realize there are only 6 ICU beds in the hospital.

**Key Points:**
- Triage models should be equitable, ethical, and transparent.
- Institutions should create locally relevant guidelines incorporating objective parameters and clinical judgment.
- Validated risk stratification tools can help quantify illness severity and inform triage decisions.
- Clinical judgment in combination with objective risk stratification tools may be superior to using objective criteria alone for ICU admission decisions.
severity of illness. (4) Many physicians have reported difficulty with ICU admission decisions, in part due to disagreement with local triage guidelines. (5) Ongoing research in the application of triage principles to ICU care may assist physicians, nurses, and other healthcare workers in approaching these challenging decisions.

Institutions/physicians confront complex questions when formulating local triage guidelines:

1. **Equity**: How will we maintain equal access to ICU care for patients of all ages, race, and socioeconomic backgrounds?

2. **Ethics**: How should ICU admission policies identify patients who “will benefit most” from ICU care? How do we define futile care?

3. **Transparency**: Who will help develop these guidelines? How will we make them accessible?

**Organizational Guidelines**

National and international organizational guidelines provide a framework for answering these questions. In 1999, the Society of Critical Care Medicine (SCCM) published its first national guidelines for ICU admission, prioritizing admission to those most likely to recover from acute, intensive management. The model separates patients into 4 groups, from highest priority (priority 1) to lowest priority (priority 4). High priority patients warrant admission while low priority patients are not likely to benefit from ICU care. (6)

1. **Priority 1**: critically ill, unstable patients in need of immediate intensive treatment and monitoring that cannot be provided outside of the ICU

2. **Priority 2**: patients who require intensive monitoring and may potentially need immediate intervention

3. **Priority 3**: unstable patients who are critically ill but have a reduced likelihood of recovery because of underlying disease or nature of their acute illness

4. **Priority 4**: patients who are generally not appropriate for ICU admission due to

   A) little or no anticipated benefit from ICU care (too well to benefit from ICU care) or

   B) patients with terminal and irreversible illness facing imminent death (too sick to benefit from ICU care)

While providing a general framework, this model does not incorporate specific strategies for categorizing patients. In 2016, a multidisciplinary task force updated the SCCM guidelines based on extensive review of contemporary ICU admission and discharge practices. (7) In addition to clarifying terminology, this
**Table 1.8.1: Clinical Scoring Systems Used in Intensive Care Unit Admission Decisions**

<table>
<thead>
<tr>
<th>Model</th>
<th>Components</th>
<th>Numeric Range</th>
<th>Application</th>
<th>Advantages</th>
<th>Pitfalls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Physiology and Chronic Health Evaluation (APACHE)(^a)</td>
<td>20 physiologic variables, data collected over 24 hrs</td>
<td>0-299</td>
<td>Risk-stratify/predict hospital mortality on first day of ICU admission</td>
<td>Variables are weighted, which adds to this score's high precision (AUROC = 0.90)</td>
<td>Large number of variables, some based on invasive testing; model is vulnerable to changes in clinical care</td>
</tr>
<tr>
<td>Mortality Prediction Model (MPM)(^b)</td>
<td>15 physiologic variables (1 for each positive variable)</td>
<td>0-15</td>
<td>Predict hospital mortality at ICU admission and 24 hrs</td>
<td>Estimates at ICU admission are independent of subsequent ICU care; score independent of underlying diagnosis (AUROC = 0.82)</td>
<td>Model not validated in burn, coronary care, or cardiac surgery patients, which may mean limited efficacy in these populations</td>
</tr>
<tr>
<td>Simplified Acute Physiology (SAP)(^c)</td>
<td>17 physiologic variables</td>
<td>0-163</td>
<td>Predict hospital mortality at ICU multiple admission settings,</td>
<td>Model not validated in burn, coronary care, or cardiac surgery patients, which may mean limited efficacy in these populations</td>
<td></td>
</tr>
<tr>
<td>Modified Early Warning Score (MEWS)(^d)</td>
<td>6 physiologic variables</td>
<td>0-14</td>
<td>Identify patients at risk for clinical deterioration; predicts need for higher level of care; score ≥4 indicates high risk</td>
<td>Simple, easy for non-clinicians to use, intended for application to any patient population</td>
<td>Low positive predictive value, intended as tool for non clinicians</td>
</tr>
<tr>
<td>Sequential Organ Failure Assessment (SOFA)(^e)</td>
<td>4-point score for each of 6 organ systems</td>
<td>4-24</td>
<td>Risk-stratify at admission and every 48 hours</td>
<td>Few parameters requires invasive testing including arterial sampling</td>
<td></td>
</tr>
<tr>
<td>Surgical APGAR(^f)</td>
<td>3 physiologic variables</td>
<td>0-10</td>
<td>Predicts 30-day mortality and postoperative ICU admission</td>
<td>Not applicable to nonsurgical patients</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)APACHE available in versions I-III; data here based on APACHE III \([8]\)

\(^b\)MPM scores I and II; data here from MPMII \([9]\), different scoring at admission versus at 24 hours

\(^c\)SAPS available in versions 1-3; data here based on SAPS 2 \([10]\)

\(^d\)MEWS score \([11]\)

\(^e\)SOFA, Quick SOFA (qSOFA) available as 3 point score \([12]\)

\(^f\)Surgical APGAR (SAS) score \([13]\)

update recommended a combination of objective criteria and clinical judgment when creating local policies. Many institutions have used risk stratification models to assist in this process.

**Clinical Scoring Models**

Risk stratification models, derived from prospective and retrospective cohort studies, are designed to predict the risk of hospital mortality upon ICU admission (Table 1). Physicians can use these models during the triage process to assess illness severity and determine the urgency of ICU admission. There is a tradeoff between the simplicity and the precision of the risk estimates provided by these scoring models. For example, the MEWS and SOFA scores are easily calculated in a variety of clinical settings, but have variable precision in practice. \((14,15)\) In contrast, the APACHE III and SAPS II have higher sensitivity and specificity, but may be difficult to calculate due to the amount of clinical data required.
Clinician Judgment

Triage decisions ultimately involve some clinical judgment, particularly in emergencies when objective data is not readily available. Physician judgment has been shown to be a valid estimate of patient mortality risk, and may even exceed the performance of clinical scoring models. For example, a comparison between mortality-risk assessment by a critical care fellow and the APACHE score showed comparable receiver operator curves (0.79 for APACHE, 0.89 for physician). Discrimination improved when physician judgment and APACHE were used together compared to APACHE alone (0.88, p <0.05). (16) However, triage decisions are ethically complex. They are emotionally taxing, contribute to provider burnout, (17) and are susceptible to bias. During periods of high ICU strain (high census, high proportion of new admissions), there is a significantly shorter time to the withdrawal of care compared to times of decreased ICU strain. (18) Rapid response teams (multidisciplinary groups including physicians, nurses, and respiratory therapists) have been utilized for triage. These teams may diffuse the ethical responsibility from a solo practitioner and be a feasible alternative model in settings where physician intensivists are unavailable.

Future Directions

As global populations age and the availability and technology of ICU care improves, the demand for critical care services is anticipated to increase. Automatically increasing the supply of ICU care may not be an appropriate allocation of healthcare resources. (19) Triage is an essential tool for practitioners to deliver care to those patients who will most benefit. While objective and subjective tools are available, they must be adapted to local contexts and triage models must remain faithful to the basic tenets: equity, ethics, and transparency.

References:


Review Questions:

1. What is triage:
   a. Determining the medical/surgical care unit a patient should be admitted to
   b. Allocation of resources and personnel to deliver care to those that will benefit the most
   c. Care management strategy to be used in emergency situations only

2. What are benefits of using risk stratification models in triage?
   a. Provides evidence based objective criteria
   b. Limits the influence of emotion in the decision making process
   c. Serves to make the triage process equitable and transparent
   d. All of the above

3. Which of the following are false regarding triage strategies based on clinical judgment alone?
   a. Provider burnout
   b. Decisions are less sensitive/specific than those based on risk stratification tools
   c. Decisions are impacted by ICU environment factors (i.e.: high capacity)
Telemedicine in critical care is the remote delivery of clinical services using advanced audiovisual conferencing technologies in an attempt to supplement or provide critical care to existing ICUs or to ICUs where an intensivist presence is lacking.

There is limited data at the moment to truly evaluate the efficacy of teleICU, but recent effectiveness studies do show a small, but statistically significant decrease in 90-day mortality.

In facilities with training programs, having access to a tele-intensivist can help augment a resident’s educational experience and sometimes provide much needed supervision in critical areas such as ventilator management, code supervision, and the initial management of an unstable patient.

A 75 year-old woman with a history of hypertension, congestive heart failure, diabetes mellitus type two presents to her local community hospital with dyspnea, nausea, vomiting, peripheral edema, and a grossly distended abdomen. Two weeks prior to admission, she underwent an elective hysterectomy for post-menopausal bleeding. In the Emergency Department (ED), she quickly decompensates and develops hypoxic respiratory failure, and then proceeds to vomit and aspirate during the intubation attempt. After her airway is secured, an arterial blood gas reveals severe hypoxia and acidosis. A brain natriuretic peptide laboratory result indicates decompensated heart failure. A CT scan of the abdomen is significant for a small bowel obstruction. A nasogastric tube, a central venous catheter, and an arterial catheter are placed in the ED and she is then transported to the ICU, where a tele-intensivist is prepared to assist the on-site staff in her evaluation and management.

Telemedicine

Telemedicine, or teleICU (intensive care unit) is defined as the remote delivery of critical care services using advanced audiovisual technology. This technology allows the teleICU provider to directly interface with the monitoring systems at the
patient’s bedside and view data in real time in order to facilitate clinical decision making. The current prevalence of the teleICU model in adult critical care is about 11% of nonfederal hospital ICU beds, which is approaching the current rate of bedside intensivist-led ICU models, which is 14%. The expected growth rate is 1% per year, indicating that critical care delivery models that include telemedicine support will be more common than the standard bedside intensivist-led programs. In addition, an aging population with an increased need for critical care services, coupled with a limited supply of trained intensivists and critical care nurses has led to a shortage of critical care practitioners. Implementing a teleICU model appears to be a logical way to increase the availability of critical care expertise and alleviate this shortage. This holds true especially for small hospitals in rural areas. Despite this expansion of teleICU services, concerns still exist regarding its efficacy in influencing patient outcomes. Most existing studies are before-after studies limited to single centers that lack control groups. A recent case-control national effectiveness study based on Medicare claims data using 132 US telemedicine hospitals did find a small reduction in 90-day mortality in those hospitals after implementation of a teleICU service. However, even this well-conducted study cites limitations based on the heterogeneity of teleICU practice at the varying hospitals.

The Platform

One of the more common platforms in use is the Philips eCareManager ™ (Philips Healthcare, Andover, MA). This system can pull data from each hospital’s electronic medical record (EMR) in real time and assimilate it into a one-page graphically-enhanced spreadsheet. Through eCareManager ™, a physician or nurse can then readily access the data during rounds or when preparing to intervene. The single page shows a brief patient description, list of pertinent diagnoses, treatments in progress, a graphical vital signs trend, list of lines, tubes, drains, and antibiotics (including start dates), mechanical ventilation data, most recent lab trends, as well as intake/output status. Patient rooms are all equipped with a camera and monitor for the audiovisual interface, as well as a button that on-site staff can press that sends an alert signal to the physician or nurse in the teleICU indicating the need for an urgent intervention. Most systems are even capable of order entry, though the individual hospitals’ clinical practitioner order entry system (CPOE) can also be accessed by the teleICU intensivist.

Telemedicine and Medical Education

Telemedicine in the ICU has certain implications regarding medical education. There is concern that its implementation in teaching hospitals will limit a resident’s sense of independence and also hinder their ability to learn through experience. However, studies on the impact of teleICU on medical education have not validated these concerns. In fact, most housestaff welcome the
assistance of a critical care specialist to assist in management, especially during off-hours when the bedside attending physician is either asleep or off the unit. Survey studies have been sent to residents and fellows to gauge the level of acceptance at various teaching institutions. One such report at a hospital where residents rotate through ICUs that have, and do not have telemonitoring, found that 82% of residents prefer to train in an ICU equipped with teleICU coverage. Specific advantages cited include assistance with ventilator management, initial management of an unstable patient, supervision during situations requiring advanced cardiac life support, management of acute changes in patient status, and interpretation of diagnostic tests. However, most of the residents and fellows surveyed regard teleICU presence to be the least helpful in situations involving end-of-life care or with certain ICU procedures. At the moment, the data indicates that the addition of a teleICU service provides an additional resource for residents and fellows and helps augment their sense of patient safety.

Medicolegal Aspects of Telemedicine in Critical Care

In order to provide teleICU care, a provider must be licensed in that state, credentialed and granted privileges at the specific hospital, and have malpractice liability insurance. There are also specific requirements per the Centers for Medicare and Medicaid Services that affect credentialing for teleICU providers. Systems and platforms must also comply with federal health privacy laws.

One of the most commonly expressed concerns from teleICU providers is that dependence on telemedicine could increase the frequency of malpractice claims and costs. The fear is that because the providers are not at the bedside, their position will be less defensible in court. To help measure this, a study was conducted in a large multistate, nonprofit health care center that has 450 ICU beds across 5 states. They found that the frequency of malpractice claims was significantly lower at those ICUs that implemented the teleICU program. In fact, one of the hospitals studied has not had a claim in over 5 years since the implementation of the teleICU program. The results are still early, but they appear promising.

Conclusions

Telemedicine in critical care is poised to play a major role in the expansion of critical care services to hospitals that otherwise would not have access to intensivists. Technological advances now permit an intensivist to remotely interact with a patient thousands of miles away and to assist on-site staff in clinical decision making. Medical education stands to benefit, too, as the addition of a teleICU can provide a background level of patient safety. In addition, the teleICU physician can serve as both a teacher and consultant to on-site residents and fellows at the bedside in a manner that can improve medical education. As telemedicine in critical care continues to expand, its effects on patient outcomes and its medicolegal implications can be more
thoroughly studied. For the moment, a teleICU service can supplement an existing intensivist-led service and also bring much-needed critical care expertise to areas that would otherwise lack intensivist support.

References:


Review Questions:

1. A teleICU physician can provide all of the following services EXCEPT:
   a. Critical care consultant services for ICUs without an intensivist presence
   b. Special assistance to on-site housestaff or affiliate providers during changes in patient status
   c. Triage and perform the initial diagnostic workup of a patient newly-admitted to the ICU
   d. Leave his station and enter the ICU to assist the staff in person

2. With regards to medical education, residents and fellows likely find assistance from the teleICU to be the LEAST helpful in which of the following situations?
   a. Interpreting ventilator waveforms and adjusting the settings
   b. Assisting with end-of-life issues
   c. Helping to supervise a “code blue” situation
   d. Serving as a consultant for issues at night that would otherwise require a phone call to the bedside intensivist.
Chapter 2: Monitoring Topics
Key Points:

- In the ICU, continuous hemodynamic monitoring, rapid interpretation of monitors and integration of the results of the physical exam 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 (BP), temperature and capnography.

- 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.

Blood pressure:

Noninvasive Blood Pressure:

1. Manual BP

BP cuffs are initially inflated above systolic blood pressure (SBP) and slowly deflated. The first Korotkoff sound is heard when the cuff is deflated to the point that the cuff pressure drops below SBP. The second Korotkoff sound occurs when the cuff is deflated further below diastolic blood pressure (DBP) and no longer achieves arterial compression with absence of turbulent flow. Mean arterial pressure (MAP) is a calculated value according to the formula MAP = \( \frac{1}{3} \text{Systolic BP} + \frac{2}{3} \text{Diastolic BP} \).

Patient Case:

78 year-old man with history of coronary artery disease, hypertension, poorly controlled diabetes and COPD is admitted to the ICU for the management of respiratory failure and hypotension requiring significant vasopressor support. An arterial-line is placed for continuous blood pressure monitoring and frequent arterial blood sampling. His initial BP is 100/60 mmHg.
Inappropriately sized cuffs produce erroneous measurements. A cuff that is too small over-estimates BP and a cuff that is too large under-estimates BP. A cuff positioned too low, relative to the patient’s heart, over-estimates BP and a cuff positioned too high, under-estimates BP.

BP cuff placement should generally be avoided on the ipsilateral arm of a previous radical mastectomy, PICC line placement, fast-flowing peripheral IV and/or AV-fistula. In patients with significant peripheral vascular disease there can be a discrepancy between BP measurements on different limbs.

2. **Automatic BP (Oscillometric method):**

With oscillometry, the 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 the MAP. SBP and DBP are then calculated. Shivering and excessive movement may lead to erroneous measurements.

**Invasive BP:**

Invasive BP measurement utilizes an indwelling arterial catheter attached to an external pressure transducer via fluid filled non-compliant tubing. MAP is obtained by calculating the area under the transduced pressure curve.

Intra-arterial cannulation is prudent with ongoing or anticipated hemodynamic instability, requirements for significant vasopressor support, circumstances necessitating frequent arterial blood sampling, poorly pulsatile blood flow in patients receiving mechanical circulatory support (i.e. left ventricular assist device, cardiopulmonary bypass, extracorporeal membranous oxygenation) and for anatomic reasons making other methods of measurement difficult (i.e. significant obesity, severely burned extremities, etc.).

The **radial** artery is the most commonly utilized location for placement of an intra-arterial cannula. Alternative sites include the femoral, axillary, brachial 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.

Air bubbles and/or medications should not be injected into intra-arterial blood pressure monitoring catheters since this may lead to limb ischemia and necrosis. Additionally, bubbles in the transducer tubing can lead to inaccurate results. The transducer is generally placed at the level of the anatomic site of interest, if the transducer is too low, the measured pressure over-estimates BP and if the transducer is too high, the measured pressure under-estimates BP.
**Pulse Oximetry:**

Pulse oximetry is an optical monitoring technique that utilizes two wavelengths of light. The ratio of 660 nm/940 nm absorbance is determined and compared with population data to determine the percentage of hemoglobin (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 curve of pulsating absorbance is usually displayed and known as the plethysmographic trace.

There are various clinical circumstances that can interfere with pulse oximetry readings and in certain circumstances a falsely elevated Hb saturation. Nail polish, the injection of dyes such as methylene blue and indigo carmine, and intense ambient light may cause interference with pulse oximetry readings.

Carbon monoxide (CO) poisoning is a life-threatening clinical situation involving a falsely elevated pulse oximetry reading. CO replaces O$_2$ at the same binding site on the Hb molecule, the absorbance of Carboxy-Hb and Oxy-Hb is the same at the emitted wavelength of 660nm. In this case the pulse ox will continue to report adequate saturation despite impaired O$_2$ transport.

Methemoglobinemia is another acquired disorder of impaired hemoglobin binding secondary to an oxidation of the iron-containing portion of the heme molecule. In methemoglobinemia, the pulse-ox reads about 85% and is relatively unresponsive to supplemental O$_2$. The most common potential causes include; benzocaine (ingredient of Cetacaine spray), prilocaine (ingredient of EMLA cream), nitric oxide, nitroglycerin, sodium nitroprusside, and acetaminophen overdose.

**EKG:**

In the ICU, the 7 lead EKG is frequently the standard monitoring approach; this consists of leads I, II, III, AVF, AVL, AVR and V5. V5 is most sensitive to ischemia, while lead II is the most sensitive for detecting arrhythmias. For increased accuracy in EKG interpretation a 12 lead EKG should be obtained.

Identifying the rate, rhythm, axis, and signs of ischemia are the basic components of EKG interpretation. When interpreting rate, the standard cutoffs identify bradycardia as < 60 bpm and tachycardia as > 100 bpm.

Basic indications of ischemia are indicated by ≥1 mm ST-segment depression or T-wave inversion while an acute MI may present with ≥1 mm ST segment elevation in ≥2 anatomically contiguous leads.

**Temperature:**

Temperature can be measured from a patient’s core (PA catheter, tympanic membrane, bladder, rectal, esophageal) or on the
Hypothermia a common complication that can lead to confusion, delirium, delayed awakening from anesthesia, coagulopathy, and shivering. Hypothermia increases O$_2$ demand and may be deleterious in patients that exist in a state where there is a small margin between oxygen delivery and oxygen consumption.

Fever greater than 42°C is associated with enzyme dysfunction and multi-organ failure; in this situation patients may require active cooling. Febrile states may be particularly deleterious in patients with ischemic, hemorrhagic or traumatic brain injury and post-cardiac arrest.

**Capnometry:**

Capnometry is a graphical representation of the measurement of the partial pressure of CO$_2$ (ETCO$_2$) in expired gas. This monitor can be utilized to confirm endotracheal tube placement and detect esophageal intubation and to provide information about cardiac output. The morphology of the capnometry waveform can be utilized to increase suspicion for states such as bronchospasm or endotracheal tube occlusion *(Figure 1)*.

ETCO$_2$ normally ranges from 35 – 45 mmHg. Decreases in ETCO$_2$ can be secondary to ventilatory causes such as hyperventilation as well as circulatory causes leading to decreased cardiac output, e.g. functional dead space. With minimal or absent ETCO$_2$ the differential diagnosis includes equipment failure such as in ETCO$_2$ occlusion or disconnection, ventilation problems (apnea, ETT occlusion, esophageal intubation, bilateral pneumothoraces), and circulatory collapse.

An increase in ETCO$_2$ may indicate an acute increase in metabolism such as in a hyper-metabolic state where there is an increase in the production of CO$_2$ (sepsis, hyperthyroidism, malignant hyperthermia) or with administration of sodium bicarbonate that when metabolized creates CO$_2$ as a byproduct.

**CVP:**

Central venous pressure (CVP) is the measurement of venous blood pressure at the junction between the superior vena cava (SVC) and right atrium (RA). A “normal” CVP is about 5-10
cmH₂O; CVP may aid in the diagnosis of a variety of pathological conditions including atrial fibrillation, complete AV block, tricuspid valve regurgitation and stenosis.

The specific CVP waves (Figure 2) include the **a wave** which demonstrates an increase in the venous pressure caused by the right atrial (RA) contraction, the **c wave** which signifies the increase in RA pressure secondary to bulging of the tricuspid valve (TV) toward the RA during early right ventricular (RV) contraction, the **x descent** indicates a decrease in RA pressure (RA relaxation) secondary to the downward displacement of the TV during systole, the **v wave** is created by the increase in RA pressure from venous filling of RA against closed tricuspid valve (generally immediately after peak of T wave on EKG) and the **y-descent** is a result of the decrease pressure in the RA from emptying of RA upon opening of the tricuspid valve (diastolic filling).

Abnormal CVP waveforms can be seen in pathologic conditions such as **atrial fibrillation** where there is an obliteration of the a wave and a prominent c wave while in **complete AV block** cannon a waves can be seen as the RA contracts against a closed tricuspid valve leading to a significant increase in RA pressure.

**References:**


4. Deborah J. Cook D, Simel D: Does This Patient Have Abnormal Central Venous Pressure? JAMA 1996; 275:630-4


**Review Questions:**

1. What EKG lead is most sensitive to ischemia?
   a. V5
   b. V4
   c. II
   d. AVL

2. 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

3. An arterial line is placed for blood pressure monitoring and frequent blood sampling. BP is 100/60. If the arterial line transducer is accidentally lowered by 80 cm, what pressure will be displayed on the monitor?
   a. 190/130 mmHg
   b. 160/120 mmHg
   c. 100/60 mmHg
   d. 60/40 mmHg
Key Points:

- The adequacy of cardiac output should be based on clinical 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 estimate cardiac preload and guide fluid therapy in selected patients.

Patient Case:
You are working in the surgical intensive care unit and taking care of a 57-year-old man with end-stage liver disease, status-post orthotopic liver transplantation. His heart rate is 90 beats/minute, blood pressure of 90/50 mmHg and his urine output has been declining over the last three hours. He remains intubated on propofol, and norepinephrine infusions. There are multiple invasive monitors in place including an introducer with 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 with 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 a voltage or electrical signal. The electrical signal is transmitted to the monitor and is amplified, filtered and displayed into the pressure pulse wave.
In order to assess the accuracy of the arterial pressure waveform, a bedside fast-flush test is used, which evaluates the resonant frequency of the system. 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 1 or 2 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. This is often prompted by scenarios such as oliguria, hypotension, or tachycardia, suggesting that intravenous fluid therapy may be warranted. Other information such as chest auscultation, chest radiograph, examination of mucous membranes, orthostatic vital signs, 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.

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 assumes 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 measurements of cardiac filling pressures have not been shown to be an effective tool for guiding fluid therapy. It is likely that the failure in these measurements is secondary to a combination of inaccurate data, misinterpretation of the numbers and the fact that CVP and PCWP reflect static measurements rather than dynamically determining the response to a fluid challenge.
In clinical scenarios in which a provider is considering fluid therapy, the question is whether there will be a clinically significant increase in cardiac output if fluids are administered. This question can be answered by assessing physiologic changes in stroke volume and cardiac output that occur with positive pressure mechanical ventilation.

**Physiologic basis of pulse pressure variation**

The stroke volume varies throughout the respiratory cycle due to the interaction between venous return and cardiac function. Changes in pleural pressure affect 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 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. Due to the pulmonary transit time of approximately two seconds, there is a delay in the resulting decrease in left ventricular preload and cardiac output. The left ventricle is also affected by inspiration: positive pleural pressure decreases the transmural pressure required to eject blood into the aorta, effectively decreasing left ventricular afterload.

A decrease in venous return to the right ventricle and a decrease in left ventricular afterload occur with a positive pressure breath. This produces an increase in stroke volume during inspiration due to the decreased left ventricular afterload. This results in an inspiratory increase in systolic blood pressure and a greater pulse pressure. Subsequent stroke volumes will decrease, reflecting the previously decreased venous return to the right ventricle. After the positive pressure breath is delivered, these smaller stroke volumes will result in a delayed 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 the venous return and cardiac functions 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 the static measures, 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 PPV is a convenient index to obtain with modern monitoring equipment, SPV is readily
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 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).

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:

1. Regular cardiac rhythm
2. Mechanical ventilation with tidal volumes >8 mL/kg predicted body weight and PEEP between 0–5 cmH₂O
3. Passive interaction between patient and ventilator
4. Normal intraabdominal pressure

Pulse pressure variation (Figure 2) is calculated as a percentage based on the greatest and least pulse pressures measured during a respiratory cycle:

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

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:

1. Malfunctioning arterial line and measurement system
2. Irregular cardiac rhythm or frequent extra-systoles
3. Mechanical ventilation with lung protective strategies (<8 ml/kg)
4. Patient-ventilator dyssynchrony or spontaneous breathing
5. Open-chest conditions
6. Presence of right ventricular failure or pulmonary hypertension

While PPV is limited to ventilated patients with larger tidal volumes, the changes in pleural pressure also occur in spontaneously ventilating patients. Newer monitors can calculate a PPV to stroke volume variation (SVV) ratio. SVV is a dynamic measurement similar to PPV which estimates change in stroke volume and is calculated from an arterial line waveform. PPV/SVV provides an estimate of dynamic arterial elastance in spontaneously ventilating patients. Dynamic arterial elastance is defined as the change in pressure for a given volume over a single respiratory cycle to estimate arterial load. The higher the dynamic arterial elastance, the greater the slope on the pressure-volume curve, and the more likely a patient will respond to a fluid
challenge. This measure may predict volume responsiveness in both mechanically and spontaneously ventilating patients, however further studies are needed.

References:


Review Questions:

1. A slow dP/dT on the arterial waveform would favor selection of which of the following drugs?
   a. Vasopressin
   b. Furosemide
   c. Phenylephrine
   d. Dobutamine

2. Of the following, which is the best measurement to determine fluid responsiveness?
   a. CVP
   b. PPV
   c. PCWP
   d. Left ventricular end-diastolic area index
3. In a hypotensive patient with normal cardiac function, which of the following could indicate the need for fluid therapy?

a. CVP 6 cm H$_2$O

b. PPV 20%

c. PCWP 10 cm H$_2$O

d. PPV 9%

4. The delta down on the systolic pressure variation reflects:

a. Preload

b. Afterload dependence

c. Contractility

d. Diastolic dysfunction

5. Which of the following would limit the application of PPV?

a. General anesthesia

b. Vasopressor use

c. Diuretic use

d. Pressure support ventilation
Introduction

Ultrasonography is an indispensable and evidence-based tool in the practice of critical care medicine. Its safety and portability allow for rapid noninvasive bedside assessment to aid diagnosis and management of critically ill patients. Bedside cardiac ultrasound is particularly useful in determining the cause of undifferentiated shock in medically complex patients. Resuscitation efforts can often be redirected based on ultrasound findings.

The American College of Chest Physicians and Society of Critical Care Medicine have now made recommendations on critical care ultrasound competencies. (1,2)

Patient Case:
A 65-year-old obese man with a history of pulmonary hypertension and heart failure (with preserved ejection fraction) arrives to the intensive care unit after an exploratory laparotomy for diverticulitis. The patient remains intubated and is hemodynamically unstable. Interventions initiated include: fluid boluses, norepinephrine and epinephrine infusions. He remains tachycardic (123 bpm), hypotensive (87/50), with increasing oxygen requirements. Central venous pressure is estimated at 18 mmHg and pulmonary pressures are estimated at 65/34 with a pulmonary artery occlusion pressure of 30 mmHg.
Furthermore, recent literature validates ultrasound for making management decisions in the intensive care unit. (3) Ultrasound can also be helpful in the intensive care unit for vascular access and evaluation of thrombosis; abdominal evaluation of free fluid, hydronephrosis and abdominal aortic pathology; and thoracic evaluation for pneumothorax, pleural effusion and pulmonary edema. Lung ultrasound has made great advances over the past 10 years, particularly in the evaluation of causes of respiratory distress. (4,5)

Both transthoracic and transesophageal echocardiography can be used to evaluate cardiovascular compromise. Various ‘protocols’ have been developed for the evaluation of the acute hypotensive patient (RUSH, FATE, FEEL, CAUSE, etc.). As both the clinician managing the patient and ultrasound operator, the intensivist has the advantage of making immediate decisions that impact 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 Sonography in Trauma) to FAST (Focused Assessment with Sonography in Trauma), which shows a change from organ focus (abdomen) to problem focus (trauma).

The case presentation above illustrates the difficulty that can be encountered when treating hemodynamic instability. Despite dual vasoactive infusions, the patient continues to be hemodynamically unstable. Although central venous and pulmonary catheter data are available, the diagnosis remains unclear. The clinical picture could be consistent with ventricular failure (right or left), sepsis, or hemorrhage. Bedside cardiac ultrasound can provide real time images to distinguish between these etiologies.

Ultrasonography, particularly echocardiography, requires formal education. The outline below simply aims to provide a basic understanding of the potential uses 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 educational site at http://anest.ufl.edu/clinical-divisions/critical-care-medicine/critical-care-ultrasonography/

The following outline lists applications and particular situations where ultrasound may be useful. Please refer to the following website to obtain more comprehensive resources and discussions on each individual topic listed. (http://anest.ufl.edu/clinical-divisions/critical-care-medicine/critical-care-ultrasonography/didactics/):

I. **Cardiac** Critical Care Ultrasound Examinations

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) Respiratory distress  

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 pathology – tear, mass, stricture  
b) Dysphagia/odynophagia unevaluated  
c) Cervical spine Instability  
2. Relative  
a) Esophageal varices  
b) Recent esophageal/gastric surgery  
c) Oropharyngeal carcinoma  
d) Upper GI bleeding  
e) Atlantoaxial disease
E. Echocardiography findings in hemodynamic instability (LV function is best assessed at the parasternal short papillary muscle level) - hypovolemic, cardiogenic, obstructive shocks all have specific findings.

1. Hypovolemic shock
   a) Decreased end-diastolic area
   b) “Kissing” papillary muscle
   c) Hyperdynamic function

2. Cardiogenic shock
   a) Failing left ventricle
      1. Decreased area change
      2. Increased end-diastolic area
      3. Increased end-systolic area
   b) Failing right ventricle
      1. Increased right ventricular size
      2. Intraventricular septum bulges towards left ventricle
      3. Pulmonary embolus if echogenic density present

3. Valvular pathology
   a) Mitral regurgitation or stenosis
   b) Aortic regurgitation or stenosis

4. Cardiac tamponade
   a) Pericardial effusion
   b) Diastolic collapse of right ventricle

II. Lung Critical Care Ultrasound Examinations

A. Pleural
   1. Pneumothorax identification - absence of lung sliding, and/or lung point (junction between sliding lung and absent sliding, near 100% specific for PTX)
   2. Effusion identification, characterization and quantification
   3. Guidance during thoracentesis

B. Lung
   1. Identification of aerated normal lung
   2. Identification of consolidated lung
   3. Identification of pulmonary edema (Interstitial syndrome) - “B” lines with lung sliding found in anterior lung zones

III. Vascular Critical Care Ultrasound Examinations

A. Identification of deep vein thrombosis - non-compressible vein

B. Vascular access (central vein, artery, hemodialysis)

IV. Abdomen Critical Care Ultrasound Examinations
A. Identification, quantification and characterization of intraperitoneal fluid. Routinely done with FAST 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
   1. Hydronephrosis
   2. Distended bladder (ureteral jets)

C. Identification of abdominal aortic aneurysm and dissection


**Images**

The images below illustrate how ultrasonography can change management in a critical care setting. In each of these cases, decision making was altered through the use of ultrasound.

**Figure 2.3.1 Cardiac Ultrasound**

Pericardial effusion is shown in a patient with shortness of breath and chest pain with evidence of diastolic collapse of the right ventricle.

**Figure 2.3.2 Chest Ultrasound**

Anterior chest B lines on lung ultrasound are shown in a patient with pulmonary edema when initially COPD was the suspected cause of distress. This patient was given diuretics and afterload reducing agents to treat acute CHF exacerbation instead of being treated for COPD exacerbation.
Conclusion

Ultrasonography provides a point of care tool to rapidly assess a patient’s condition. The most important quality of bedside/portable/point of care ultrasound is reproducibility. Real-time diagnosis based-on images obtained still require proper clinical context in order to make expedient and correct interventions without delay. Improvements in image quality and acquisition allows further developments for new applications in ultrasonography. As experience with this diagnostic modality increases, routine application has become the standard in the ICU setting.

References:


Figure 2.3.3 Abdominal Ultrasound

Free fluid in abdomen is shown in a patient who was taken to the operating room for hypotension. This was a trauma patient who had no other obvious cause of bleeding and was found to have a liver laceration.

Figure 2.3.4 Vascular Ultrasound

Long axis and short axis view of wire confirmation in vein used to confirm proper placement of catheter in a typical ICU patient.


**Review Questions:**

1. Which of the following is not evaluated during a typical FAST exam?
   a. Pericardial space
   b. Hepatorenal space
   c. Splenorenal space
   d. Aorta

2. Which pulmonary pathology is ultrasound unable to assess?
   a. Pneumothorax
   b. Pulmonary edema
   c. Pneumonia
   d. Ultrasound is able to aid in diagnosis of all of these etiologies

3. A middle-age man is a victim of a stab wound to the chest. He is hypotensive. A bedside cardiac ultrasound is performed and the image below is obtained. What is located by the area indicated by the “X”?
   a. Pneumothorax
   b. Pulmonary edema
   c. Pneumonia
   d. Ultrasound is able to aid in diagnosis of all of these etiologies
a. Left ventricle

b. Right ventricle

c. Lung

d. Pericardial effusion
Introduction

In caring for critically ill patients, the timely diagnosis and treatment of life threatening issues is 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 1). These processes take time and the interval between laboratory test order to treatment decision is referred to as the therapeutic turn-around time (TTAT).

**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.

- POCT is available for many laboratory tests commonly obtained in the ICU including glucose, hemoglobin, blood gas analysis, 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.

**Patient Case:**

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 transferred urgently 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?
the therapeutic turnaround time (TTAT). In the ICU, the clinical condition of unstable patients can change quickly. 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 testing, 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 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.

Disadvantages of POCT

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
POCT Devices and Tests

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 (SvO₂). 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 ANALYSIS

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 are not consistent across all studies. For example, in a report of one center’s experience with POCT for blood gas analysis, inaccuracies in PCO₂ 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 patient management. 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 or 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 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. (Figure 3)

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 Control with POCT**

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.

**Ultrasound**

Ultrasound is a point of care technology that is rapidly becoming
an invaluable tool in the diagnosis and management of a variety of life threatening conditions such as pneumothorax, cardiac tamponade, acute heart failure, and severe hypovolemia (12). (see Chapter 2.3) Other uses of point-of-care ultrasound include facilitation of central venous catheter and arterial line placement, evaluation for deep vein thrombosis, and assessment of fluid responsiveness. The point of care ultrasound has been described as “the stethoscope of the future.” As with the other point-of-care tests, it is essential that ultrasound be performed by competent personnel to avoid misdiagnosis and unwarranted treatment.

References:


**Review Questions:**

1. Which of the following is true for point of care testing?
   
   a. Reduces therapeutic turn around time
   
   b. Has been consistently shown 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

2. Advantages of POCT include all of the following EXCEPT?
   
   a. Reduction in therapeutic turn around time
   
   b. Use of smaller blood volumes minimizing iatrogenic blood loss
   
   c. No need for a critical values notification system
   
   d. Cost savings

3. Regarding POCT of coagulation studies, all of the following are true EXCEPT?
   
   a. Activated clotting time (ACT) is often used in the OR 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
Chapter 3

Neurologic Topics
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, which occurs between 2-5 days post ischemia, can cause significant brain swelling and possibly herniation.

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

Patient Case:
A 52 year old man with past medical history of HTN and DM, is admitted to the ICU with acute onset of right hemiplegia 2 hours ago. He received systemic tPa prior to arrival with no resolution of symptoms. The decision was made to take him to interventional radiology for intra-arterial thrombolysis. Since he is at a high risk for malignant cerebral edema, a neurosurgery consultation is placed for consideration of decompression with hemi craniectomy. In this patient you can see the left hemisphere compared to right, there is a decrease in CBF (bottom left picture), increased mean transit time (MTT) (bottom middle picture) and minimal CBV (top middle picture). This prolonged MTT, decreased CBF and reduced CBV, identifies a large infarcted core. The penumbra can be identified by prolonged MTT, moderately reduced CBF and normal or increased CBV. Time to peak (TTP) is the time it takes the contrast to reach maximum, and would be expected to be decreased in ischemic tissue such as this patient.
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 1) Global flow is 50ml/100 grams/min. If flow decreases < 20 ml/100 grams/minute, cells will shift to anaerobic metabolism and pyruvate production, which leads to acidosis and cell death. The brain oxygen utilization (CMRO$_2$) is 3.5 ml/100 grams/min. (1)

CSF is produced by the choroid plexus, which is 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 foramen 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 a 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 blood flow) is counteracted by increased arterial pO$_2$ and decreased pCO$_2$.

Figure 3.1.1 Circle of Willis

Four main arteries carry blood to the base of the brain and form the Circle of Willis. Two vertebral arteries merge to form the basilar artery and its branches, forming the posterior circulation. Two internal carotid arteries take a tortuous course through the bony skull and divide into the middle cerebral and anterior cerebral arteries, forming the anterior circulation.
in intracranial pressure, ICP) occurs with lowering of pCO$_2$ levels. Excessively decreasing pCO$_2$ below 25 mmHg exhausts the CNS buffering capacity and causes intense cerebral vasoconstriction resulting in ischemia. In times of impending herniation, a moderate lowering of pCO$_2$ to 30 mmHg can be lifesaving 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 have 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 mmHg and 150 mmHg. If the MAP decreases below 50 – 70 mmHg, intense cerebral vasodilatation occurs. A MAP above 150 mmHg will result in cerebral vasoconstriction. It is important to note that this mechanism of cerebral autoregulation may not be intact in the injured brain, and cerebral perfusion may be passively dependent on MAP.

**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$_2$) consumption. CMRO$_2$ can be slowed through the use of hypothermia, barbiturates, 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 elevating the head of the 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. As mentioned above, mild hyperventilation to lower pCO$_2$ levels to approximately 30 mmHg can decrease blood flow through the brain temporarily through cerebral vasoconstriction and can be used as a temporizing measure to decrease ICP until other therapies take effect.

The brain tissue compartment can be decreased by hypertonic saline or diuresis (usually osmotic diuresis with mannitol), which decreases intracellular fluid volume.
The CSF compartment can be decreased via neurosurgical intervention with CSF diversion via an extra ventricular drain (EVD) or lumbar drain.

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 aneurysmal subarachnoid hemorrhage (aSAH) is estimated at 10 per 100,000. (3) 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. (4)

Patients often present with a thunderclap, worst headache of their life and photophobia, which is the hallmark sign of an acute aSAH. Other symptoms include: nausea, vomiting, meningismus, brief loss of consciousness and focal neurological deficits. (4)

Initial work up consists of a non-contrast CT scan. Once subarachnoid blood is identified on CT scan, a CT angiogram or interventional radiology (IR) angiography should be completed to identify the location, size, and type of aneurysm to aid in operative planning (open craniotomy versus endovascular repair). The aneurysm needs to be secured as soon as possible, usually in the first 24 to 48 hours. If the patient is coagulopathic, they should be reversed with FFP or prothrombin complex. Reversal of antiplatelet therapy should be determined on a case by case basis. Grading scales are used to estimate the risk for vasospasm and predicted morbidity. (Table 1 and Table 2) The Fisher score predicts risk of vasospasm, and Hunt-Hess grade predicts patient mortality and morbidity.

**Table 3.1.1: Hunt Hess Grade**

<table>
<thead>
<tr>
<th>GRADE</th>
<th>Clinical Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Asymptomatic or mild headache +/- nuchal rigidity</td>
</tr>
<tr>
<td>2</td>
<td>CN palsy, moderate to severe headache, nuchal rigidity</td>
</tr>
<tr>
<td>3</td>
<td>Mild focal deficit, lethargy or confusion</td>
</tr>
<tr>
<td>4</td>
<td>Stupor, moderate to severe hemiparesis, early decerebrate rigidity</td>
</tr>
<tr>
<td>5</td>
<td>Deep coma, decerebrate rigidity,</td>
</tr>
<tr>
<td></td>
<td>Add 1 grade for serious systemic disease or severe vasospasm.</td>
</tr>
</tbody>
</table>

Adapted from Rosen et al (4)

**Table 3.1.2: Fisher Grade**

<table>
<thead>
<tr>
<th>Grade</th>
<th>CT findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No subarachnoid blood</td>
</tr>
<tr>
<td>2</td>
<td>Diffuse or vertical layers &lt; 1 mm</td>
</tr>
<tr>
<td>3</td>
<td>Localized clot and/or vertical layer &gt;= 1 mm</td>
</tr>
<tr>
<td>4</td>
<td>Intracerebral extension or intraventricular clot</td>
</tr>
</tbody>
</table>

Adapted from Rosen et al (4)

Mortality increases drastically if the aneurysm re-bleeds, therefore, strict blood pressure control is pivotal. The American Heart Association’s (AHA) aSAH guidelines do not state an absolute blood pressure goal, but less re-bleeding occurred in
patients whose systolic blood pressure was kept below 160 mmHg. The benefit of blood pressure control must be balanced with the risk of decreased cerebral perfusion pressure. (4) 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, but shorter acting agents are preferred. Nicardipine is quick onset and offset and has minimal effect on heart rate. Labetalol could also be used. Nitrates cause vasodilatation, which may increase cerebral blood flow, can cause reflex tachycardia and headache, which may complicate care. The use of an antifibrinolytic for clot stabilization can also be used for 24-48 hours while awaiting definitive intervention if the patient does not have coronary artery disease.

The decision to clip (via craniotomy) or coil (endovascular) is based on aneurysm morphology [i.e.: size, location, neck size and characteristics (saccular, fusiform or blister)], ease of reaching aneurysm site, and experience of the neurosurgeon.

**Complications from aSAH**

Hydrocephalus: CSF diversion via extra ventricular drain (EVD) or by serial lumbar punctures can improve the neurologic exam and relieve 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 has been shown to reduce the incidence and long-term morbidity from delayed cerebral ischemia caused by vasospasm. Other measures shown to reduce morbidity include: 3-7 days of antiepileptic medications, and maintenance of euvolemia (avoidance of hypovolemia). (4)

Hyponatremia may occur 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 in this patient population, to maintain euvolemia and normonatremia via oral salt solutions, hypertonic saline and/or a mineralocorticoid administration.

Other complications of aSAH that are less common include: neurogenic pulmonary edema, neurocardiogenic shock, and seizures.

**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-contrast 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 and oxygenation, hemodynamic support and avoidance of hypertension. The AHA stroke guidelines state systolic blood pressure should be below 140 mmHg, but there is no conclusive evidence to support a specific goal. (5) The risks of cerebral ischemia from decreased perfusion pressure, must be balanced by the benefits of hematoma expansion prevention.

Hematoma evacuation is recommended for infratentorial hematoma volume >3 ml, brainstem compression, hydrocephalus, or supratentorial hematoma <1 cm from the cortex or >30 ml in volume with deteriorating neurological status. (5)

Once the patient is stabilized, management should focus on prevention of secondary 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 Glasgow 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-contrast CT of the head to rule out intracranial hemorrhage 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 (Table 3) and other coexisting diseases. Common absolute contraindications to receiving tPA include: persistent hypertension above 185/110, INR above 1.7 or receiving anticoagulation, 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. (7)
### Table 3.1.3: NIHSS National Institute of Health Stroke Scale

<table>
<thead>
<tr>
<th>Score</th>
<th>Alertness</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Alert; Responsive</td>
</tr>
<tr>
<td>1</td>
<td>Not alert; Verbally arousable or aroused by minor stimulation</td>
</tr>
<tr>
<td>2</td>
<td>Not alert; Only responsive to repeated or strong and painful stimuli</td>
</tr>
<tr>
<td>3</td>
<td>Totally unresponsive; Responds only with reflexes or is areflexic</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Score</th>
<th>Squeeze and release hand</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Correctly answers both questions</td>
</tr>
<tr>
<td>1</td>
<td>Correctly answers one question</td>
</tr>
<tr>
<td>2</td>
<td>Does not correctly answer either question</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Score</th>
<th>Extraocular movement</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal; Able to follow pen or finger to both sides</td>
</tr>
<tr>
<td>1</td>
<td>Partial gaze palsy; gaze is abnormal in one or both eyes, but gaze is not totally paralyzed. Patient can gaze towards hemisphere of infarct, but can't go past midline</td>
</tr>
<tr>
<td>2</td>
<td>Total gaze paresis; gaze is fixed to one side</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Score</th>
<th>Visual Field</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No vision loss</td>
</tr>
<tr>
<td>1</td>
<td>Partial hemianopia or complete quadrantanopia</td>
</tr>
<tr>
<td>2</td>
<td>Complete hemianopia</td>
</tr>
<tr>
<td>3</td>
<td>Bilateral blindness, including blindness from any cause</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Score</th>
<th>Facial Palsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal and symmetrical movement</td>
</tr>
<tr>
<td>1</td>
<td>Minor paralysis; function is less than clearly normal, such as flattened nasolabial fold or minor asymmetry in smile</td>
</tr>
<tr>
<td>2</td>
<td>Partial paralysis; particularly paralysis in lower face</td>
</tr>
<tr>
<td>3</td>
<td>Complete facial hemiparesis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Score</th>
<th>Arm strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No arm drift; the arm remains in the initial position for the full 10 seconds</td>
</tr>
<tr>
<td>1</td>
<td>Drift; the arm drifts to an intermediate position prior to the end of the full 10s</td>
</tr>
<tr>
<td>2</td>
<td>Limited effort against gravity</td>
</tr>
<tr>
<td>3</td>
<td>No effort against gravity</td>
</tr>
<tr>
<td>4</td>
<td>No movement; patient has no ability to enact voluntary movement in this arm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Score</th>
<th>Leg Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No leg drift; the leg remains in the initial position for the full 5 seconds</td>
</tr>
<tr>
<td>1</td>
<td>Drift; the leg drifts to an intermediate position prior to the end of the full 5 seconds</td>
</tr>
<tr>
<td>2</td>
<td>Limited effort against gravity</td>
</tr>
<tr>
<td>3</td>
<td>No effort against gravity</td>
</tr>
<tr>
<td>4</td>
<td>No movement</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Score</th>
<th>Limb Ataxia</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal coordination; smooth and accurate movement</td>
</tr>
<tr>
<td>1</td>
<td>Ataxia present in 1 limb</td>
</tr>
<tr>
<td>2</td>
<td>Ataxia present in 2 or more limbs</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Score</th>
<th>Sensory</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No evidence of sensory loss</td>
</tr>
<tr>
<td>1</td>
<td>Mild to moderate sensory loss</td>
</tr>
<tr>
<td>2</td>
<td>Severe to total sensory loss on one side</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Score</th>
<th>Language</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal; no obvious speech deficit</td>
</tr>
<tr>
<td>1</td>
<td>Mild to moderate aphasia</td>
</tr>
<tr>
<td>2</td>
<td>Severe aphasia</td>
</tr>
<tr>
<td>3</td>
<td>Unable to speak or understand speech</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Score</th>
<th>Speech</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal; clear and smooth speech</td>
</tr>
<tr>
<td>1</td>
<td>Mild to moderate dysarthria</td>
</tr>
<tr>
<td>2</td>
<td>Severe dysarthria</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Score</th>
<th>Extinction and Inattention</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal; patient correctly answers all questions</td>
</tr>
<tr>
<td>1</td>
<td>Inattention on one side in one modality; visual, tactile, auditory, or spatial</td>
</tr>
<tr>
<td>2</td>
<td>Hemi-inattention</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Score</th>
<th>Stroke severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No stroke symptoms</td>
</tr>
<tr>
<td>1-4</td>
<td>Minor stroke</td>
</tr>
<tr>
<td>5-15</td>
<td>Moderate stroke</td>
</tr>
<tr>
<td>16-20</td>
<td>Moderate to severe stroke</td>
</tr>
<tr>
<td>21-42</td>
<td>Severe stroke</td>
</tr>
</tbody>
</table>
Medical management of ischemic stroke includes continuous hemodynamic and telemetry monitoring, supplemental oxygen to keep SpO\textsubscript{2} 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. (7)

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, and in younger patients. Edema usually occurs between post ischemic day 2–5, and can persist for 7 days. During this time, it is crucial to monitor neurological status and serum sodium. Hypertonic saline can be used to push serum sodium to 145–155 mEq/L in an attempt to reduce edema. Measures to prevent secondary injury as discussed above should be implemented. Patients below the age of 55 are at increased risk of severe cerebral edema and herniation, termed malignant cerebral edema. In this case, a decompressive hemi-craniecotomy may be needed.

Recently, an increasing number of clinical trials have demonstrated the efficacy of endovascular treatment for ischemic stroke. Based on data from 8 randomized clinical trials of endovascular treatment for acute ischemic stroke, the American Heart Association (AHA)/American Stroke Association (ASA) published revised guidelines for endovascular therapy in acute ischemic stroke. The highlights of these recommendations include the following:

1. Patients who are eligible for intravenous tPA should receive tPA regardless of whether or not endovascular therapy is also being pursued.

2. Patients who meet the following criteria should receive endovascular therapy with a stent retriever:
   A. Prestroke MRS (modified Rankin Scale) score 0 to 1 (score of 0 is no symptoms at all, 1 is no disability despite some symptoms)
   B. Acute ischemic stroke receiving tPA w/in 4.5 h according to current guidelines
   C. Occlusion of the ICA or proximal MCA (M1)
   D. Age > 18 years
   E. NIHSS score ≥ 6
   F. ASPECTS ≥ 6 (Alberta Stroke Program Early CT Score, quantitative score with a score < 7 correlating with poor functional outcome and symptomatic intracerebral hemorrhage)
G. Groin puncture can happen w/in 6 hours of symptom onset.

3. Reduced time from symptom onset to reperfusion with endovascular therapy leads to better clinical outcomes and should be achieved w/in 6 hours of symptom onset if possible.

4. After 6 hours of symptom onset, the benefit of endovascular therapy is unknown at this time.

5. In patients with anterior circulation strokes in whom tPA is contraindicated, it is reasonable to pursue endovascular treatment, although the clinical efficacy is uncertain.

6. Endovascular therapy can be considered in patients who do not meet all of the criteria listed above who have anterior circulation strokes and can be considered in patients who have occlusion of the M2 or M3 portion of the MCA, anterior cerebral arteries, vertebral arteries, basilar artery, or posterior cerebral arteries; however, there is still insufficient data in both of these populations.

7. There is no need for an observation period to assess for clinical response to intravenous tPA before pursuing endovascular therapy.

8. Endovascular therapy with stent retrievers is recommended over intra-arterial tPA whenever possible.

The role of endovascular treatment for acute ischemic strokes continues to grow, and there are ongoing trials evaluating the efficacy of different devices and benefits in extended criteria patients (those who cannot receive tPA, who are outside of tPA window, or who have occlusions other than in the anterior circulation). (8)

**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. (9)

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 drug) are considered non-responders to standard treatment and are considered to be in refractory status epilepticus (RSE). (9)

Initial treatment should be focused on seizure control, 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 diazepam 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 viral 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. (10)

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. (10)

Acute respiratory failure secondary to muscle weakness can occur rapidly. Depolarizing muscle relaxants are contraindicated because of the risk of hyperkalemia. Non-depolarizers can be used, but should be done with great caution as their use may result in prolonged weakness. (11)

**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 non-depolarizers, as MG patients are at risk for prolonged profound weakness. (11)

A paraneoplastic form of MG, called Eaton Lambert, results in weakness, but the pathogenesis 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. Daily forced vital capacity (FVC) and negative inspiratory force (NIF) are used to help gauge when intubation is necessary. 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-depolarizing NMB can cause prolonged weakness (11)

References


**Review Questions:**

1. A patient with myasthenia gravis exacerbation is admitted to the ICU to receive plasmapheresis. Daily NIF and FVC are monitored. On assessment, she has increased work of breathing and is anxious with copious oral secretions. Her NIF is -15 and FVC 800 ml. Which of the following options would be the BEST choice for intubation?

   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

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 vasoospasm. Her serum Na has decreased from 140 to 131 mEq/L in the last 36 hours. Her CVP is 6 cm H₂O and she is 1L 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. 0.5 gm/kg of mannitol
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 will lower the ICP the fastest?

a. Furosemide

b. Mannitol bolus

c. 23.4% Saline

d. Elevate the head of bed
Physiology

Normal intracranial pressure (ICP) is between 8-15 mmHg. (1) Under normal physiologic conditions, there is a stable equilibrium between the components within the rigid cranial vault: blood, brain parenchyma, and cerebrospinal fluid (CSF). Within the fixed volume of the skull, there is little ability to compensate for increases in the volume of any of the three components. When there is an increase in the volume of one component, the volume of the other components decrease, to a point. However, after the limited capability for compensation is exhausted, ICP increases exponentially with any additional increase in intracranial volume. This is known as the Monro-Kellie Doctrine. Examining each of the cranial components allows understanding of normal physiology, as well as aberrations causing elevated ICP.

Patient Case:
A 41-year-old woman is involved in a high speed motor vehicle accident and hits a tree. In the emergency room her vital signs are as follows: temperature 36.9°C, HR 122 bpm, BP 88/62 mmHg, RR 14/min, SpO₂ 100% on 4L nasal cannula O₂. On exam, she has numerous superficial abrasions, an actively bleeding left eyebrow laceration, clear breath sounds bilaterally, and normal heart sounds. Her GCS is 6 (E1, V1, M4) with pupils 4mm and equally reactive.
Cerebral blood flow (CBF) and cerebral blood volume (CBV) are influenced by multiple factors, but the main control of CBF is autoregulation. Autoregulation is the brain’s ability to maintain a constant CBF when systemic mean arterial pressure (MAP) is between 60-160 mmHg. When BP is outside the range of autoregulation, CBF is proportional to MAP.

In addition to autoregulation, the brain is responsive to metabolic conditions. There is flow-metabolism coupling of CBF in which increased cerebral cellular metabolism produces excess tissue metabolites, causing increased CBF. States of increased metabolism include seizure and fever. In the same way, high pCO₂ or low pO₂ will cause an increase in CBF. The response to hypercarbia is much more robust than the response to hypoxemia.

Any of these mechanisms of CBF control can lead to an increase in intravascular CBV leading to increased ICP. Extravascular blood increases total CBV and is always pathologic. It can present clinically as subarachnoid hemorrhage (SAH), subdural hematoma (SDH), epidural hematoma (EDH), intraparenchymal hemorrhage (IPH) or intraventricular hemorrhage (IVH).

Cerebrospinal fluid

Cerebrospinal fluid is produced by the choroid plexus at a rate of 20ml/kg/day (approximately 500ml/day in adults). The same volume is resorbed daily by the arachnoid villi resulting in stable intracranial CSF volume. Production of CSF greater than absorption leads to hydrocephalus. There are two distinct types of hydrocephalus: obstructive and communicating.

Obstructive hydrocephalus is when the ventricular system within the brain is disrupted and the ventricles are no longer patently connected. This causes buildup of CSF that cannot get to the arachnoid villi to be resorbed. Communicating hydrocephalus is a problem with resorption of CSF. This can be caused by damage to the arachnoid villi or by blood in the subarachnoid space.

Brain

The third component in the ICP equation is the brain parenchyma. Also falling into the category of increased parenchyma are space occupying lesions which can refer to tumors (benign or malignant), as well as abscesses. Increased brain parenchyma presents as cerebral edema and there are two types: vasogenic and cytotoxic.

Vasogenic edema is caused by breakdown or inundation of the blood brain barrier (BBB). This occurs when osmotic and hydrostatic pressure favor plasma water leaving the intravascular space into the extravascular space. This can occur with rapid electrolyte or osmolar shifts, hypertensive emergency, and venous outflow obstruction. Additionally, the BBB becomes more permeable (leaky) secondary to inflammation from tumors or...
abscesses. Cytotoxic cerebral edema is caused by direct neural injury and cell death resulting in cellular edema. This is seen in traumatic brain injury (TBI) and ischemic stroke.

**Monitoring**

Monitoring ICP is required to calculate cerebral perfusion pressure (CPP). CPP = MAP – ICP (or CVP if it is higher than ICP). Normal CPP is 70-100 mmHg. There is no evidence based CPP goal, but 60-70 mmHg is commonly used. EEG data consistently show generalized slowing at CPP of 50 mmHg or less. ICP monitoring allows for assessment of treatment response or progression of the primary process. The definition of elevated ICP, also called intracranial hypertension, is ICP >20 mmHg for 5 minutes or more in the absence of noxious stimuli such as suctioning.

Noninvasive monitoring strategies involve frequent clinical reassessment for changes in mental status or repeated head CT scans. Radiologists are able to see trends by comparing repeated scans. (2) However this method is intermittent, inexact, expensive, and exposes the patient to radiation.

Objective monitoring of ICP can only be done invasively. There are many different ways, but the most common method and gold standard is via an intraventricular catheter (ventriculostomy catheter) connected to an external pressure transducer. The catheter is most commonly inserted in the lateral ventricle. These procedures are typically performed by neurosurgeons or neurocritical care providers. The entire system of catheter, pressure transducer and drainage bag is called an extraventricular drain (EVD). EVDs have therapeutic benefit in that CSF can be removed to lower ICP. Risks of placing an EVD include bleeding and infection. Additionally, over-drainage of CSF may result in a subdural hematoma or herniation.

Subdural microtransducers can be used to measure ICP beneath the dura in a particular location. The measurement obtained may not always reflect the global ICP. Intraparenchymal microtransducers allow for the measurement of ICP within the brain parenchyma. They allow precise measurement of ICP in a certain area of interest in the brain. However, they are not useful if placed incorrectly and cannot be recalibrated once inserted. Both are placed by neurosurgeons or neurocritical care providers with the same risks as an EVD, but without the therapeutic benefit of CSF drainage.

Indications for invasive ICP monitoring are somewhat subjective except in the setting of TBI (Table 1). In TBI, the patient must have a Glasgow Coma Score (GCS) <9 after resuscitation with an abnormal head CT, OR GCS <9 with a normal head CT AND 2 of the following: age >40, SBP <90mmHg, or any motor posturing. (3) Other indications for invasive ICP monitoring include: SAH, symptomatic hydrocephalus, acute liver failure, massive hemispheric ischemic stroke, imaging indicating elevated ICP, or
Table 3.2.1 Indications for Invasive ICP Monitoring

<table>
<thead>
<tr>
<th>Traumatic Brain Injury:</th>
</tr>
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<tbody>
<tr>
<td>1. GCS &lt; 9 and abnormal head CT or</td>
</tr>
<tr>
<td>2. GCS &lt; 9 and 2 of the following: age &gt; 40 years; SBP &lt; 90 mmHg, any motor posturing</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
</tr>
<tr>
<td>Symptomatic hydrocephalus</td>
</tr>
<tr>
<td>Acute liver failure</td>
</tr>
<tr>
<td>Hemispheric ischemic stroke</td>
</tr>
<tr>
<td>Imaging indicating elevated ICP</td>
</tr>
<tr>
<td>Post neurosurgical intervention</td>
</tr>
</tbody>
</table>

Management

Normal ICP is <15 mmHg, however, the goal when managing elevated ICP is to maintain ICP <20 mmHg. In the setting of TBI. Studies show that patients with less intracranial hypertension have better outcomes. The aim of ICP and CPP monitoring and management is to ensure adequate tissue perfusion and oxygenation, prevent ischemia, and prevent progression to herniation.

The Neurocritical Care Society treatment protocols and guidelines are published as The Emergency Neurologic Life Support (ENLS) algorithm for management of elevated ICP. (4) Presented here is a summary of those recommendations (Figure 1).

Tier 0 includes initial noninvasive treatment for the patient with suspected elevated ICP. It includes raising the head of bed (HOB) >30°, treatment of hyperthermia, correction of hyponatremia, adequate treatment of pain, addressing agitation, ensuring adequate cerebral venous drainage (tracheostomy ties and cervical collars are major offenders), and leveling and re-zeroing.
ICP transducer (if present). High dose corticosteroids are indicated in cases of vasogenic edema caused by a tumor, abscess or neuroinflammatory process. There is no role for steroids in any other cause of elevated ICP. Consider checking labs and imaging to further explain etiology of elevated ICP. Treatment aims include an ICP <20 mmHg and CPP 60-70 mmHg. If Tier 0 interventions fail to improve ICP, move to Tier 1.

**Tier 1** treatment strategies include securing the airway, short term hyperventilation (effective for up to 6 hours), bolusing mannitol 0.5-1 mg/kg, consideration of emergent placement of EVD, drainage of 5-10 ml CSF if EVD in place, and begin hypertonic saline (2-3%) infusion at 10-20 ml/hr. If starting hypertonic saline infusion, check labs every 2-4 hours for a goal serum sodium of 140-150 mEq/L. Remember that concentrations of NaCl >2% require central venous access to administer. Consider head imaging if not yet obtained. Mannitol was the gold standard osmotic therapy for lowering ICP before hypertonic saline was readily available. Multiple meta-analyses show that hypertonic saline is slightly more effective and has a longer effect at lowering ICP than equimolar doses of mannitol. (5) If no improvement in ICP, continue to Tier 2.

**Tier 2** interventions include hypertonic saline (2-23.4%) boluses to quickly attain serum sodium levels within goal parameters or starting propofol to reduce ICP and CMRO\textsubscript{2}. Hypertonic saline boluses have been proven to reverse transtentorial herniation. Propofol infusion decreases CMRO\textsubscript{2} and CBF, but also decreases MAP which can decrease CPP. If there is no improvement in ICP, surgical decompression should be considered.

Surgical decompression via craniectomy allows for brain swelling and relieves elevated ICP as the cranial vault is no longer intact. Surgical removal of blood clots, abscesses or masses can also alleviate elevations in ICP. However, not all patients are surgical candidates and surgery comes with its own inherent risks.

If the patient’s intracranial pressure has not responded to Tier 2 interventions and the patient is not a surgical candidate, Tier 3 options are the last available interventions to lower ICP. These interventions have a significantly higher risk of morbidity and mortality associated with them.

**Tier 3** interventions include burst suppression on EEG via barbiturate coma or hypothermia. Both interventions decrease CMRO\textsubscript{2} and may allow time for other testing and treatment options to be completed. Also at this tier, vasopressors may be used to artificially increase MAP in order to optimize CPP.

*This chapter is a revision of the original chapter authored by Matthew R Hallman MD.*

**References:**


**Review Questions:**

1. Which of the following would decrease intracranial pressure:

   a. Vigorous suctioning

   b. Trendelenberg position

   c. Hyperventilation

   d. Administration of hypotonic IV fluids

2. Which of the following is not a Tier 0 intervention for elevated intracranial pressure?

   a. Head of bed > 30°

   b. Hypertonic saline

   c. Reduction of hyperthermia

   d. Treatment of pain and agitation

3. In which of the following scenarios are systemic corticosteroids indicated?

   a. Intracerebral tumor with elevated ICP

   b. Subarachnoid hemorrhage with elevated ICP

   c. Right thalamus ischemic stroke with elevated ICP

   d. Traumatic brain injury with elevated ICP
Delirium in the Intensive Care Unit

Delirium is a prevalent neuropsychiatric syndrome characterized by acute waxing and waning levels of consciousness, inattention, and disturbed perception and cognition. As many as 8 in 10 mechanically ventilated ICU patients have been reported to develop delirium during their course of ICU care, approximately twice the prevalence of delirium in patients who do not require ventilatory support. Three subtypes of delirium describe two constellations of specific symptoms in each domain. Hyperactive delirium encompasses those symptoms associated with excessive or distorted cognition, including hallucinations, delusions, agitation, and...
restlessness. Hypoactive delirium presents with symptoms associated with diminished cognition, including lethargy, behavioral withdrawal, and impaired motor skills. Patients who display cardinal features of both hyperactive and hypoactive delirium are diagnosed with the mixed subtype of the syndrome.

In critically ill adults, delirium has been associated with a significant worsening of patient-centered outcomes, including hospital mortality, mortality at 6 months, increased intensive care unit (ICU) and hospital length of stay, and social and functional dependence upon discharge. During admission to the intensive care unit, delirium is also associated with longer requirements for mechanical ventilation and an increased use of physical and chemical restraints. Although hyperactive delirium may appear to require greater resources to manage the dramatic symptoms, hypoactive delirium has historically been associated with the greatest risk of poor outcomes following discharge from the ICU. Notably, both clinical phenotypes may represent either medication-induced, rapidly reversible delirium or persistent delirium of critical illness. Evidence is mounting that persistent delirium, regardless of the clinical phenotype, is associated with poor patient-related outcomes during and following treatment in the ICU. (1)

In contrast to other commonly encountered diseases with neuropsychiatric sequelae requiring ICU care, such as severe alcohol withdrawal or hepatic encephalopathy, no single pathophysiological mechanism has yet been identified to fully explain the delirium of critical illness (ICU delirium). Considered a form of acute organ dysfunction, the symptoms of ICU delirium are nonspecific and related to complex relationships between metabolic derangements, neurotransmitter imbalance, inflammation, and alterations in cerebral perfusion. These physiological states are instigated or exacerbated by acute, severe injury or illness, deliriogenic medications, dysregulated and inadequate sleep cycles, immobility, pain, and the disorientation of artificial, unfamiliar ICU environments.

**Risk Factors**

A multitude of risk factors are associated with an increased risk for the development of delirium during admission to the ICU (Table 1). Age, genotype, tobacco use, alcohol dependence, hypertension, depression, and baseline neurocognitive impairment exemplify predisposing risk factors that are inherent to the patient prior to critical illness, as is the severity of illness (e.g., APACHE II score) on admission to ICU-level care. Precipitating risk factors are those the patient acquires while in intensive care including mechanical ventilation, anemia, hypotension, lack of daylight, isolation, immobility, disturbed sleep, coma, exposure to benzodiazepines, and the number and variety of medication infusions used during the course of their illness (Table 2). Acquired, modifiable risk factors are the targets of interventions intended to prevent or manage delirium in the
### Table 3.3.1 Risk Factors for ICU Delirium

<table>
<thead>
<tr>
<th>Patient Factors</th>
<th>Acute Illness Factors</th>
<th>Treatment Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol/tobacco (use or withdrawal)</td>
<td>Sepsis</td>
<td>Impaired sleep/noisy environments</td>
</tr>
<tr>
<td>Increased age (&gt;65 years)</td>
<td>Fever</td>
<td>Medications (see table 2)</td>
</tr>
<tr>
<td>Depression</td>
<td>Shock</td>
<td>Foley catheters</td>
</tr>
<tr>
<td>Dementia</td>
<td>Anemia</td>
<td>Gastric tubes</td>
</tr>
<tr>
<td></td>
<td>Respiratory disease (hypercarbia or hypoxemia)</td>
<td>Immobility</td>
</tr>
<tr>
<td>Myocardial dysfunction</td>
<td>Sensory deprivation (hearing aids, glasses, dentures)</td>
<td></td>
</tr>
<tr>
<td>Electrolyte abnormalities (hyponatremia, azotemia, hypocalemia, metabolic acidosis)</td>
<td>Fecal or urinary retention</td>
<td></td>
</tr>
</tbody>
</table>

*ICU DELIRIUM(s) is a mnemonic to aid clinicians in identifying the risk factors and etiology of ICU delirium. One of many available at [http://www.icudelirium.org/terminology.html](http://www.icudelirium.org/terminology.html)*

intensive care unit. (2) Numerous mnemonic tools are available to aid clinicians in identifying the source(s) of ICU delirium (ICU DELIRIUMS).

### Table 3.3.2 Medications Associated with ICU Delirium

<table>
<thead>
<tr>
<th>Prescription Drugs</th>
<th>Nonprescription Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazapines</td>
<td>Diphenhydramine</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>Mandrake</td>
</tr>
<tr>
<td>Narcotics</td>
<td>Henbane</td>
</tr>
<tr>
<td>Antiparkinson agents</td>
<td>Jimson week</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>Belladonna extract</td>
</tr>
<tr>
<td>H₂ blockers</td>
<td>Valerian</td>
</tr>
<tr>
<td>Scopolamine</td>
<td>Loperamide</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>TCA's</td>
</tr>
<tr>
<td>Lithium</td>
<td>Digitalis</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>Muscle relaxants</td>
</tr>
<tr>
<td>Steroids</td>
<td></td>
</tr>
</tbody>
</table>

### Prevention

Over the past decade, two bundled delirium prevention protocols have emerged as effective strategies to mitigate the incidence and prevalence of delirium in the ICU. The “Awakening and Breathing Coordination, Delirium monitoring/management, and Early exercise/mobility” (ABCDE) bundle involves target-based
sedation and spontaneous awakening and breathing trials that aim to liberate patients from the restraints of mechanical ventilation and pharmacological sedation as soon as the removal of such interventions are safe. (3) The “Pain, Agitation, and Delirium” (PAD) clinical guideline bundle supplements these practices with specific, evidence-based protocols that address adequate pain management, early mobilization, and family involvement during the patient’s residence in the ICU. (4)

These and other prominent clinical practice guidelines outline the importance of non-pharmacologic interventions prior to the use of medications. In addition to an ongoing evaluation of the need for mechanical ventilation and sedation, pain management, and family empowerment, patients at risk for delirium in the ICU benefit from environmental adaptations that mimic diurnal rhythms, including a protected sleep schedule in a dark, quiet room. Consistency in personnel and locations and deliberate reorientation may also decrease the risk of delirium in the ICU. In the United States, early exercise and mobility, often in the form of bedside physical and occupational therapy sessions, is emphasized as an empirically effective and safe intervention for all patients at risk for delirium.

Although pharmacologic prophylaxis of delirium with medications is theoretically attractive, little evidence supports the use of medications for this purpose. Numerous trials have evaluated the use of typical and atypical antipsychotics, steroids, cholinergic agents, and statins in the prevention of delirium. Currently, no evidence supports the use of medications for the prophylaxis of delirium in undifferentiated adult MICU and SICU patients. (4,5)

**Diagnosis**

Given the fluctuating nature of delirium, twice or thrice daily surveillance – optimally coordinated with sedation breaks to distinguish medication-induced from persistent delirium- is required to adequately detect its onset and progression. Although psychiatric evaluation continues to be the gold standard for diagnosis of delirium, objective clinical tools have been developed and validated to aid health care providers in routine monitoring of ICU patients for delirium. When used in concert with the Richmond Agitation-Sedation Scale, the Confusion Assessment Method for the ICU (CAM-ICU) is a 4 item decision tool based on DSM-III criteria that queries each patient for fluctuating mental status, inattention, altered level of consciousness, and disorganized thinking. (Figure 1) It has been validated against DSM-IV criteria, adapted for use in nonverbal patients and is available in multiple languages. The Intensive Care Delirium Screening Checklist (ICDSC) is fundamentally based on DSM-IV criteria, and accounts for symptom progression in its screening algorithm (Table 3). (7) There is significant reliability between both tools, (8) so tool selection should be determined by resource and training of the ICU staff. In all patients, regardless of the detection method, delirium is often masked by language barriers, underlying...
Table 3.3.3 Intensive Care Delirium Screening Checklist.

<table>
<thead>
<tr>
<th>Feature 1: Acute Onset or Fluctuating Course</th>
<th>Score</th>
<th>Check here if Present</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the pt different than his/her baseline mental status? OR Has the patient had any fluctuation in mental status in the past 24 hours as evidenced by fluctuation on a sedation scale (i.e., RASS, GCS, or previous delirium assessment?)</td>
<td>Either question Yes →</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feature 2: Inattention</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Letters Attention Test (See training manual for alternate Pictures)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Directions: Say to the patient, “I am going to read you a series of 10 letters. Whenever you hear the letter ‘A’,” indicate by squeezing my hand.” Read letters from the following letter list in a normal tone 3 seconds apart.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAVEHAART</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Errors are counted when patient fails to squeeze on the letter “A” and when patient squeezes on any letter other than “A.”</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feature 3: Altered Level of Consciousness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present if the Actual RASS score is anything other than alert and calm (zero)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feature 4: Disorganized Thinking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes/No Questions. (See training manual for alternate set of questions)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Will a stone float on water? 2. Are there fish in the sea? 3. Does one pound weigh more than two pounds? 4. Can you use a hammer to pound a nail?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Errors are counted when the patient incorrectly answers a question.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Command</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Say to patient: “Hold up this many fingers” (Hold 2 fingers in front of patient) “Now do the same thing with the other hand” (Do not repeat number of fingers) *If pt is unable to move both arms, for 2nd part of command ask patient to “Add one more finger.” An error is counted if patient is unable to complete the entire command.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall CAM-ICU</td>
<td>Criteria Met →</td>
<td>CAM-ICU Positive (Delirium Present)</td>
<td>Criteria Not Met →</td>
<td>CAM-ICU Negative (No Delirium)</td>
</tr>
<tr>
<td>Feature 1 plus 2 and either 3 or 4 present = CAM-ICU positive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


...dementia, and comorbid conditions that alter cognition and attention. Clinicians must maintain a high-level of suspicion for delirium, especially for reversible delirium associated with the use of sedative medications.

Management
First and foremost, the treatment of ICU delirium starts by addressing each patient’s critical illness. Significant imbalances in volume status, electrolytes, glucose, nutrition status, and oxygen delivery should be optimized first. Deliriogenic medications should be discontinued or reduced. Interventions including adequate analgesia, environmental adaptations that promote continual reorientation and natural sleep, physical and occupational therapy, and interaction with familiar family and caregivers should be emphasized if it is safe to do so.

Medications may augment these strategies in the management of delirium. Although short-term pharmacologic or physical restraints may be required when patient safety is compromised, there is no evidence to support the use of agents like haloperidol for treatment or prevention. Cholinergic agents, statins, and steroids are also without benefit in the treatment of delirium. However, the atypical antipsychotic, quetiapine, may reduce the duration of delirium in MICU and SICU patients. Similarly, when compared to benzodiazepines in ICU patients requiring sedation, dexmedetomidine has been associated with an increase in days without delirium. Furthermore, when compared to haloperidol in the management of intubated patients with hyperactive delirium, dexmedetomidine was associated with a shorter duration of delirium. Both medications carry the risk of significant side effects (QTc prolongation for haloperidol, and hypotension and bradycardia for dexmedetomidine). As in all other care settings, the risks and benefits of each medications should be carefully considered prior to administration. In all cases, the short-term use of physical and pharmacological restraints should be discontinued as soon as it is safe to do so, and all other agents used in the treatment of delirium should be discontinued prior to the patient’s discharge to standard care.

Clinical practice guidelines addressing the treatment of critically ill patients with delirium are expected to evolve, as the efficacy and safety of many interventions are currently under active investigation. (2,4)

Sequelae of Critical Illness

Following discharge from the intensive care unit, patients and their families undergo an often prolonged period of rehabilitation in order to regain social and occupational function and physical well-being lost during the critical illness. As post-ICU survival time continues to increase, two conditions are of particular significance in the successful rehabilitation of post-discharge ICU patients.

ICU Acquired Weakness

Critical-illness polyneuropathy/critical-illness myopathy (CIP/CIM) together encompass the constellation of symptoms associated with the syndrome ICU acquired weakness (ICU-AW). As with other conditions specific to critically ill patients, the underlying disease mechanisms are complex and heterogeneous. Currently, muscle catabolism due to immobility and hyperglycemia have
been reported to be modifiable risk factors for this syndrome and thus targeted for interventions.

CIP is a disease of primary axonal degeneration without demyelination that preferentially affects proximal neuromuscular group (axial skeleton joint girdles) motor nerves in a symmetric pattern. The disease occasionally affects the respiratory muscles, but usually spares facial and ocular muscles. Since nerve myelin is preserved, electrophysiological studies in affected patients will reveal normal nerve conduction velocity alongside reductions in the amplitude of compound muscle action potentials (CMAPs). Likewise, CIM is a primary myopathy that shares a phenotype with CIP, including attenuation of CMAPs, but it is distinguished by typically mild elevations in creatine kinase that are absent in CIP. The clinical manifestation of CIP and CIM is often confounded by the effect of glucocorticoids, neuromuscular blocking agents, and other variables that underlie physical dysfunction in ICU patients.

There is a broad differential diagnosis for persistent weakness in ICU patients. The diagnosis of ICU-AW in one of exclusion, sought after a critically ill patient’s ongoing weakness has no other plausible etiology. Serial administration of the Medical Research Council (MRC) scale for muscle group strength with scores less than 48 may indicate the need for electrophysiological or histological evaluation. Current evidence supports the use of moderate glucose control and early exercise and mobility. (9,10)

Post-Intensive Care Syndrome

Post-Intensive Care Syndrome (PICS) encompasses multiple long-term impairments across emotional, cognitive, and physical domains. Patients who survive critical illness and their families are at risk for PICS, which may present as a cluster of related symptoms or as a series of heterogeneous and multidimensional symptoms. Depression, anxiety, and posttraumatic stress disorder (PTSD) are common emotional sequelae associated with PICS, whereas new or worsened neurocognitive impairment and decrements in physical function and well-being, including ICU-AW, cachexia, sexual dysfunction, chronic pain, and organ dysfunction are representative of the cognitive and physical sequelae of PICS. (11)

As PICS is a condition that is under active investigation, a formal, standardized definition, diagnostic criteria, and management protocols are forthcoming. Current evidence indicates that ICU delirium is a cardinal risk factor for cognitive and emotional symptoms attributed to PICS, such that interventions intended to decrease the risk of delirium in ICU patients are also protective of PICS upon discharge. (12) Diagnosis relies on a high index of suspicion and standardized neurocognitive tests, emotional inventories, and quantitative evaluation of physical function, including surveillance for ICU AW.

Trials to evaluate the efficacy and safety of prevention and rehabilitation initiatives are currently underway. ICU diaries may
mitigate the symptoms of PTSD in patients with PICS. Effective interventions otherwise target modifiable risk factors associated with PICS, including those that predispose critically-ill patients to ICU delirium and ICU AW. (11)

**Links**

CAM-ICU Training Manual:  
http://www.icudelirium.org/docs/CAM_ICU_training.pdf

CAM-ICU Language Options:  
http://www.icudelirium.org/delirium/languages.html

CAM-ICU and ICSDC Tools  
http://www.icudelirium.org/delirium/monitoring.html

Delirium Mnemonic Tools  
http://www.icudelirium.org/terminology.html

**References:**


Review Questions:

1. Which of the following subtypes of ICU delirium has been reported to carry the greatest risk of death and long-term cognitive impairment?
   a. Hyperactive
   b. Hypoactive
   c. Mixed
   d. Organic

2. Which of the following combinations 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

3. Of the following interventions, which is best supported by current evidence to help prevent the onset of delirium in the ICU?
   a. Avoidance of benzodiazepines
   b. Adequate analgesia
   c. Opening the windows during the daytime to allow natural light
   d. Early mobilization and rehabilitation

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. Quetiapine
   c. Risperidone
   d. Dexmedetomidine
Chapter 4

Respiratory System Topics
Institution of invasive mechanical ventilation can be a lifesaving procedure in critically ill patients. However, the extremes of physiology and poor physiologic reserve encountered in the ICU place patients in need of urgent or emergent airway management at significantly increased risk of serious, life-threatening complications when compared to surgical patients in the operating room. Familiarity with site-specific airway equipment, availability and communication with ICU team members, and patient-specific anticipation of airway management needs are essential components of a safe airway placement plan. Airway bundles are standardized.

**Key Points:**

- The 3 major indications for airway management in the ICU are need for: (1) oxygenation; (2) ventilation; and/or (3) to provide a patent airway.

- Patient-specific factors will determine the airway management plan: awake intubation, routine asleep intubation, rapid sequence intubation.

- All robust airway management plans have several backup options should the first fail.

- Complications of endotracheal intubation and invasive mechanical ventilation are more common in the ICU than in the OR. Optimal patient positioning and the use of an ICU-specific intubation bundle can minimize these risks.

**Patient Case:**
A 22-year-old man 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.
protocols specific to critically ill patients that aid operators in the development and execution of safe airway management in the ICU.

**Indications for Invasive Airway Management**

There are three general indications for invasive airway management: (1) the need for oxygenation, (2) the need for ventilation, or (3) the need for a patent airway (Table 1).

**Table 4.1.1 Indications for Airway Management**

<table>
<thead>
<tr>
<th>Need for Oxygenation</th>
<th>Need for Ventilation</th>
<th>Need for a Patient Airway</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxemic respiratory failure</td>
<td>Hypercapnic respiratory failure</td>
<td>Airway obstruction or suppressed upper airway reflexes</td>
</tr>
<tr>
<td>CHF</td>
<td>Neuromuscular disease</td>
<td>Facial or neck trauma</td>
</tr>
<tr>
<td>Pulmonary contusion</td>
<td>Cervical spinal cord injury</td>
<td>Oropharyngeal or laryngeal edema</td>
</tr>
<tr>
<td>ALI/ARDS</td>
<td>Diaphragmatic paralysis</td>
<td>TBI, stroke, SAH</td>
</tr>
<tr>
<td>Morbid obesity</td>
<td>COPD exacerbation</td>
<td>GCS &lt; 9</td>
</tr>
<tr>
<td></td>
<td>Severe asthma exacerbation</td>
<td>Sustained seizure activity</td>
</tr>
<tr>
<td></td>
<td>Drug intoxication</td>
<td>Copious secretions</td>
</tr>
</tbody>
</table>

*These categories are not mutually exclusive, thus the indication may fall into more than one category.*

Application of positive airway pressure aids in maintaining or increasing functional residual capacity (FRC), which improves respiratory mechanics, decreases intrapulmonary shunt, and improves hypoxemia. Other specific indications for invasive mechanical ventilation are 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. A more comprehensive list of specific indications by category is presented in *Table 1*. Critically ill patients may benefit from intubation for any combination of these indications. For example, a patient suffering neuromuscular weakness due to Guillain-Barré syndrome may have atelectasis, a decreased FRC, and elevated intrapulmonary shunt fraction (need for oxygenation). Additionally, bellows fatigue and increased elastic work of breathing 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 a patent airway). (1,2)

**Intubation in the ICU**

Ideally, intubation in the ICU is performed with the same level of advance preparation as in the OR, with selection of a risk-minimizing, patient-specific airway management plan, 2-3 backup airway management plans, and at least two experienced...
operators. Intubation bundled checklists aid operators in maintaining a high-level of advanced preparation (Table 2). (3,4)

**Table 4.1.2 ICU Intubation Bundle Worksheet**

<table>
<thead>
<tr>
<th>Prior to Intubation</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Two operators available</td>
<td>2. Small fluid bolus (250-500 ml) in absence of cardiogenic pulmonary edema</td>
<td>3. Long-term sedation available</td>
</tr>
</tbody>
</table>

**Intubation**

1. Rapid sequence induction: propofol, etomidate or ketamine followed immediately by succinylcholine in the absence of hyperkalemia, severe acidosis, neuromuscular disease, spinal cord trauma or burn injury > 48 hour. Rocuronium can be used to replace succinylcholine
2. Cricoid pressure (Sellick maneuver) until confirmation of secure airway

**After Intubation**

1. Confirmation with capnography, followed by CXR
2. Initiation of long-term sedation
3. Initiation of mechanical ventilation with TV of 6-8 ml/kg

Adapted from Jaber et al (3)

**Patient Considerations**

In all critically ill patients for whom invasive ventilation may be a necessary therapeutic step, perform an external airway examination during the routine physical exam. With familiarity of patient-specific factors already in mind, an urgent or emergent airway management plan may be more efficiently tailored to meet the patient’s needs. Repeat the airway examination and a thorough review of the patient’s hemodynamic status, head and neck precautions/limitations, current medications, allergies, recent laboratory results, and mental status prior to intubation if possible, especially when selecting backup airway management plans.

The external airway examination attempts to predict the ease of mask ventilation and intubation an operator will encounter with

**Table 4.1.3 Characteristics Predictive of Difficulty with Ventilation or Intubation**

<table>
<thead>
<tr>
<th>Predictors of Difficult Ventilation</th>
<th>Predictors of Difficult Intubation</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI &gt; 30</td>
<td>Facial trauma or swelling</td>
</tr>
<tr>
<td>Macroglossia</td>
<td>Airway swelling or bleeding</td>
</tr>
<tr>
<td>Edentulous</td>
<td>Anatomical anomalies</td>
</tr>
<tr>
<td>Facial trauma or swelling</td>
<td>Thyromental distance &lt; 3 fbs</td>
</tr>
<tr>
<td>Snoring</td>
<td>Mouth opening &lt; 2 fbs</td>
</tr>
<tr>
<td>Limited jaw protrusion</td>
<td>Decreased neck ROM</td>
</tr>
<tr>
<td></td>
<td>Significant overbite</td>
</tr>
<tr>
<td></td>
<td>Short, thick neck</td>
</tr>
<tr>
<td></td>
<td>Mallampati class &gt; 2</td>
</tr>
</tbody>
</table>

* fbs = fingerbreaths; ROM = range of motion. Adapted from Barasch et al (12)
each patient. Classic risk factors for a difficult airway (Table 3), including Mallampati grading (Figure 1), (5) have been shown to have poor positive and negative predictive value in forecasting a difficult intubation or laryngeal view on direct laryngoscopy (e.g., Cormack-Lehane Score; Table 4). (6,7,8) For the purposes of procedural planning, airway difficulty should be expected. A 7-item score has recently been developed and validated to predict difficult intubation in critically ill patients (Table 5), (9) and may provide the most accurate guidance for operators in the ICU.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>All or part of glottis visible</td>
</tr>
<tr>
<td>2</td>
<td>Posterior glottis only</td>
</tr>
<tr>
<td>3</td>
<td>Only epiglottis is visible</td>
</tr>
<tr>
<td>4</td>
<td>No laryngeal structures visible</td>
</tr>
</tbody>
</table>

Adapted from Cormack and Lehane (6)

Procedure Selection, Equipment and Medications

First, determine the urgency of the clinical situation. In all but the most emergent airway management scenario, ICU staff and a respiratory therapist should be notified of an impending intubation prior to the procedure. Whenever possible, discuss the risks and benefits of intubation and mechanical ventilation with the patient and his or her designated healthcare representatives. Next, use the patient’s clinical status to select an airway management approach that minimizes risk to the patient: awake, routine asleep, or rapid sequence intubation.

An awake intubation is generally performed with a fiberoptic device after topicalization of the airway when there is significant concern for the inability to adequately mask-ventilate the patient. This approach may require special equipment and advanced
training that may or may not be available in the ICU setting. The technique also requires time and a patient who is adequately cooperative and clinically stable. It is generally reserved for patients with significant head and neck pathology, or oropharyngeal obstruction, including severely limited oral opening. The sensory nerves of the airway - glossopharyngeal, superior laryngeal and the recurrent laryngeal – are anesthetized prior to the procedure to prevent excessive gagging and coughing. Sedation with minimal changes in respiratory drive or muscle tone can be achieved with low-dose infusions of either dexmedetomidine or ketamine.

Routine asleep intubation is performed when the operator is reasonably confident that the patient can be ventilated by mask and intubated, and when there is low concern for aspiration of gastric contents during the procedure. In this approach, the ability to bag mask ventilate the patient is verified before a paralytic is administered. For these reasons, it is often a more conservative and safer choice to select rapid sequence intubation (RSI) in critically ill patients for whom the risk of aspiration is generally high. An RSI involves the immediate administration of a neuromuscular blocking agent after adequate sedation is delivered, while applying cricoid pressure (Sellick maneuver) until the airway is secure.

Although direct laryngoscopy is the most common procedure for routine asleep and rapid sequence intubation, establishing a secure airway can be facilitated with adjunct equipment, including video laryngoscopy, intubating LMA, Eschmann stylet or a flexible fiberoptic bronchoscope.

Patient positioning should be optimized prior to intubation to the extent possible permitted by time and clinical status. Back-up head-elevated (BUHE; Figure 2) positioning, achieved by (1) placing the patient’s head even with the top of the mattress in Trendelenberg; (2) elevating the head of the bed to 30 degrees; and (3) using a bump (towel roll is common) to place the spine in cervical flexion with extension at the atlanto-occipital joint (“sniff” position), significantly decreases the risk of a difficult intubation.

### Table 4.1.5 MACOCHA Score Calculation

<table>
<thead>
<tr>
<th>Factors</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient Factors</strong></td>
<td></td>
</tr>
<tr>
<td>1. Mallampati score III or IV</td>
<td>5</td>
</tr>
<tr>
<td>2. Obstructive sleep apnea</td>
<td>2</td>
</tr>
<tr>
<td>3. Cervical spine immobility</td>
<td>1</td>
</tr>
<tr>
<td>4. Mouth opening &lt; 3 cm</td>
<td>1</td>
</tr>
<tr>
<td><strong>Disease Factors</strong></td>
<td></td>
</tr>
<tr>
<td>1. Coma</td>
<td>1</td>
</tr>
<tr>
<td>2. Hypoxemia</td>
<td>1</td>
</tr>
<tr>
<td><strong>Airway management experience</strong></td>
<td></td>
</tr>
<tr>
<td>1. Junior operator *</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
</tr>
</tbody>
</table>

*Junior operator defined by fewer than 12 months anesthesia-specific airway training (10) Scored from 0 to 12. 0 = easy, 12 = very difficult. Adapted from DeJong et al (4)
intubation techniques are discouraged until there is no safe alternative. A surgical airway is always a viable option if no other airway can be established. Site-specific protocols for establishing a surgical airway, including team member selection, should be reviewed at the outset of an airway management plan. The difficult airway algorithm endorsed by the American Society of Anesthesiologists (ASA) (Figure 3) (11) can guide operators and related complications. (10)

If a Grade 1 view (visualization of the entire vocal cords) is acquired on the first attempt, the endotracheal tube can be directly inserted between the vocal cords. An Eschmann stylet (“bougie”) may aid in the placement of the ET tube with a Grade 2 or 3 view of the larynx. An alternative technique should be employed immediately if laryngoscopy reveals a Grade 4 view, whether it is due to anatomy or blood or secretions in the airway. Blind
through technique selection. Notably, difficult airway algorithms were chiefly developed for the elective surgical patient. When intubation is a necessary and potentially life saving procedure outside the OR, waking the patient up is not an option. In the ICU, the act of endotracheal intubation is not the primary goal; rather, operators seek a definitive method to oxygenate and ventilate the patient. All effective means to achieve this goal in the event of an unsuccessful intubation attempt must be rapidly and seriously considered.

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. A thorough understanding of the pharmacologic profile and common side effects of each class of medication (i.e.: analgesic, amnestic, sedative, and paralytic) used in intubation will minimize risk to the patient. Hemodynamic instability is of particular concern during intubation, as many sedative hypnotic medications cause or exacerbate hypotension. Choice of neuromuscular blocking agent should also be tailored to the patient’s clinical status. A list of commonly used medications during emergent tracheal intubation are listed in Table 6.

Vasopressors, including ephedrine (5 mg/mL), phenylephrine (0.1 mg/mL), and epinephrine (10 mcg/mL), and other medications to support the patient through the process of intubation safely should be available at the bedside, and potentially initiated prior to the start of the procedure depending on the patient’s clinical status.

### Table 4.1.6 Common Medications Used in Endotracheal Intubation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/kg)</th>
<th>Onset</th>
<th>Duration</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anesthetics and Sedatives</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etomidate</td>
<td>0.2-0.3</td>
<td>Rapid</td>
<td>Short</td>
<td>Minimal cardiorespiratory effects.</td>
</tr>
<tr>
<td>Propofol</td>
<td>2</td>
<td>Rapid</td>
<td>Short</td>
<td>Hypotension common. Reduces airway resistance.</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>0.5-1*</td>
<td>Slow</td>
<td>Long</td>
<td>Hypotension common. Occasional hypertension. Does not suppress respiratory drive.</td>
</tr>
<tr>
<td>Ketamine</td>
<td>1-2</td>
<td>Rapid</td>
<td>Moderate</td>
<td>Hypertension common. Reduces airway resistance. Does not suppress respiratory drive.</td>
</tr>
<tr>
<td>Midazolam</td>
<td>0.1-0.2</td>
<td>Medium</td>
<td>Long</td>
<td>Minimal cardiorespiratory depression. Increased risk of delirium in ICU patients.</td>
</tr>
<tr>
<td><strong>Depolarizing Neuromuscular Blocking Agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Succinylcholine</td>
<td>1</td>
<td>Rapid</td>
<td>Short</td>
<td>Bradycardia. Contraindications: Hyperkalemia, pseudocholinesterase deficiency.</td>
</tr>
<tr>
<td><strong>Non-depolarizing Neuromuscular Blocking Agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rocuronium</td>
<td>0.6</td>
<td>Medium</td>
<td>Moderate</td>
<td>Minimal cardiorespiratory effects.</td>
</tr>
</tbody>
</table>

* ug/kg. These values are general guidelines. For specific pharmacokinetic and pharmacodynamic values, please refer to a reference source. Rapid: < 60 seconds; Medium: < 5 minutes; Slow: > 5 minutes; Short: < 10 minutes; Moderate: 10-20 minutes; Long: hours

### 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 7). The most immediate and severe complications are worsening hypoxemia and/or severe cardiovascular collapse. Use of an ICU-specific intubation treatment bundle has been demonstrated to significantly reduce the occurrence of these adverse events. (3)

Table 4.1.7 Complications of Endotracheal Intubation

<table>
<thead>
<tr>
<th>During Intubation</th>
<th>Post Intubation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trauma - dental, lip or oral mucosa injury; perforation or dislocation of pharyngeal, laryngeal or tracheal structures</td>
<td>Kinking or blockage of tube</td>
</tr>
<tr>
<td>Pulmonary - hypoxia; esophageal intubation; laryngospasm; bronchospasm</td>
<td>Misplacement of tube</td>
</tr>
<tr>
<td>Cardiovascular - hypo or hypertension; arrhythmias</td>
<td>Ischemia of tracheal tissue</td>
</tr>
<tr>
<td>Neurologic - increased ICP; passage of tube into cranial vault during nasal intubation in patient with basilar skull fracture</td>
<td>Vocal cord injury</td>
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<td>Sinusitis after nasal intubation</td>
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References:


Review Questions:

1. After administering IV 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 intubate the tracheal. The patient’s saturation is now 84%. After calling for help, what is your next step?
   a. Placement of an LMA
   b. Attempt to intubation with a different blade (i.e.: Macintosh to Miller)
   c. Fiberoptic intubation
   d. Attempt face mask ventilation

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 with full 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. There is clear evidence-based medicine supporting the use of cricoid pressure to decrease aspiration of gastric contents during RSI.
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 methods of intubation is BEST?

   a. An awake blind nasal intubation  
   b. An asleep nasal intubation via direct laryngoscopy  
   c. An awake fiberoptic intubation through the mouth  
   d. An awake fiberoptic intubation through the nose

4. A 37 year-old woman presents to the ER 2 hours after sustaining 3rd degree burns 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

5. You are called to the ICU to intubate a patient with respiratory distress. The patient is a 27 year-old G1P0 woman at 30-weeks gestation. She has a history of cystic fibrosis, chronic HTN, and 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 NMBA is appropriate since the patient’s last meal was over 8 hours ago.  
   b. Patients with diabetes always have delayed gastric emptying and therefore 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
I. Ventilators

A. Positive pressure ventilators operate by applying positive pressure (via flow of O\textsubscript{2} and/or air) to the airways during inspiration. In the ICU, mechanical ventilation is almost exclusively positive pressure ventilation.

B. 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.

Patient Case:
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, V\text{t}=500 mL, freq=18, F\text{IO}_2=0.4, P\text{EEP}=5). His fluid requirements decrease and he is hemodynamically stable in the morning. He has an ABG of pH 7.38 / p\text{CO}_2 37 /p\text{O}_2 92 and a 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)?
II. 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) or tidal volume (V) 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 “breath stacking” will occur (the full preset V will be delivered on top of the patient’s spontaneous V). 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 reduced 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 \( V_t = 600 \text{mL} \) and freq=8 and the patient makes 30 inspiratory efforts per minute, the ventilator will deliver \( 600 \text{mL} \times 30 \), or 18 L/min of ventilation.

III. 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 practitioners in the ICU. Adding to the complexity, 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 this airway pressure is based on patient demand, and affected by the airway resistance and the compliance of the lungs and chest wall. Tidal volume is the dependent variable. 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 tidal volume is set and the ventilator delivers variable pressure control breaths in order to achieve the desired 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 the necessary airway pressure higher or lower during the next breath. For example, if the set tidal volume is 500 mL and the current breath has an airway pressure of 15 cm H$_2$O resulting in an actual tidal volume of 420 mL, the ventilator will automatically increase the airway pressure on the next breath in an attempt to achieve 500 mL.

IV. 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, but adjustable on many ventilators). Most modern ventilators have the potential for preset backup pressure control modes that alarm and take over in the event of prolonged apnea.

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, and acute post-operative respiratory failure.

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 PaCO₂.

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

Permissive hypercapnia is an approach to limit ventilator-induced lung injury through deliberate tolerance of elevated PCO\textsubscript{2} in the setting of hypoventilation. Contraindications include elevated ICP, right ventricular failure, and severe ongoing acidemia.

V. 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 stretching of alveoli rather than excessive pressure. “Atelectrauma”, also referred to as derecruitment injury, 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 positive pressure mechanical ventilation.

B. Oxygen toxicity: Prolonged exposure to high concentrations of oxygen may cause lung damage through the production of reactive oxygen species and release of inflammatory mediators. Prolonged periods of high oxygen tension can also lead to atelectasis and increase V/Q mismatch. Normal lung units are at highest risk for oxygen toxicity because these areas receive the most ventilation. The FiO\textsubscript{2} should be reduced when possible provided that arterial oxygenation is adequate. In adults, an FiO\textsubscript{2} of less than 0.5 is considered safe.

VI. Mechanics

A. Airway pressures (Figure 1)

1. Peak (P\textsubscript{peak}) is the pressure reached at end inspiration during positive pressure volume control ventilation. P\textsubscript{peak} is the sum of the pressure required to overcome airway resistance (including the ventilator circuit, endotracheal or tracheostomy tube and the patient’s tracheo-bronchiolar tree) and the pressure required to overcome the elastic properties of the lung, chest wall and abdomen (if it impedes diaphragm movement).

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

**Figure 4.2.1 Peak and Plateau Pressures**

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 elastic properties 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 airway 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 transpulmonary 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

\[ \text{Flow} = \frac{P_L}{R}, \text{ where } P_L = P_A - P_{pl}. \]

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,

\[ \text{Flow} = \frac{(P_{plat} - P_{es})}{R}. \]

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.

VII. 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. 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. Newer co-oximetry devises are capable of measuring multiple hemoglobin moieties (including: oxyhemoglobin, deoxyhemoglobin, methemoglobin, carboxyhemoglobin and total hemoglobin), however, their clinical adoption in the ICU setting in not yet widespread.

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 $\text{PaO}_2$) makes up a small portion of the total arterial oxygen content. The oxygen content of arterial blood ($\text{CaO}_2$) consists of two components: oxygen bound to hemoglobin (which determines the $\text{SaO}_2$) and the oxygen dissolved in plasma (which determines the $\text{PaO}_2$). $\text{CaO}_2$ is described by

$$\text{CaO}_2 = [1.34 \times \text{Hgb} \times \text{SaO}_2] + [\text{PaO}_2 \times 0.003]$$

1.34 mL O$_2$ per gram Hgb is a constant, Hgb is hemoglobin in g/dL, $\text{SaO}_2$ is the arterial oxygen saturation and should be in decimal form (e.g. 98% is written 0.98), $\text{PaO}_2$ is in mmHg, and 0.003 mL O$_2$ per mmHg per dL is a constant.

3. 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:

$$\frac{\text{Qs}}{\text{Qt}} = \frac{(\text{CcO}_2 - \text{CaO}_2)}{(\text{CcO}_2 - \text{CvO}_2)}$$

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.

4. Global oxygen delivery ($\text{DO}_2$) is the product of arterial O$_2$ content and the cardiac output:

$$\text{DO}_2 = \text{CaO}_2 \times \text{CO} \times 10$$

$\text{DO}_2$ is in mL/min, CaO$_2$ is in mL/dL, CO is cardiac output in L/min, and 10 converts L into dL.

5. Oxygen consumption ($\text{VO}_2$) is calculated by the Fick equation

$$\text{VO}_2 = \text{CO} \times (\text{CaO}_2 - \text{CvO}_2)$$

$\text{VO}_2$ 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 $\text{PaCO}_2$. 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 does the metabolism of lipids or proteins.

4. Dead space (Vd) refers to ventilation that does not participate in gas exchange. The total dead space (also known as physiological dead space) is the sum of the anatomical dead space plus the alveolar dead space. The dead space ratio is calculated from the Bohr equation, which measures the ratio of dead space to tidal volume:

\[
\frac{Vd}{Vt} = \frac{(PaCO_2 - PeCO_2)}{PaCO_2}
\]

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.

VIII. 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. This effect is especially pronounced during recruitment maneuvers and ventilation with elevated levels of PEEP. 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.

IX. Miscellaneous

A. Hyperbaric oxygen (HBO) therapy involves breathing 100% oxygen at > 1 atmosphere of pressure. HBO therapy 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 FiO₂ delivery. Most studies use a helium:oxygen mixture of 80:20 or 70:30 to achieve benefit. Many ICU patients cannot tolerate an FiO₂ 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 (via the Venturi effect) 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. With closed circuit HFJV there is a risk of barotrauma, pneumothorax and pneumomediastinum.

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.

X. 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 and partial liquid ventilation utilizing perfluorocarbons instead of gas, 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, there is little consensus in the literature to support one mode over another if barotrauma, volutrauma and atelectrauma are limited. Therefore the recovery of patients in respiratory failure depends mostly on clinicians’ vigilance and ability to modify therapy appropriately in accordance with each individual patient’s needs.

References:


Review Questions:

1. Static compliance will be independently affected by:
   a. Pulmonary edema
   b. Bronchospasm
c. Kinked endotracheal tube
d. Mucus plugging

2. Goals of adding PEEP to routine ventilation settings might include all of the following EXCEPT:
   a. Improved lung compliance
   b. Improved PaO₂
   c. Decreased work of breathing
d. Reduced dead space

3. A contraindication to permissive hypercapnia is:
   a. Hypoxia
   b. Plateau pressure > 25 cm H₂O
c. Brain injury with very high intra-cranial pressures
d. ARDS
Introduction

In the United States, approximately 800,000 patients per year require mechanical ventilation (MV). (1) **Weaning** is the process of liberating a patient from MV. It encompasses a continuum of care that starts once the underlying cause of respiratory failure has been addressed, and involves continuously assessing readiness for weaning and testing the patient’s ability to breath spontaneously prior to extubation. (1) For many patients the weaning process is uncomplicated and can be accomplished expeditiously. However, for patients with acute or chronic respiratory failure this process is often considerably more complicated and protracted. Minimizing the duration of MV is an important goal because prolonged MV is associated with a host of adverse outcomes including ventilator-associated pneumonia (VAP) and ventilator-induced lung injury, increased hospital and ICU length of stay (LOS), health care costs, and mortality. (2-5)

Evidence based strategies to improve outcomes and reduce the duration of MV include low 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 VAP. (1)

In order to reduce the duration of MV, shortening the weaning process is another

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**Key Points:**

- Prolonged mechanical ventilation is associated with adverse outcomes such as ventilator associated pneumonia, increased ICU LOS, 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.
- 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.
key consideration, as weaning accounts for an average of 40-50% of time spent receiving MV. (6) It is therefore critical to continuously assess readiness for weaning, start the weaning process as soon as appropriate, liberate patients from mechanical ventilation as soon as extubation criteria are met, and take steps to prevent reintubation. A proactive, protocol driven, evidence-based approach to the weaning process dramatically shortens the duration of mechanical ventilation and improves outcomes. (1, 7-9)

Weaning Readiness

In any mechanically ventilated patient, daily assessment for weaning readiness should be initiated once the inciting respiratory insult has begun to improve. (1) Clinicians are sometimes overly conservative; although unplanned extubation ranges from 0.3-16% (10) nearly half of these patients do not require reintubation. (11) The optimum approach typically involves a bedside evaluation of the patient by the clinician. Before assessing the patient, the effects of any neuromuscular blocking agents must be reversed and sedatives that suppress the respiratory drive should be weaned or held. (12,13)

Criteria for weaning readiness include the following: (14,15)

1. **Cause(s) of respiratory failure are sufficiently improved**

2. **Stable hemodynamics** (the patient should have a minimal requirement for vasoactive support, or if higher doses of
vasoactive medications are needed the patient should be on a stable or de-escalating dose)

3. **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\(_2\)O, tidal volume > 5ml/kg, PaCO\(_2\) < 60)

4. **Acceptable oxygenation** (SpO\(_2\) >90% on FiO\(_2\) < 0.4 PEEP < 8 cmH\(_2\)O, PaO\(_2\) > 60mmHg, PaO\(_2\):FiO\(_2\) ratio > 150). [Of note, modifying these criteria might be reasonable to account for baseline abnormalities].

5. **Acceptable acid-base status** (pH > 7.25)

6. **Optimized volume status** (euvolemia or net negative fluid balance)

7. **Acceptable electrolyte profile** (potassium, calcium, and phosphate are important for muscle function)

8. **Adequate mentation** (mental status must at least be sufficient to cooperate with the weaning process, however a low Glasgow Coma Score (GCS) is not necessarily, in and of itself, a contraindication to weaning or extubation; studies have not found an association between low GCS and higher rate of weaning failure) (16)

**Evidence Based Weaning Strategies**

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

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 progressively longer durations. PS was found to significantly reduce the duration of weaning. (8)

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. They found once daily versus multiple daily T-piece trials were equivalent, and that both approaches were superior to either SIMV or PS. (9)

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. (14)

Attempts have been made to wean patients from MV using alternative (or newer) modes of ventilation with mixed success. One such strategy is automatic tube compensation (ATC). ATC
uses a closed-loop feedback system to compensate for endotracheal tube (ETT) resistance and overcome the increased work of breathing associated with an artificial airway. Studies have found it to be equally efficacious as a T-piece or PS for weaning. (12) Although consideration should be given to ATC for patients failing a SBT because of small ETT diameter, there is a lack of evidence to make definite statements about the use of ATC for difficult to wean patients at this time. (14,17)

The Weaning Process / Spontaneous Breathing Trial

Neither clinical experience alone nor complex algorithms have been shown to accurately predict whether mechanically ventilated patients can breathe spontaneously. Rather, the current “gold standard” to gauge a patient’s readiness for spontaneous breathing is the spontaneous breathing trial (SBT), which involves assessing both clinical criteria and physiologic parameters. (1) An SBT is performed with minimal to no ventilatory support. It is accomplished by switching from a mode that provides full or a higher level of support to one of the following strategies: pressure support (PS), continuous positive airway pressure (CPAP), or a T-piece. The SBT is a test in which failure is 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

In 1991, 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 parameter to measure during an SBT. Specifically, an RSBI > 105 was found to accurately predict extubation failure; however, an RSBI < 105 was not as accurate at predicting patients who could be successfully extubated. (18) These findings have been subsequently corroborated by a systematic review of multiple RSBI studies. (19)

Ideally, sedative infusions that suppress respiratory drive and level of consciousness should be held at the time of the SBT; (1,20) daily sedation holidays have been shown to decrease duration of MV and ICU LOS. (12) However, in patients with high levels of anxiety or agitation, it may be beneficial to utilize a sedative that has limited effects on respiratory mechanics (i.e. dexmedetomidine), and continue this sedative during the SBT, since anxiety and agitation have a significant role in non-pulmonary causes of weaning failure. (21)
Esteban et al. conducted a multicenter prospective randomized controlled trial in 526 medical-surgical ICU patients to determine the effect of SBT duration on extubation success. They found equal efficacy for a SBT targeted to 30 versus 120 minutes in duration. (22) Thus unless clinical circumstances require a longer assessment, a 30 minute SBT is typically adequate.

Final considerations following a successful SBT and prior to extubation include ensuring the patient can maintain a patent airway, assessing the quantity and consistency of secretions, presence of a strong cough, adequate gag reflex and/or swallow, and verifying an endotracheal tube cuff leak (in patient populations at high risk for airway edema). (14) Mental status is also a key component regarding the patient’s ability to “protect” their airway, although studies have not shown a low GCS score to be associated with higher rate of failure to wean from MV. (16) In these circumstances, clinical judgment plays a crucial role along with the other aforementioned parameters.

Another weaning strategy involves the use of a standardized protocol, as demonstrated by at least one meta-analysis. (7) Protocols may be automated or clinician-directed. Up to 25% reduction in total duration of mechanical ventilation was demonstrated in both clinician-directed and automated protocolized groups. Recent studies have specifically evaluated the impact of automated systems, such as SmartCare™, compared to clinician-directed protocols. (23,24) As opposed to the traditional clinician-dictated decrease in ventilator support, the automated system continuously monitors and adjusts ventilator settings, potentially decreasing delays in the weaning process. A meta-analysis showed decreased time to weaning of MV by about 30%, (24) decreased time to extubation, and decreased ICU LOS. (6,23) Further evaluation of these systems is warranted but they seem promising. Other potential benefits include decreased incidence of reintubation, and decreased incidences of ventilator associated pneumonia and mortality. (25)

**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. One such system, developed by an international task force in 2007, also helps with risk stratification: (13,14,26)

1. Simple: Patients who are successfully extubated following a first attempt (approximately 60% of ICU patients).
2. 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).
3. 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).

**Prolonged Weaning and Weaning Failure**

Weaning failure occurs when a SBT is not successful or a patient requires reintubation within 48 hours of extubation. (14) In assessing reasons for weaning failure, the following causes should be considered:

1. **Fatigue** (weaning to exhaustion)

2. **Respiratory** [The primary issue is an imbalance between respiratory load and capacity. Considerations include an unresolved primary insult, excessive work of breathing due to other disease processes, air trapping (auto-peep), etc.]

3. **Cardiovascular** (myocardial ischemia, left or right ventricular failure; weaning might 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. (14) Reintubation is associated with prolonged hospital stay and increased mortality. (1) Strategies for preventing reintubation include non-invasive positive pressure ventilation (NIPPV) and high-flow nasal cannula (HFNC).

In certain patient populations NIPPV might prevent reintubation. In a meta-analysis of 16 trials, COPD patients extubated to NIPPV had decreased mortality, decreased ICU LOS, decreased weaning failure, decreased time of MV, and decreased VAP. (27) Furthermore, in a recent multicenter, randomized trial evaluating respiratory failure following abdominal surgery, NIPPV decreased the risk of reintubation as compared to the use of conventional supplemental oxygen. (28) Other studies have not found the same benefits to this approach. (29-31)

Recently, the use of high flow nasal cannula (HFNC) for preventing reintubation has been evaluated in mixed medical and surgical populations, specifically for patients with non-hypercapneic respiratory failure and in post-cardiac surgery patients. (32-34) This approach is based on the premise that delivery of oxygen at very high flow rates (up to 60L/min) is beneficial. (35) Hernández et al. assessed 527 patients who required MV for greater than 12 hours, at low risk for post-
extubation respiratory failure in seven ICUs and compared HFNC to standard supplemental oxygen; they found a lower rate of reintubation in the HFNC group. (32) Further studies are needed to better elucidate the relative benefits of NIPPV and HFNC for preventing reintubation. (29,30,35)

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.

Tracheotomy should be considered when weaning is especially prolonged. Rationale for early tracheotomy includes easier airway suctioning, improved patient comfort, and enhanced ability to communicate (decreased requirement for sedatives). However, the timing of tracheotomy remains controversial. (see Chapter 4.5) A meta-analysis concluded insufficient evidence to warrant recommending early tracheotomy. (36) Thus the decision to perform a tracheotomy should be based on clinical judgment and the desires of the patient and/or surrogate decision makers.

**Summary**

Mechanically ventilated patients should be assessed daily for weaning readiness. Patients who meet criteria should be promptly placed on an SBT. In general, an SBT should be targeted to 30-minute duration and performed by placing the patient on low-level PS or CPAP. Patients who pass an 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 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. (1) “Best practice” in the ICU should incorporate a structured, protocolized and evidence-based approach to weaning from MV.

References:


Cochrane systematic review and meta-analysis. Critical Care 2015; 19:48


35. Spoletini G, Garpestad E, Hill NS: High-flow nasal oxygen or noninvasive ventilation for postextubation hypoxemia. JAMA 2015; 315(13):1340-1342


Study Group. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. JAMA 2009; 301 (5): 489-499


Review Questions:

1. In reference to the case description at the beginning of this chapter, what is the next best step in this patient’s management?
   a. Proceed directly to extubation
   b. Place the patient back on AC for 24 hours then repeat the SBT
   c. Place the patient back on AC or an alternative “resting mode” of mechanical ventilation, search for and attempt to correct the underlying etiology of weaning failure, and repeat the SBT as soon as clinically indicated
   d. Switch to synchronized intermittent mandatory ventilation (SIMV) with pressure support and gradually decrease pressure support.

2. Which of the following conditions would most likely negatively impact a weaning trial?
   a. Glasgow Coma Score = 7
   b. Overfeeding
   c. PaO₂ 60 mmHg on FiO₂ 35%
   d. Q4 hour suctioning requirement for thin secretions
3. Each of the following predict extubation failure except:

   a. PaCO₂ > 45 mmHg

   b. Copious secretions

   c. Prior failed weaning trial

   d. Duration of MV = 30 hours
Introduction

Acute Respiratory Distress Syndrome (ARDS) is a form of acute hypoxemic respiratory failure characterized by inflammatory pulmonary edema. Recent studies have estimated the incidence of ARDS in ICU patients to be roughly 10% with a mortality rate ranging between 35-46%. The pathophysiology of ARDS is

Key Points:

• Acute Respiratory Distress Syndrome (ARDS) is defined as acute non-cardiogenic hypoxemic respiratory failure secondary to severe inflammatory edema resulting in bilateral opacities on radiologic imaging.

• ARDS is a common diagnosis in critically ill patients and associated with a high mortality rate.

• The key component in the management of ARDS is the use of a lung protective ventilation strategy. Management includes low tidal volume ventilation (6-8 mL/kg of ideal body weight), high PEEP, permissive hypercapnia, prone positioning, and judicious fluid administration.

Patient Case:

A 62-year-old woman with a past medical history of HTN and T2DM is admitted to the ICU for hypoxic and hypercarbic respiratory failure. Four days prior to her transfer to the ICU she was admitted to the medical ward with 3 days of fevers, chills, malaise, and a productive cough. On admission she was noted to have a right lower lobe consolidation and was started on antibiotics for treatment of community acquired pneumonia. Over the next several days her oxygenation deteriorated and her CXR worsened with evidence of diffuse bilateral infiltrates. Prior to transfer to the ICU, her vitals were T 38.1, HR 105, BP 105/65, and RR 33 with an ABG showing a pH 7.25 / pCO\textsubscript{2} 52 / pO\textsubscript{2} 50 on 100% non-rebreather. She was transitioned to high-flow nasal cannula showing minimal improvement in her oxygenation with a PaO\textsubscript{2}/FiO\textsubscript{2} ratio of < 200 mmHg and was intubated shortly thereafter. What ventilator strategies would you initially employ in this patient who meets criteria for ARDS?
related to large amounts of non-ventilated alveolar units creating intrapulmonary shunting and diffuse alveolar damage resulting in poor lung compliance. The intrapulmonary shunting results from a combination of atelectasis and pulmonary edema from protein-rich fluid. Furthermore, ventilator associated lung injury may itself promote further lung damage and worsen lung compliance. The combination of shunting and dead space ventilation can lead to both hypoxemic and hypercarbic respiratory failure.

The current Berlin Definition of ARDS was established in 2012 and replaced the previous American-European Consensus Conference criteria. Notably, acute lung injury is no longer a diagnosis and ARDS has three sub-categories of severity. The current Berlin criteria includes the following clinical and radiologic criteria:

1. Acute respiratory failure or a known insult occurring within 7 days of symptoms.

2. Bilateral opacities visualized on chest x-ray or computerized tomography not fully explained by effusions, lobar/lung collapse, or nodules. *(Figure 1)*

3. Pulmonary edema not fully explained by fluid overload or cardiac failure.

4. Hypoxemia categorized into

- **Mild:** $200 \text{ mmHg} < \frac{\text{PaO}_2}{\text{FiO}_2} \leq 300 \text{ mmHg}$ with PEEP or CPAP $\geq 5 \text{ cmH}_2\text{O},$

- **Moderate:** $100 \text{ mmHg} < \frac{\text{PaO}_2}{\text{FiO}_2} \leq 200 \text{ mmHg}$ with PEEP $\geq 5 \text{ cmH}_2\text{O},$ or

- **Severe:** $\frac{\text{PaO}_2}{\text{FiO}_2} \leq 100 \text{ mmHg}$ with PEEP $\geq 5 \text{ cmH}_2\text{O}$

**Management**

The management of ARDS is mostly supportive and focused on
the use of evidence-based ventilation strategies. Despite the lack of effective therapies, a thorough workup should be undertaken to identify and treat the underlying etiology of ARDS, whether direct or indirect. Examples of both direct and indirect etiologies include pneumonia, sepsis, trauma, burns, recent surgery, and ischemia-reperfusion injury.

Invasive ventilation is the standard of care for airway protection and pulmonary support, but recent evidence suggests potential benefit in the use of noninvasive ventilation (NIV). A recent study demonstrated a statistically significant reduction in mortality and intubation rates when using a noninvasive helmet compared to facemask oxygen in nonhypercapnic acute hypoxemic respiratory failure. High-flow nasal cannula has also been shown to decrease 90-day mortality compared to traditional NIV or facemask oxygen, although it had no effect on intubation rates. Currently, there is not sufficient evidence to advocate for broad use of NIV for ARDS management.

The key component in the management of ARDS is use of a lung-protective ventilation strategy. A landmark paper in 1998 demonstrated benefit with a 25% reduction in mortality by implementation of lower tidal volumes (TV) (6 mL/kg of ideal body weight [IBW]) and high positive end expiratory pressure (PEEP) versus traditional TV’s (12 mL/kg of IBW) and low PEEP. These findings were confirmed by the Acute Respiratory Distress Syndrome Network which showed a 22% reduction in mortality, reduced ventilator days, and decreased amounts of inflammatory markers. Once a patient is stabilized with adequate oxygenation by adjusting levels of PEEP, FiO\textsubscript{2} should be adjusted for a goal PaO\textsubscript{2} of \( \geq 55 \) mmHg (SpO\textsubscript{2} \( \geq 88\% \)) while using non-toxic levels of oxygen when possible (FiO\textsubscript{2} < 0.6). A recent meta-analysis suggested decreased mortality when using high PEEP but cautioned restriction to patients who met ARDS criteria versus universal application in all ventilated patients. The use of computer tomography (CT) imaging following alveolar recruitment may demonstrate which patients will benefit from the use of high PEEP. Use of low lung volumes may result in hypercapnia, especially in the ARDS population. Permissive hypercapnia may have several benefits including improved oxygen unloading, reduced ventilation/perfusion mismatching, increased cardiac output, reduced cellular stress from free radicals, and organ protection during reperfusion. As such, one should not attempt to correct mild hypercapnia as intracellular pH is usually well compensated, even in critically ill patients. Heavy sedation and pharmacologic paralysis can assist with ventilator synchrony in ARDS and reduce O\textsubscript{2} consumption while improving chest wall compliance. Fluid management is an important aspect of all critical care patients. Protocols for minimizing fluid administration can reduce ventilator days and improve oxygenation, but have not been demonstrated to reduce mortality. Prone positioning has been shown to improve gas exchange in severe ARDS patients by means of increased functional residual capacity, redistribution of
pulmonary perfusion, improved clearing of secretions, and changes in diaphragm motion.

In summary, Initial therapeutic strategies should include the following:

1. Set initial TV between 6-8 mL/kg of IBW. Volume control or pressure control ventilation may be employed (if using pressure control, close monitoring of delivered TV is necessary).

2. Set initial PEEP at 10 cmH₂O and FiO₂ of 100%. Wean FiO₂ as tolerated.

3. Initially maintain deep sedation and consider muscle paralysis in order to optimize lung-protective ventilation and facilitate measurements of lung mechanics.

4. Measure Pplat via an inspiratory hold maneuver with a goal Pplat < 30 cmH₂O and calculate driving pressure (driving pressure = Pplat – PEEP) with an absolute goal < 14 cmH₂O. Make further adjustments to TV and PEEP if Pplat or driving pressure is out of range.

5. Employ recruitment maneuvers early on.

6. Tolerate hypercapnia to a pH of 7.25 unless hemodynamically unstable.

7. In more severe cases of ARDS consider prone positioning.

In cases of refractory ARDS not responding to standard treatment it may be necessary to trial adjuvant therapies with less evidence-based support. The type, indications, and duration of such therapies are usually institution or provider dependent. Strategies for refractory cases include the following:

1. Inhaled nitric oxide (iNO) and prostacyclin (iPG) are effective pulmonary vasodilators and help ventilation/perfusion matching but neither has proven to reduce mortality. iNO is simpler to use but is also costlier compared to iPG.

2. More advanced modes of ventilation such as airway pressure release ventilation (APRV) and Bi-Level have good theoretical advantages and have been employed successfully in refractory cases but have not been supported by literature.

3. High frequency oscillatory ventilation should be avoided in cases of ARDS as demonstrated by two recent studies that showed increased mortality.

4. Initiation of veno-venous extracorporeal membrane oxygenation (ECMO) should be considered in patients refractory to other strategies. Consider early consultation of ECMO specialists or transfer to facilities with ECMO capabilities in patients not responding to early therapeutic strategies.

5. Steroids were shown to be beneficial in earlier studies however the ARDSnet trial did not show benefit.
References:


Review Questions:

1. Which of the following is the primary reason for the use of prone positioning in ARDS?
   a. Improved mobilization of secretions
   b. Fewer self-extubations
   c. Improved cephalad position of diaphragm
   d. Improved ventilation-perfusion matching
2. What should the lowest targeted SpO₂ be during management of ARDS?
   a. 88%
   b. 90%
   c. 92%
   d. 94%

3. What is the optimal ventilation strategy for ARDS management in a patient who is unable to protect their airway?
   a. Noninvasive helmet
   b. Intubation; TV 6-8 ml/kg of ideal body weight + low PEEP
   c. Intubation; TV 6-8 ml/kg of actual body weight + moderate/high PEEP
   d. Intubation; TV 6-8 ml/kg of ideal body weight + moderate/high PEEP

4. How do you calculate static lung compliance and what is a normal value in an adult. (PIP = peak inspiratory pressure)
   a. TV/(PIP - Pplat); 1 ml/kg/cm/H₂O
   b. TV/(Pplat - PEEP); 1 ml/kg/cm/H₂O
   c. (PIP - Pplat)/TV; 0.5 ml/kg/cm/H₂O
   d. (Pplat - PEEP)/TV; 0.5 ml/kg/cm/H₂O
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

Patient Case:

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. His ICU course is complicated by persistently elevated intracranial pressures requiring deep sedation and paralysis, ventilator-associated pneumonia, and acute lung injury. 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.

Key Points:

- There are no major outcome differences between surgical versus percutaneous tracheostomies.
- There is 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.
- Ultrasound guidance is becoming increasingly popular as a tool for accessing the trachea in percutaneous tracheostomy.
commonly seen in the ICU for patients requiring prolonged mechanical ventilation.

**Indications**

Clinical indications for tracheostomy include the following. (1)

1. Prolonged or expected prolonged intubation/mechanical ventilation
2. Upper airway obstruction
3. Inability to manage secretions (including aspiration or excessive broncho-pulmonary secretions)
4. Ventilator support to facilitate rehabilitation
5. Inability to be orally or nasally intubated
6. As an adjunct to manage head and neck surgery or significant head and neck trauma
7. Chronic mechanical ventilation due to chronic respiratory failure

The benefit of early (within 10 days of endotracheal intubation) versus late tracheostomy continues to be 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) This was supported by a large randomized controlled trial (TracMan) comparing early ($\leq$ 4 days) to late ($\geq$ 10 days) tracheostomy. 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. The most recent 2016 Cochrane review reported a slight decrease in mortality [risk ratio (RR) 0.83, 95% confidence interval (CI) 0.70-0.98; P value 0.03] and possible decrease in duration of mechanical ventilation for those who underwent early tracheostomy, but noted that the data is still inconclusive and not of high quality. (9)

Contraindications to tracheostomy include the following: (5)

1. Patient or surrogate refusal to consent
2. Infection at the site of potential tracheostomy placement
3. Anatomic aberrations obscuring neck anatomy
4. Patient instability, including high oxygen requirements or ventilator settings
5. Coagulopathy
**Technique**

The tracheotomy is typically performed between the 2nd and 3rd or 3rd and 4th tracheal ring interspace. (Figure 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 2006 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) This result was supported by a 2016 Cochrane Review which noted significantly lower rates of wound infection/stomatitis and scarring for the percutaneous technique but again did not show any decrease in major complications. (10) It did comment, however, on the lack of evaluation of long-term outcomes and limited patient population in most studies. (10) Recent studies have focused on ultrasound guidance of tracheal puncture in patients undergoing percutaneous tracheostomies. These have demonstrated longer procedural times but improved rates of first pass puncture and puncture accuracy. (11,12)

**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 tracheostomy include the following (Figure 2):
1. Single cannula
2. Double cannula (inner and outer cannulas)
3. Neck flange
4. Obturator
5. Cuff
6. Pilot Balloon

**Figure 4.5.2 Components of Tracheostomy Tube**

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.

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 and the patient is tolerating a tracheostomy with a cap or one-way valve in place, 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)

1. Major bleeding
2. Tube dislodgment
3. 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) It is essential for providers to be aware of the difference between a tracheostomy and a stoma for a total laryngectomy, as the latter group of patients have no connection between their oropharynx and trachea and attempted oro-tracheal intubation is futile and results in wasted time in an emergency situation. Experienced providers should only undertake the passage of a tube through the tracheostomy site when tracheal rings are 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:

1. Granuloma formation with tracheal stenosis
2. Tracheomalacia

3. 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 changing the tube size, cautery of granulation tissue, and/or laser ablation. (5) Tracheomalacia results from cuff over-inflation or excessive traction from 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.

A 2014 randomized prospective trial compared the incidence and types of complications that occurred with both percutaneous tracheostomy and surgical tracheostomy. While the exact complications differed, the study found no difference between the frequency or severity of complications. (13)

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 and no significant differences have been noted between the two techniques with respect to complications. 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.

References:


Review Questions:

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

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

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

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

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
Chapter 5

Cardiovascular System Topics
Shock is defined as a life-threatening, generalized form of acute circulatory failure associated with impaired oxygen delivery and organ perfusion. Oxygen demand exceeds oxygen supply resulting in tissue hypoxia. Perfusion is characterized by oxygen delivery, the product of cardiac output and the arterial oxygen content. Oxygen content is determined primarily by arterial oxygen saturation and hemoglobin concentration, though partial pressure of oxygen may play a role in

**Key Points:**

- **Shock is a generalized, acute form of circulatory failure associated with inadequate oxygen delivery (or utilization) and organ perfusion.**
- **Shock is classified into hypovolemic, cardiogenic, distributive and obstructive etiologies. Multiple forms of shock may present in the same patient, and treatment should be directed towards the underlying cause.**
- **Initial resuscitation should focus on establishment of circulating blood volume, achievement of an adequate minimum blood pressure, optimization of cardiac function, and restoration of oxygen delivery.**
- **Response to therapy should be continuously evaluated. While many tools are available to evaluate response, no one measure should be used in isolation to guide management.**

**Patient Case:**

A 72 year-old man with a history of CHF, moderate aortic stenosis, COPD, and CKD presents to the emergency department with cough, fever, and altered mental status. His wife reports his cough and SOB started approximately one week ago and he was prescribed prednisone and azithromycin by his primary care physician. She says his cough has persisted and he started acting confused this morning. On exam, the patient is in moderate distress, oriented only to person, with increased work of breathing and cold, clammy extremities. A crescendo-decrescendo murmur is auscultated over the right second intercostal space, and expiratory wheezing is heard bilaterally. Home medications include metoprolol, furosemide, spironolactone, prednisone, azithromycin, and inhaled albuterol. His vital signs are: Temp 38.7C, HR 110, BP 72/41, RR 24, SpO2 86% on 15L non-rebreather mask. CXR reveals cardiomegaly, pulmonary edema, and a dense right middle lobe infiltrate.
extreme situations. Microcirculatory dysfunction and defects in oxygen utilization at the cellular level may also play a role in hypoxia.

Shock affects multiple organ systems, and early recognition of the signs and symptoms of shock may aid in reducing morbidity and mortality. A table of common organ system involvement is outlined in Table 1.

Four major shock syndromes exist based on specific hemodynamic parameters and primary pathology, though the presence of one syndrome does not exclude the presence of another. Often multiple processes are at work in the same patient. As an example, as many as one-third of patients in septic shock also have some degree of myocardial dysfunction, and post-cardiac surgery patients may suffer from post-cardiopulmonary bypass vasoplegia in addition to cardiogenic shock. The classification, along with specific pathologic subtypes, is as follows in Figure 1 and Table 2.

Table 5.1.1 Organ System Involvement in Shock

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Signs/Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurologic</td>
<td>Altered mental status, lightheadedness, dizziness</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Chest pain, arrhythmia, jugular venous distension, peripheral edema</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>ARDS, hypoxemia, hypercarbia, tachypnea</td>
</tr>
<tr>
<td>Gastrointestinal/Renal</td>
<td>Ileus, abdominal pain, oliguria, acute kidney injury, elevated LFTs, elevated Cr</td>
</tr>
<tr>
<td>Endocrine/Hematologic</td>
<td>Hyper- or hypoglycemia, thrombocytopenia, abnormal coagulation tests</td>
</tr>
<tr>
<td>Laboratory Findings</td>
<td>Altered mixed venous oxygen saturation, elevated serum lactate</td>
</tr>
</tbody>
</table>

The goal of resuscitation is to restore tissue perfusion, and treatment should be tailored to a specific pathologic process. Initial management can be broadly separated into establishment of effective circulating volume, achievement of an adequate minimum blood pressure, optimization of cardiac function, and restoration of oxygen delivery.

**Hypovolemic Shock**

Characterized by low filling pressures, decreased cardiac output, and increased systemic vascular resistance, hypovolemic shock
can be categorized into hemorrhagic and non-hemorrhagic shock. Initial resuscitation should focus on restoration of circulating volume, with the type of resuscitation fluid geared towards the underlying process. For hemorrhagic shock, the trauma literature supports resuscitation with blood products in a ratio mirroring whole blood with massive transfusion protocols utilizing a 1-2:1:1 ratio of packed red blood cells (PRBCs):fresh frozen plasma (FFP):platelets (PLTs) early in resuscitation. In these cases, avoidance of hypothermia, acidosis, and coagulopathy, the so-called “lethal triad” of trauma, is of critical importance. Source control for bleeding should be obtained surgically, endoscopically, or via interventional radiology. Non-hemorrhagic hypovolemia can occur secondary to increased fluid losses (eg: vomiting or diarrhea, burn injury) and/or inadequate intake. In these patients, fluid resuscitation with isotonic crystalloids is recommended, as clinical data does not support the use of colloids (albumin, hydroxyethyl starch, FFP). The use of hydroxyethyl starches (HES) is additionally discouraged due to concerns for increased mortality, induced coagulopathy and need for renal replacement therapy (dialysis).

**Cardiogenic Shock**

Characterized by low cardiac output, high filling pressures, and increased systemic vascular resistance, cardiogenic shock can be categorized into arrhythmogenic, myopathic or valvular etiologies. Tachyarrhythmias affect diastolic filling and cardiac output. Additional lack of coordination between atrial and ventricular contraction (atrial fibrillation) may result in significant decreases in cardiac output. In the unstable patient, electrical cardioversion may be necessary to restore perfusion. Bradyarrhythmias resulting in cardiogenic shock may require temporary or permanent pacing. Electrolyte abnormalities, hyper- and hypovolemia, ischemia, and other physiologic stressors can all lead to development of arrhythmias. Treatment of arrhythmogenic shock is summarized in the Advanced Cardiac Life Support (ACLS) algorithms. Patients with myopathic disease, including acute myocardial ischemia, exacerbations of heart failure, or myocardial stunning post-cardiopulmonary bypass, may benefit from inotropic support with associated preload or afterload reduction. In refractory cases, mechanical support via intraaortic balloon pump, veno-arterial extracorporeal membranous oxygenation (VA-ECMO), or a ventricular assist device (VAD) may be required. In cases of acute ischemia [ST-elevation myocardial infarction (STEMI)], prompt consultation with cardiology is warranted to pursue the appropriate reperfusion strategy. Severe acute or chronic valvular abnormalities may cause hemodynamic derangements. The sequelae of aortic or mitral stenosis may be insidious and not present until the patient experiences additional physiologic stresses or reserve is exhausted. Acute aortic insufficiency may be the result of endocarditis or aortic dissection, while new onset severe mitral regurgitation may be secondary to an acute myocardial insult. Treatment refractory to medical management may include
Distributive Shock

Characterized by decreased systemic vascular resistance (SVR), low filling pressures, and high cardiac output, distributive shock can be categorized into septic, anaphylactic, adrenal, or neurogenic etiologies. In septic shock, circulating toxins cause vasoplegia, resulting not only in low SVR but also decreased effective circulating volume. Initial goals of therapy include fluid resuscitation, typically with a 30mL/kg bolus of crystalloid solution, followed by the addition of vasopressor administration if volume fails to resolve hypotension. Norepinephrine is considered first line therapy. Vasopressin is added as a second line therapy for escalating vasopressor requirements. Rapid treatment with broad spectrum antibiotics is equally important in improving outcomes in septic shock. Cultures (blood, urine, sputum) should be obtained as early as possible but should not delay antibiotic therapy. Source control, through surgical or interventional radiology procedures, is vital for selected infections (necrotizing soft tissue infection, urinary obstruction, intraabdominal abscess). Anaphylactic shock is diagnosed by physical exam findings consistent with vasoplegic shock physiology and a temporal association with administration of an inciting agent. Patients may exhibit signs of bronchospasm, airway and mucosal edema, rash, tachycardia and hypotension. Treatment hinges on discontinuation of the offending agent and supportive care, including the administration of epinephrine (intramuscular or intravenous) with antihistamines, steroids, and bronchodilators. Adrenal crisis may present as the result of acute stress in an already adrenally suppressed patient or de novo in the case of adrenal infarction (as can be seen with severe meningococcal infections). Rapid recognition in at-risk patients is necessary and treatment includes stress-dose steroid administration (hydrocortisone). Neurogenic shock is the result of a blockade of sympathetic outflow, most commonly from high spinal cord injury or brain damage. In addition to low systemic vascular resistance, these patient may also suffer from potentially fatal bradyarrhythmias. If unresponsive to pharmacologic therapies such as atropine or epinephrine, these patients may require temporary or permanent pacing. Neurogenic shock is sometimes listed as a separate category of shock, though the physiology is similar to other sources of distributive shock.

Obstructive Shock

Characterized by low cardiac output, high filling pressures, and increased systemic vascular resistance, obstructive shock is physiologically similar to cardiogenic shock, and is sometimes considered a subcategory of cardiogenic shock. Though less common, obstructive shock has the potential for rapid reversal depending on etiology. Classifications include cardiac tamponade, tension pneumothorax, massive pulmonary embolism, and restrictive pericarditis. Management for all
etiologies include fluid resuscitation to maintain intravascular volume and cardiac preload, and inotropic support as indicated until definitive treatment can be undertaken. Cardiac tamponade is the result of increased pericardial pressure causing decreased diastolic cardiac filling and eventually outflow obstruction. Causes include hemorrhage into the pericardial space, especially in post-cardiothoracic surgical patients, or pericarditis resulting in large volume accumulation. Atrial collapse during diastole is an early echocardiographic finding. Clinically, the patient may have symptoms/signs of shortness of breath, chest pain, increased jugular venous pressure, muffled heart sounds, pulsus paradoxus, and electrical alternans on ECG. Definitive treatment is drainage of the effusion, either by pericardiocentesis or a pericardial window procedure. Tension pneumothorax is caused by the accumulation of air in the pleural space, resulting in compression of the great vessels with decreased cardiac filling and cardiac output. Initial therapy consists of needle thoracostomy or tube thoracostomy placement. Constrictive pericarditis may be the result of a number of infectious, rheumatologic or oncologic sources. Treatment includes management of the underlying disease process, preload optimization, and occasionally surgical consultation.

**Monitoring Response to Treatment**

Active and continuous evaluation of treatment response is vital to ongoing therapy. Signs of shock resolution include: improved blood pressure, restoration of adequate urine output (0.5mL/kg), clearance of lactate, improvement in base deficit, and an improved mixed venous oxygen saturation (~65-70%). Though helpful, these signs may be insensitive or delayed in presentation. Preload responsiveness is defined by a 10-15% increase in cardiac output (CO) with the administration of fluid. A number of different modalities have been developed to measure preload responsiveness, though each has its limitations. Increases in CVP and PAOP indicate that preload has been successfully manipulated, but offers no data on cardiac output. Arterial blood pressure may reflect CO but also depends on vascular tone. Invasive cardiac output monitoring with a pulmonary arterial catheter is no longer routinely recommended though may be helpful in certain situations (post-cardiac surgery or in mixed-shock states). Dynamic response measurements such as pulse pressure variation and stroke volume variation are increasingly

<table>
<thead>
<tr>
<th>Physiologic States</th>
<th>Cardiac Output</th>
<th>Filling Pressures</th>
<th>Systemic Vascular Resistance</th>
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<tbody>
<tr>
<td>Hypovolemic</td>
<td>↓</td>
<td>↓</td>
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<tr>
<td>Cardiogenic</td>
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<tr>
<td>Distributive</td>
<td>↑</td>
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<td>↓</td>
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<tr>
<td>Obstructive</td>
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</table>
utilized at the bedside, but are best validated in mechanically ventilated patients without spontaneous respiratory effort. (see Chapter 2.2) Transthoracic and transesophageal echocardiography provide valuable information on cardiac function and ventricular filling, but offer only a snapshot in time of these parameters. Serial evaluation is advantageous, but can be costly, time intensive and operator dependent. In summary, each of these measures is useful, but should not be used in isolation, and all available information regarding hemodynamic status and organ perfusion should be utilized in concert to guide management.

This chapter is a revision of the original chapter authored by David P Ciceri MD.

References:


Review Questions:

1. An 89 year-old woman presents from a nursing home with altered mental status, tachycardia, tachypnea, hypotension and fever. Her extremities are warm to the touch. Urinalysis reveals the presence of a UTI. The following hemodynamic parameters are most characteristic of her shock subtype.
   a. Decreased filling pressures, increased CO, decreased SVR
   b. Increased filling pressures, decreased CO, increased SVR
   c. Decreased filling pressures, decreased CO, increased SVR
   d. Increased filling pressures, increased CO, decreased SVR

2. Each of the following are indicated for the management of septic shock except:
   a. Administration of norepinephrine as a first line vasopressor
   b. 30 mL/kg fluid bolus of either crystalloid or colloid
c. Hold antibiotic administration until all cultures are obtained

d. Continuous evaluation of response to therapy

3. Which of the following tools may be used as a stand-alone monitor of preload responsiveness in shock?

   a. Pulmonary artery catheter

   b. Stroke volume variability

   c. Transthoracic echocardiography

   d. None of the above
I. 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.

Patient Case:
A 67 year-old man with a history of hypertension, diabetes mellitus, and COPD was admitted to the ICU 1 day ago following a colectomy for bowel perforation. The nurse calls you because the patient has a marginal BP, low urine output, and this ECG for 2 hours.
options in managing the most common arrhythmias encountered in the ICU.

II. PATHOPHYSIOLOGY

A. Atrial Bradyarrhythmias

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.

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.

AV nodal blockade (AVB) may be incomplete (1\textsuperscript{st} and 2\textsuperscript{nd} degree) or complete (3\textsuperscript{rd} degree). The block may be temporary or permanent. 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.

First degree AVB: Is defined as a PR interval $> 200$ ms. It is caused by 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 is more ominous because it can proceed to complete third degree heart block.

Third degree AVB: 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, depending on where it originates, with a HR of 40-60 bpm.

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.

B. Atrial Tachydysrhythmias

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.

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

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.

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.

AVNRT (AV nodal reentry tachycardia) and AV reentry tachycardia (AVRT) are reentry SVT's 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 with conduction via the bypass tract.

Multifocal atrial tachycardia (MAT) is uncommon, but usually presents as an irregular rhythm with at least three different P wave morphologies. The PR intervals are also variable.

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.

C. Ventricular Dysrhythmias
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).

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.

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, or heart failure.

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.

Polymorphic VT has an irregular QRS pattern and is often an irregular rhythm. It can quickly deteriorate into ventricular fibrillation.

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, droperidol), and methadone.

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.

III. Management

When evaluating a patient with a dysrhythmia, obtain a 12 lead ECG. Knowing the answers to the questions below 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?

A. Bradycardia

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

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 3rd degree AVB.

Epinephrine (2-10 mcg/min IV) is a potent β₁ agonist which increases HR and contractility, as well as systemic vascular resistance (via α₁ receptor activity). Epinephrine administration can lead to tachydysrhythmias. Other chronotropic agents such as dopamine and isoproterenol can be used to treat symptomatic bradycardia as an alternative to epinephrine. Electrical pacing via a transcutaneous or transvenous route is recommended in cases of Mobitz II and 3rd degree AVB.

B. 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. 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.

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.

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.

Amiodarone (150 mg IV bolus over 10 minutes followed by infusion) acts on Na⁺, K⁺, and Ca²⁺ 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.

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).

C. Other Treatment Modalities

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 recurrence of the arrhythmia.

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.

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.

Carotid sinus massage can be used as a cheap diagnostic tool to distinguish the type of SVT. It increases vagal tone in the SA and AV node. It’s important to determine the presence of carotid stenosis by reviewing the records or to
auscultate for carotid bruit prior to performing this maneuver because of the stroke risk. Also ensure that you have continuous EKG and adequate IV access in case of bradycardia.

This chapter is a revision of the prior chapter authored by Ryan Laterza, MD and Adam S. Evans, MD

References:


Review Questions:

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

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, SpO\textsubscript{2} 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

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 dissociation 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
Background

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

Physiology

The energy demands of the heart are determined by oxygen supply and demand. 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

Patient Case:

A 55 year old morbidly obese woman is status post elective gastric bypass surgery. Estimated blood loss was 500ml. While complaining of upper abdominal pain in the PACU, she vomits and desaturates to 85%. Her BP is 164/79 mmHg and heart rate is 117 bpm. CXR reveals bilateral pulmonary edema. She is intubated for airway protection and transferred to the ICU where she remains tachycardic, with saturations in the low 90%’s on \( \text{FiO}_2 \) 0.8. Labs from the PACU show a troponin of 14 ng/mL.
disruption of an atheromatous plaque resulting in an intracoronary thrombus or an imbalance between the supply and demand of oxygen from other causes. The latter mechanism is 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 1). The difference between aortic diastolic and left ventricular end diastolic pressures determines the coronary perfusion pressure to the left ventricle. 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 (in patients with normal right heart physiology). When ventricular end diastolic pressure exceeds aortic diastolic pressure, myocardial ischemia can occur. Additionally, as the heart rate increases, less time is spent in diastole, thereby decreasing coronary perfusion via decreased supply (and increased demand – see below).

Smaller arteries have increased resistance to flow as governed by Poiseuille’s law (flow is related to the radius to the 4th power and inversely related to length and viscosity). 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 concentration and oxygen saturation (and to a lesser extent PaO₂) will increase the oxygen content of blood.

\[
\text{Oxygen content} = 1.36 \times \text{SaO}_2 \times \text{Hgb} + 0.003 \times \text{PaO}_2
\]
Myocardial oxygen demand

The heart consumes between 8 and 70 ml of O$_2$/100g depending on its demands. This is the most variation in the human body and meets, or exceeds, the maximal demand of contracting skeletal muscle. As the number or force of cardiac myocyte contractions increase, the oxygen demand increases. 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:

1. Extravascular fluid mobilization increases preload and myocardial wall tension
2. Hypercoagulable state from postoperative inflammation and activation of the coagulation cascade
3. Catecholamine surges (e.g., post-operative pain, etc.) increase heart rate and systemic vascular resistance, thus increasing afterload and wall tension
4. 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 nonspecific such 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. Figure 2 shows an algorithm for the diagnosis of post-operative MI.

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 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, corresponding to the coronary anatomy, 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 are used to identify the anatomic location of the culprit atherosclerotic lesion (Figure 3).

**Classification**

Several classification schemes exist to describe MI:
1. *Anatomic:*
   a. Transmural versus nontransmural
   b. Involved segments of myocardium (inferior, anterior, septal, etc.)

2. *EKG:*
   a. Q wave MI versus non Q wave MI
   b. ST elevation MI (STEMI) versus non-ST elevation MI (NSTEMI)

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

**Complications:**

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

1. *Electrical*
   a. **Bradyarrhythmias:** occur when the conduction system becomes ischemic.
      i. Sinus bradycardia, junctional bradycardia with or without ventricular escape, and complete heart block.
   b. **Tachyarrhythmias:** occur when ischemia leads to irritability of the myocardium and disorganized transmission of electrical impulses.
      i. Atrial: sinus tachycardia, supraventricular tachycardias (SVTs) and atrial fibrillation or flutter with or without rapid ventricular response
      ii. Ventricular: ventricular tachycardia (VT) and ventricular fibrillation (VF)

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

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

c. Acute mitral regurgitation: may occur when rupture of ischemic papillary muscle causes flail leaflet and acute, severe MR.
  i. Has a poor prognosis.
  ii. Usually occurs with inferior infarcts.
  iii. Classically presents as shock, pulmonary edema and a new murmur.

d. LV aneurysm: is caused by dyskinetic, scarred apical tissue leading to ballooning.
  i. LV thrombus may form due to stasis and turbulent flow in LV aneurysm.
  
ii. Embolisms may be distributed to organs supplied by the LV, including brain, kidneys, extremities, and gut.
  iii. Persistent ST elevations are common in the apical territories, despite lack of evidence for reduced morbidity or mortality.

### Therapy

Oxygen: improves oxygen content of arterial blood, theoretically increasing supply, and remains standard of care despite lack of evidence for reduced morbidity or mortality.

1. **Pharmacologic Therapies**
   
   a. Morphine: decreases sympathetic outflow which decreases heart rate, causes decreased preload and afterload secondary to histamine release
   
   b. Antiplatelet agents: prevent platelet aggregation, adhesion and cohesion.
      
      i. Aspirin (cyclooxygenase inhibitor) reduces mortality and is used as immediate therapy
      
      ii. Thienopyridines (clopidogrel, ticlopidine) maintain stent patency after PCI.
   
i. Effective in first 48hrs of MI

ii. Avoid in acute inferior wall MI as it can cause profound hypotension

d. Beta-blockers: decrease myocardial oxygen demand (decreased heart rate and contractility), increase myocardial oxygen supply (increased diastolic time), and reduce mortality in the first week post-MI. They are also anti-arrhythmogenic.

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

i. Administered as an infusion acutely until long-term anticoagulation is established

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

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

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

i. Use caution in patients with renal injury

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

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

i. 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.

j. Hemodynamic support:

i. Inotropes (milrinone, dobutamine, epinephrine): increase myocardial contractility, increasing cardiac output

ii. Vasopressors (norepinephrine, phenylephrine, vasopressin): increase peripheral vascular resistance to increase mean aortic diastolic pressure and coronary perfusion pressure.

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

2. Invasive Therapies

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

i. This is preferable to fibrinolysis for PMI after noncardiac surgery given lower bleeding risk

b. Surgical Revascularization (CABG):

i. Must have appropriate anatomy

ii. Urgent if PCI has failed (left main disease, unable to restore flow)

iii. Urgent if patient is unstable due to anatomical complications of MI

3. Support Measures

Patients may require invasive hemodynamic support, in addition to medical management, following an acute MI.

a. 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.

b. Assist devices:

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

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

iii. Temporary devices may need to be replaced with a permanent device as destination therapy or a bridge to transplant if cardiac function does not improve.

c. Veno-Arterial Extracorporeal membrane oxygenation (VA-ECMO):

i. Blood is circulated and oxygenated through an external heart-lung machine

ii. High risk for complications including bleeding, infection, ischemia, stroke, and compartment syndrome

iii. Temporary

d. Intra-aortic balloon pump: provides intra-aortic counterpulsation (see Chapter 5.5)

i. Inflates during diastole, increasing myocardial perfusion

ii. Deflates during systole, creating negative aortic pressure and decreasing afterload

iii. Temporary

iv. Contraindicated in patients with aortic regurgitation

This chapter is a revision of the original chapter authored by Katie Menzel, MD and Dawn Nye, DO
References:

1. Practice alert for the perioperative management of patients with coronary artery stents: a report by the American Society of Anesthesiologists Committee on Standards and Practice Parameters. Anesthesiology 2009; 110:22-3


Review Questions:

1. For the patient in the vignette at the beginning of the chapter, after moving her to the ICU her heart rate is 111, noninvasive blood pressure is 104/66 what is the best next step?
   a. Begin an isoproterenol infusion
   b. Begin a dopamine infusion
   c. Begin a phenylephrine infusion
   d. Bolus 5 mg metoprolol IV

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

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
Introduction

Valvular heart disease can affect patients of all ages however it is most common in elderly patients. 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, these disorders often will eventually require surgical intervention.

Patient Case:
A 70 year old woman 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 cm² in addition to a severely hypertrophied left ventricle, which demonstrated poor filling. Fluid resuscitation was initiated along with vasopressor therapy.

Key Points:
- Physiologic goals for aortic stenosis (AS) are to maintain a low heart rate with adequate preload and 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, increased risk of atrial fibrillation and increased pulmonary artery (PA) pressures.
- Mitral regurgitation (MR) also results in an enlarged left atrium with increased PA pressures, and is treated with afterload reduction. Bradycardia should be avoided.
- Physiologic goals for tricuspid regurgitation (TR) include decreasing RV afterload and increasing RV contractility using pharmacologic agents.
surgery. Recent advancements in surgical and non-invasive techniques have allowed many, who were previously considered inoperable, the opportunity for surgical repair.

Each valvular disorder presents unique management challenges. 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, 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)

1. Pathophysiology

In the elderly, degenerative calcification causes thickening and fusion of the valve leaflets. Degeneration of a congenital bicuspid valve or rheumatic aortic valve disease are other causes of AS. Persistent contraction against a fixed resistance stimulates hypertrophy of the left ventricular wall resulting in diastolic dysfunction.

2. Diagnosis

Symptoms include angina, exertional dyspnea, and syncope.

Physical exam findings include: soft ejection murmur, diminished aortic component of S2, and pulsus parvus et tardus. ECG findings include: LV hypertrophy, strain pattern T wave inversion and ST depression. 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. Left heart catheterization can be used to calculate transvalvular gradient and valve area.

3. Management

Beat to beat blood pressure monitoring with an arterial line is often required as a drop in systemic vascular resistance can be dangerous because of the degree of LVH and an increased risk of developing ischemia. An alpha agonist such as phenylephrine is the agent of choice in the setting of hypotension since it maintains diastolic filling time by reflexively lowering the heart rate. Norepinephrine might be advantageous in patients with decreased ejection fraction due to its beta-1 activity.

Patients with AS are preload dependent and judicious use of fluids is necessary. Bedside ultrasonography is often helpful for evaluation of fluid status. Maintaining sinus rhythm and avoidance of tachycardia are important to maximize filling time and cardiac output. Thus, immediate cardioversion is necessary in the setting of supraventricular arrhythmias causing hemodynamic instability.
4. Treatment

Traditional surgical aortic valve replacement (SAVR) is the most common treatment for severe AS, but there are alternatives. Transcatheter aortic valve replacement (TAVR) for critical aortic stenosis is currently being performed in many patients deemed too high risk for traditional SAVR. Percutaneous balloon valvuloplasty may also be considered, although it is typically done for palliation in patients too frail for any of the aforementioned interventions.

**Aortic Regurgitation (AR)**

1. Pathophysiology

Aortic regurgitation can develop in two ways: abnormalities of aortic valve leaflets (calcific degeneration, bicuspid valve, destruction from endocarditis, rheumatic heart disease) and aortic disease (aneurysm of ascending aorta, aortic dissection). Acute AR from dissection or endocarditis can result in acute cardiovascular collapse. Chronic AR results in chronic volume overload, progressing to left ventricular dilatation and eccentric left ventricular hypertrophy. Patients with severe AR are at risk of myocardial ischemia due to reduced diastolic blood pressure and increased myocardial work.

2. Diagnosis

Symptoms include dyspnea and orthopnea. Physical findings include a diastolic murmur, wide pulse pressure, and diastolic hypotension. Echocardiography may demonstrate thickened valve leaflets, flail leaflets, a prolapsed valve, vegetations, and/or aortic root dilatation. Echocardiography will show a regurgitant jet across the aortic valve on color flow Doppler.

3. Management

Afterload reduction is paramount in order to maintain cardiac output, reduce left ventricular wall stress, and reduce the regurgitant fraction. Drugs such as angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, nitrates, and alpha-receptor blockers will reduce afterload and myocardial stress.

Usage of an intra-aortic balloon pump (IABP) is contraindicated in patients with moderate to severe AR. Inflation of the balloon during diastole will cause massive overload to the left ventricle causing acute decompensation.

4. Treatment

Patients with chronic severe AR who are symptomatic or have left ventricular dysfunction or dilatation should undergo surgical treatment. Asymptomatic patients should be followed closely and managed medically. Chronic mild AR in the perioperative period is often well tolerated.

**Mitral Stenosis (MS)**
1. Pathophysiology

Rheumatic heart disease is the most common cause of mitral stenosis. This can lead to fibrosis, fusion and calcification of the valve apparatus. This leads to underfilling of the left ventricle with pressure and volume overload of the left atrium. Chronic underfilling of the left ventricle may lead to myocardial atrophy, wall thinning, and reduced systolic function. Chronic pressure and volume overload of the left atrium may lead to atrial fibrillation, pulmonary congestion, and pulmonary hypertension. Severe MS can eventually result in right ventricular failure.

2. Diagnosis

Symptoms include signs associated with pulmonary congestion, including dyspnea, orthopnea, and coughing. Physical findings include a diastolic rumble with an opening snap. There is an increased tendency to develop atrial fibrillation. Echocardiography is used for definitive diagnosis and quantification of severity.

3. Management

Acute decompensation usually presents with an inciting event such as pregnancy, sepsis, or new onset atrial fibrillation. Pulmonary congestion is a hallmark feature and is treated with diuretics and respiratory support. Atrial fibrillation must be controlled and anticoagulation should be initiated, if indicated.

Hypotension should be treated with fluids and inotropes and an IABP may be considered. Norepinephrine should be used with caution since it may increase left atrial pressure. Tachycardia should be avoided as it decreases diastolic filling time. Patients with pulmonary hypertension and/or right ventricular failure may benefit from pulmonary vasodilators.

4. Treatment

Patients with moderate to severe MS who are symptomatic or have left atrial or pulmonary hypertension should be considered for surgical intervention. Rheumatic MS can sometimes be treated with percutaneous balloon valvuloplasty depending on the valvular morphology. For most patients mitral valve replacement is considered the treatment of choice.

Mitral Regurgitation (MR)

1. Pathophysiology

MR is commonly caused by myxomatous degeneration, a connective tissue disorder where the mitral leaflets and chordae thicken and elongate and the annulus dilates. The mitral valve leaflets will often prolapse or flail depending whether the chordae are elongated or ruptured. MR may also present secondary to left ventricular dysfunction from severe coronary artery disease. As the left ventricle remodels and loses its cylindrical shape, the papillary muscles become tethered and the ventricle dilates, causing MR due to poor
leaflet coaptation. Other causes of MR include endocarditis, rheumatic disease and papillary muscle rupture.

Chronic MR results in progressive left ventricular volume overload which causes ventricular dilatation. Untreated MR may eventually lead to atrial fibrillation, pulmonary hypertension, and right ventricular dysfunction. Acute MR from infarction causes acute left ventricular overload causing an abrupt increase in left ventricular end-diastolic and left atrial pressure which may progress to acute pulmonary edema, pulmonary hypertension, right ventricular failure, and cardiogenic shock.

2. Diagnosis

Symptoms include dyspnea and orthopnea. Physical exam findings include tachycardia and a holosystolic murmur at the apex radiating to the axilla. ECG will show left atrial enlargement. Echocardiography is required for diagnosis since it will show the degree and nature of MR, left and right ventricular function, and presence of pulmonary hypertension.

3. Management

Management is similar to that of AR. Afterload reduction with ACE inhibitors or calcium channel blockers and reduction of pulmonary congestion with diuretics are important. Atrial fibrillation may require rate control and/or anticoagulation. Acute decompensation is usually secondary to myocardial infarction, torn chordae, or dehiscence of a mitral prosthesis. Promoting forward flow with inodilators may be warranted in patients with reduced LV function. In contrast to AR, IABP support may be an appropriate therapy in MR.

4. Treatment

Definitive treatment consists of surgical repair or replacement. Mitral valve anatomy will determine the optimal surgical approach but repair is often preferred to replacement. Concomitant MAZE procedure may be indicated for patients with atrial fibrillation.

Tricuspid Regurgitation (TR)

1. Pathophysiology

There are two types of TR: functional and structural. Tricuspid regurgitation is most commonly functional in nature as a consequence of right ventricular failure from advanced left-sided disease leading to pulmonary hypertension, right ventricular dilatation and tricuspid annular dilatation. Structural tricuspid valve disease resulting from endocarditis, rheumatic disease, or carcinoid disease will often cause right ventricular volume overload. Over time, the right ventricle will begin to fail. Pulmonary hypertension is not often seen in structural TR.

2. Diagnosis
Symptoms may include fatigue, ascites, and lower extremity edema if right ventricular failure is severe. Clinical findings include systolic murmur that increases with inspiration, increased central venous pressure, and pulsatile liver. Echocardiography is required to assess the severity of TR, right ventricular function, and presence of pulmonary hypertension. Normal pulmonary artery pressures are indicative of structural TR.

3. Management

Perioperative hemodynamic goals for patients with TR and right ventricular dysfunction include maintaining appropriate preload, decreasing right ventricular afterload, and increasing right ventricular contractility. Milrinone and dobutamine are often used in severe right ventricular dysfunction. Inhaled nitric oxide may be used in patients with severe pulmonary hypertension as a means to decrease PVR.

4. Treatment

Tricuspid valve repair is indicated for moderate to 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 Sean Kiley MD.

References:


Review Questions:

1. Which of the following is a hemodynamic goal for aortic stenosis?
   a. Decrease afterload
   b. Limit intravascular volume replacement
   c. Avoid tachycardia
   d. Avoid bradycardia

2. Which of the following is contraindicated in aortic regurgitation?
   a. Tachycardia
   b. Afterload reduction
   c. Intra-aortic balloon pump therapy
   d. Surgical correction

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
Intraaortic Balloon Pumps

The intraaortic balloon pump is the most commonly used mechanical circulatory assist device. It uses intermittent balloon inflation in the thoracic aorta to both increase coronary perfusion and increase cardiac output through afterload reduction.

The Device

The IABP is made up of a flexible catheter with two lumens, one leading to a cylindrical polyethylene balloon and the other to a distal port for aspiration, flushing, or pressure monitoring. A mobile console drives inflation of the balloon with helium gas, which is easily absorbable in the bloodstream in the event of balloon rupture.

Key Points:

- The IABP uses intermittent balloon inflation in the aorta to increase myocardial oxygen supply to demand ratio.
- The balloon is placed in the descending aorta just distal to the L subclavian artery. Precise timing of inflation and correct sizing of the balloon are important for optimal augmentation.
- Indications include high-risk PCI, acute MI, or cardiogenic shock.
- IABP should not be utilized in patients with severe aortic valvular pathology, major aortic abnormalities, or severe peripheral vascular disease.

Patient Case:

A 71-year-old man with diabetes mellitus (DM), hypertension (HTN), and hyperlipidemia (HLD) is admitted to the ICU following emergent coronary angioplasty for a ST elevation myocardial infarction (STEMI). His cardiac catheterization shows triple vessel coronary artery disease (CAD) with an ejection fraction of 10-15%. An emergent intraaortic balloon pump (IABP) is placed through the left femoral artery. What is an IABP and how does it affect hemodynamics? What are indications and potential complications of an IABP?
Placement

The IABP is placed percutaneously (rarely through surgical cutdown) through the femoral artery and less commonly through the right subclavian or axillary artery. The balloon sits in the descending thoracic aorta about 2 cm distal to the takeoff of the left subclavian artery (Figure 1). Placement of the IABP may be guided by transesophageal echo (TEE) or fluoroscopy. Additional confirmation of proper placement can be had by obtaining a chest x-ray.

 Physiology

IABP counterpulsation increases myocardial oxygen supply and decreases myocardial oxygen demand. Inflation of the balloon occurs during diastole, displacing blood to the proximal aorta and augmenting coronary perfusion. Rapid deflation just before the start of systole results in a vacuum effect, displacing blood from the aorta; this decreases left ventricular (LV) afterload and myocardial oxygen requirement.

1. The following cardiovascular changes occur with IABP counterpulsation:
   a. Decrease in systolic pressure, increase in diastolic pressure
   b. Decrease in LV wall tension and rate of LV pressure rise
   c. Increase in LV ejection fraction and cardiac output
   d. Decrease in LV end diastolic volume and pressure

2. Coronary Perfusion: In normal physiologic conditions, coronary autoregulation occurs by vasoconstriction or dilation of sphincters at the entrance to coronary arterioles and guarantees constant myocardial blood flow over a wide range of aortic pressures (60 to 140 mmHg). In situations of exhausted autoregulation, myocardial blood flow becomes
dependent on perfusion pressure, and IABP counterpulsation can improve coronary blood flow. Autoregulation may be impaired in the perfusion territory of a critical, subtotal stenosis, in ischemic myocardium, or in patients with mean arterial pressures below the autoregulatory range.

Optimizing IABP Counterpulsation

1. Balloon Sizing and Positioning
   a. Balloon length should extend from just distal to the left subclavian artery to above the renal arteries. The closer the balloon is to the aortic valve, the greater the diastolic pressure augmentation. Lengths vary between manufacturers from 22 to 27.5 cm. On chest x-ray, the balloon should be 2 cm above the left main bronchus.
   b. The ideal inflated balloon diameter is 90-95% of the descending aorta. Inflated diameters vary between 15 and 18 mm.
   c. Balloon volume should be equal to the volume of blood in the aorta at any time. Most adult IABPs utilize a 40 cc balloon, and 50 cc balloons may be used in taller patients. A balloon that is too large increases vascular morbidity, while a balloon that is too small is less effective.

2. Precise timing of balloon inflation and deflation is vital for hemodynamic optimization. Inflation occurs during diastole, beginning with aortic valve closure, and rapid deflation occurs just before the onset of LV ejection. Balloon inflation and deflation may be triggered by the patient’s EKG or arterial line waveform, a pacemaker, or a set internal rate. Slower, regular heart rhythms are optimal for IABP function.
   a. EKG triggering: Deflation is during the QRS-T interval and is triggered by the R wave (Figure 1). Inflation occurs during the T-P interval and is triggered by the T wave. Poor tracing, electrical interference, or arrhythmia may affect balloon triggering.
   b. Aortic pressure waveform triggering: Deflation occurs just prior to the upstroke which corresponds to aortic valve opening. Inflation occurs at the dicrotic notch which represents aortic valve closure.

3. IABP Waveform: Balloon inflation during diastole results in a second pressure wave during the diastolic segment of the aortic pressure waveform. The IABP may be set to augment every heart beat (i.e. 1:1) or less frequently (e.g. 1:2 or 1:3). If the IABP does not augment every beat, there will be assisted and unassisted systolic and diastolic waveforms (Figure 2). An augmentation ratio of 1:1 provides the most assistance, and 1:3 augmentation provides minimal support.
   a. Early inflation can cause premature closure of the aortic
valve, increased afterload, aortic regurgitation and increased LV end diastolic volume (Figure 3).

b. Late inflation leads to suboptimal coronary perfusion.

c. Early deflation leads to suboptimal coronary perfusion and potential for retrograde coronary and carotid blood flow as well as suboptimal afterload reduction.

d. Late deflation causes increased afterload and increased length of isovolumetric contraction.
**Indications**

While the IABP is the most widely used mechanical circulatory support device, large clinical trials have not shown a significant benefit. (3) Generally, IABP is thought to be most useful in patients during high-risk percutaneous coronary intervention (PCI), acute myocardial infarction (MI), and cardiogenic shock. Other uses of IABP include patients with severe left main coronary artery disease awaiting surgical intervention, failure to wean from cardiopulmonary bypass, and ischemic mitral regurgitation.

1. **High Risk PCI:** (5) PCI causes brief periods of ischemia which can lead to a downward spiral of worsened LV function, cardiogenic shock, and hemodynamic collapse especially when the target lesion is supplying a significant proportion of the myocardium. Several small retrospective observational and randomized studies have supported use of IABP for high-risk PCI. The BCIS-1 trial randomized 301 patients undergoing high-risk PCI to either elective IABP placement prior to PCI or no planned IABP insertion. No significant difference was found in outcome (death, acute MI, stroke, or further revascularization) at hospital discharge or 6-month follow up.

2. **Acute MI:** (6) In patients presenting with STEMI, primary PCI improves outcomes. However, even after successful PCI, a subset of patients have ongoing ischemia - possibly due to microembolization of atherosclerotic debris, vasospasm, or external compression by edema. Animal and human studies have shown that IABP insertion in high-risk patients with STEMI may reduce this outcome and improve myocardial salvage. The CRISP AMI trial randomized 337 patients with anterior STEMI without shock to either elective IABP placement prior to PCI or no planned IABP insertion. Final infarct size assessed by cardiac MRI (primary endpoint) showed no difference with a trend toward larger infarct area in the IABP group. However, all cause mortality at 6 months showed a non-significant trend toward improvement in the IABP group, and the exploratory composite endpoint of death, shock, or new worsening heart failure was significantly better for the IABP group.

3. **Cardiogenic Shock:** (7) In patients with acute MI and resulting cardiogenic shock, pharmacological therapy often fails and may worsen ischemia by increasing myocardial oxygen demand. IABP counterpulsation in this population has shown conflicting outcomes. The IABP SHOCK II trial randomized 600 patients with acute MI complicated by cardiogenic shock expected to undergo early revascularization therapy and receive optimal medical therapy to use of IABP counterpulsation or not. No significant difference was found in 30-day mortality, time to hemodynamic stabilization, length of ICU stay, serum lactate levels, dose and duration of catecholamine therapy, and renal function.
4. 2013/2014 ACCF/AHA Practice Guidelines give a class IIa recommendation for use during STEMI complicated by cardiogenic shock as well as for non-STEMI acute coronary syndrome with severe persistent or recurrent ischemia despite intensive medical therapy, especially when awaiting PCI. (9,10)

Contraindications to IABP Placement

1. Aortic abnormalities: Anything other than mild aortic regurgitation is a contraindication, as diastolic balloon inflation will worsen the degree of aortic regurgitation. Aortic dissection, clinically significant aneurysm, or presence of aortic stents are also contraindications.

2. Severe peripheral vascular disease or aortic disease increases the risk of arterial thromboembolism.

3. Other contraindications are uncontrolled sepsis, cancer with metastases, or severe coagulopathy.

Complications of IABP

1. Arterial thromboembolism can result in end organ dysfunction or failure including bowel ischemia, limb ischemia, stroke, or acute kidney injury.

2. Vascular trauma can lead to arterial dissection

3. Direct arterial occlusion can result from improper balloon placement (e.g. renal artery, left subclavian artery).

4. Balloon rupture can cause helium gas embolism.

5. Thrombocytopenia may be caused by platelet deposition on the IABP membrane or related to anticoagulation with heparin.

6. Hemorrhage, sepsis, peripheral neuropathy can be associated with any indwelling groin catheter.

7. Immobility: If prolonged IABP support is anticipated, axillary insertion may allow for more patient mobility and decreased deconditioning.

Anticoagulation

There is variability in use of anticoagulation for IABP. Many institutions routinely use anticoagulation, especially when the expected duration of support is indeterminate.

References:

1. Papaioannou TG, Stefanadis C: Basic principles of the intraaortic balloon pump and mechanisms affecting its performance. ASAIO J 2005; 51(3):296-300


**Review Questions:**

1. An elderly man is admitted with acute STEMI, and an IABP is placed emergently during PCI. Afterwards while in the ICU, the patient suddenly develops left arm pain and intermittently the radial pulse cannot be palpated. What is the most likely diagnosis?

   a. Balloon migration over the takeoff of the L subclavian artery
   b. L subclavian artery thromboembolism
   c. Worsening cardiogenic shock with poor perfusion to the extremities
   d. Vasospasm of the L radial artery
2. A patient admitted with STEMI who has undergone high-risk PCI has an IABP in place. The patient has been stable on low-dose vasopressors and inotropic support when suddenly the blood pressure begins to fall. Which is least likely causing this patient’s clinical deterioration?
   a. A new ventricular arrhythmia causing the IABP to be unable to properly sense
   b. IABP being triggered by EKG which has become disconnected
   c. IABP inflation just after aortic valve closure and deflation just prior to onset of systole
   d. IABP inflation while the aortic valve is open

3. Which patient would be the most likely to benefit from IABP placement?
   a. A 76 year-old woman with severe aortic stenosis admitted with cardiogenic shock
   b. A 25 year-old man with idiopathic dilated cardiomyopathy admitted in cardiogenic shock, on high dose vasopressors and inotropic support
   c. A 65 year-old man admitted with STEMI who has just undergone PCI and has signs of persistent ischemia including persistent ST elevations on EKG
   d. An 89 year-old man with severe peripheral vascular disease who has had a femoral-popliteal artery bypass in the past, admitted with STEMI about to undergo PCI.

4. Which of the following statements regarding IABP counterpulsation is true?
   a. IABP counterpulsation causes an increase in left ventricular end diastolic volume
   b. In patients with critical coronary artery disease, IABP improves coronary blood flow through increased diastolic perfusion pressure
   c. Augmentation is most effective when stroke volume is less than IABP volume
   d. Severe mitral regurgitation is a contraindication to IABP placement
With improvements in surgery and postoperative care, 90% of children with congenital heart disease (CHD) survive to adulthood and adults now outnumber children with CHD. These adult patients may require re-interventions and manifest long-term sequelae such as arrhythmias and heart failure. While many of these patients will remain under the care of a pediatric heart team, an increasing number are likely to present to adult ICUs. Of concern are reports suggesting that a large fraction of adults with CHD are lost to follow-up after reaching adulthood and so may present to non-regional centers.

Categories such as cyanotic vs non-cyanotic or obstructive vs non-obstructive are often used to categorize CHD. While these categories are useful for organizing the different types of CHD they have little clinical utility. Lesions are best considered separately with the understanding that different patients with the same condition may present very differently.

**Patient Case:**
A 30 yr old man presents with GI bleeding from bleeding esophageal varices secondary to hepatic fibrosis. He has a past history of having undergone a Fontan procedure as a child for hypoplastic left heart (Figure 1). He is hypotensive, cyanotic, and appears severely ill. His hemoglobin is 6 gm/dL, lactate is 12 mmol/L, and his pH is 7.15.
Issues Common to Patients with CHD

A. Vascular access:

1. Arterial pressure monitoring:

   Arterial blood pressure may be challenging for a variety of reasons in the patient with CHD. If the subclavian artery has been used to provide a blood supply to the pulmonary circulation to palliate a cyanotic heart defect such as pulmonary atresia (a modified Blalock-Taussig shunt), subclavian artery steal or occlusion may occur and monitored pressures may be inaccurate on that upper extremity. With a “classic” Blalock-Taussig shunt, the subclavian artery itself (rather than a Gore-tex graft) is sewn to the pulmonary artery. The respective arm will be fed by collaterals, and the pulse is not usually palpable and also should not be used for blood pressure monitoring, even if the shunt is taken down in subsequent surgeries. If a residual coarctation of the aorta is present, cerebral blood pressure is determined by the pre-ductal limb (the right arm in the case of a normal left-arch), while the lower extremity blood pressure reflects the renal and intestinal blood pressure. Difficult arterial line placement can also occur in the presence of a previous radial artery cut-down.

2. Central venous catheter placement:

   Venous access may also present challenges. Prior ECMO
cannulation commonly leads to occlusion/thrombosis of the internal jugular veins and ultrasound guidance should be used to assess patency prior to cannulation attempts. A persistent left superior vena cava may result in a catheter placed in the left internal jugular vein passing into the coronary sinus. Pulmonary valve prosthesis or right ventricle-pulmonary artery conduits may result in difficulty floating a pulmonary artery catheter. After a cavopulmonary anastomosis, (Glenn shunt or Fontan procedure) venous pressure monitoring from the internal jugular or subclavian vein will reflect the mean pulmonary artery pressure rather than purely central venous pressure.

B. Air embolism:

Many of these patients will have a residual intra-cardiac shunt and have the potential to allow air emboli to reach the systemic circulation. Particular attention should be paid to de-airing and de-bubbling lines, a practice which may not be well established in all adult ICUs. Air filters can be used but they add significant resistance to flow and do not substitute for vigilance.

C. Multiple organ dysfunction:

Restrictive lung disease is common in this population with a prevalence of nearly 50% and is an independent predictor of mortality. Cyanosis is due to either inadequate pulmonary blood flow or right to left shunts. Renal dysfunction is also common and is likewise present in 50% of adults with CHD. Similarly, hepatic impairment is frequent in patients with right ventricular dysfunction or single ventricle physiology and is associated with coagulation abnormalities, particularly in patients with fontan circulation. Cyanotic patients develop polycythemia and iron deficiency despite erythrocytosis, as well as thrombocytopenia, platelet dysfunction, factor deficiencies, hyperfibrinolysis and disseminated intravascular coagulation.

C. Arrhythmias:

Arrhythmias are the most common complication in patients with CHD. Of the atrial arrhythmias, atrial flutter is the most common and is particularly common in patients with diseased atria [Ebstein’s anomaly, atrial-switch procedure for d-transposition, classic right atrium to pulmonary artery Fontan, tetralogy of Fallot (TOF)]. Atrio-ventricular block is also common and vagal maneuvers or adenosine can be diagnostic. Atrial fibrillation is less common but can occur.

Hemodynamically significant flutter is treated with cardioversion whereas long-term management often consists of rhythm control with class III agents (amiodarone, sotalol, dofetilide) as rate-control can be difficult. Management may be complicated by the development of bradyarrhythmias due to co-existent sinus and AV nodal dysfunction. Ablation may be
used for refractory/symptomatic flutter and may require multiple attempts.

Cardioversion should be preceded by transesophageal echocardiography in patients with a classical Fontan. The venous conduits can be enlarged and associated with sluggish flow that support thrombus, despite anticoagulation.

Ventricular arrhythmias are 100 fold more common in patients with CHD compared to the general population and present as palpitations, syncope or cardiac arrest. They are often precipitated by hemodynamic deterioration and systolic dysfunction. Patients with TOF are at a particularly high risk of sustained ventricular tachycardia, syncope, or sudden death. Sustained wide-complex tachycardia is often an indication for an electrophysiological study, ICD implantation and/or ablation therapy.

Bradycardia and heart block can also be a problem and permanent pacing should be considered in any symptomatic patient. Lead placement may be challenging as endocardial lead thrombosis can potentially lead to systemic thromboembolism in the presence of intra-cardiac shunts. Transvenous placement may not even be possible in some patients with an extra-cardiac Fontan where the vena cavae are connected directly to the pulmonary artery.

D. Coronary artery disease:

While cyanotic CHD appears to be associated with a decreased risk of CAD, other forms of CHD may confer higher risk. Patients with coarctation of the aorta can have significant hypertension even after repair and be at increased risk of CAD. Coronary ostial stenosis should be suspected in those who have had previous coronary manipulation (transposition of the great arteries s/p arterial switch procedure, anomalous left-coronary artery from the pulmonary artery s/p reimplantation) and symptoms of ischemia or ventricular dysfunction.

E. Heart failure:

Heart failure is a major cause of morbidity and mortality in patients with CHD, particularly in those patients with single ventricle physiology, transposition of the great arteries, or systemic right-ventricles. Heart failure in CHD is more likely to be caused by right ventricular dysfunction.

F. Left ventricular outflow obstruction:

This can exist at the subvalvular, valvular or supravalvular level. The most common obstructive lesion is a bicuspid aortic valve with an estimated occurrence of 1-2% of the population. Bicuspid valve may be stenotic or regurgitant and is often accompanied by aortic root dilation that may lead to aortic aneurysm formation or dissection. While percutaneous aortic valvuloplasty is the procedure of choice in children and young adults, increasing age is associated with increased valve
thickening that may require surgical correction.

G. Right ventricular outflow obstruction:

Pulmonary valve stenosis is by far the most common cause of RV outflow obstruction and this is often associated with dilation of the distal main pulmonary artery. Percutaneous pulmonary balloon valvuloplasty is the treatment of choice unless the valve is dysplastic, heavily calcified or there is no significant pulmonary regurgitation.

Specific Conditions

A. Single ventricle physiology

The adult single-ventricle population accounts for approximately 1.5% of adults with CHD (20,000 people in the USA), but demands a disproportionate share of health care resources. The Fontan procedure was first performed in the early 1970s - originally for tricuspid atresia - however its use has expanded into the management of pulmonary atresia, hypoplastic left heart syndrome and other lesions. Many of these patients are now reaching adulthood and will require reoperation for a failing circulation - the so called “Fontan conversion”. See patient case.

B. Tetralogy of Fallot

This is the most common cyanotic congenital heart lesion, and consists of a VSD, infundibular and valvular pulmonary stenosis, overriding aorta and RV hypertrophy. It presents as a clinical spectrum from severe cyanosis to noncyanotic patients with a mild VSD and pulmonary stenosis. Surgical correction often results in pulmonary regurgitation that was once thought to be benign but is now thought to be the cause of RV dysfunction and dilation over time. RV dysfunction is also associated with arrhythmias and increased risk of sudden death. Right ventricular outflow tract or pulmonary artery procedures account for 21% of all corrective procedures performed as an adult.

C. Atrial Septal Defect

There are four types of ASD – primum, secundum, sinus venosus and coronary sinus ASD. Irrespective of the type, left to right shunting through an ASD leads to right heart enlargement and signs of RV overload. Undiagnosed, large shunts may cause pulmonary hypertension. Paradoxical embolism can occur even in the presence of predominant left to right shunting. Most people who have their ASD diagnosed as an adult are asymptomatic and the lesion may be closed in the catheterization laboratory or by surgery. Primum and sinus venosus ASDs should be closed surgically.

D. Ebstein’s anomaly

This is a congenital defect of the tricuspid valve with apical displacement of the posterior and septal leaflets. It is
associated with conduction abnormalities, tricuspid regurgitation, and RA hypertrophy. This is one of the “big 3” common abnormalities (along with the failing Fontan and pulmonary valve disease) that require surgical treatment as adults. The operation includes tricuspid valve repair or replacement with or without repair of an atrial septal defect, arrhythmia surgery (the Maze procedure) and coronary artery bypass grafting. The main risk factor for poor outcome is left ventricular dysfunction and this may warrant consideration for heart transplantation.

E. Transposition of the great arteries

With TGA, the aorta arises from the morphological RV and the pulmonary artery arises from the morphological LV causing a parallel circulation that is nonsurvivable without mixing between the two circulations. Adult survivors of the atrial switch procedure (Mustard or Senning) frequently have significant residual cardiac disease with baffle leaks or obstruction. Atrial flutter and sinus-node dysfunction are very common in these patients. The RV functions as the systemic ventricle and over time heart failure often develops.

The first arterial switch (Jatene) procedure was performed nearly 40 years ago and has undergone a number of modifications. The arterial switch procedure results in the LV remaining the systemic ventricle and the RV remaining as the pulmonary ventricle. Currently, there is an expected 90% survival at 20 years, which represents a substantial improvement over the atrial switch procedure. As part of arterial switch, the coronary arteries are surgically relocated to the neo aorta and the long-term outcome of the coronary arteries remains unknown. Coronary lesions are an important cause of mortality in long-term survivors.

F. Aortic coarctation

Aortic coarctation usually presents during childhood but may first present in an adult as a consequence of a diagnostic workup for hypertension. Re-coarctation following initial repair is also quite common. While echocardiographic evaluation of the aorta is the first diagnostic step, cardiac magnetic resonance imaging or CT angiography is usually necessary as part of a full assessment. Blood pressure cuff gradient of the pre-coarc extremity (right arm in normal aortic arch) compared to the lower-extremity blood pressure offers a quick and accurate assessment of the coarctation degree of restriction. Indications for intervention of the aorta include symptoms related to the coarctation such as exertional headache or lower limb claudication, and/or refractory hypertension. Percutaneous balloon dilation, stent placement or surgical repair may be considered.

Case Study Discussion:

The issue specific to the Fontan physiology is that there is no
functioning right ventricle and therefore blood flow is passive from the systemic veins into the pulmonary circulation and finally to the ventricle. Pulmonary blood flow/cardiac output is dependent upon the driving pressure from the systemic veins into the pulmonary artery and the transpulmonary pressure gradient. Forward flow is dependent upon maintaining low pulmonary vascular resistance, an adequate transpulmonary gradient, and a somewhat elevated systemic venous pressure. Anything that increases pulmonary vascular resistance (acidosis, hypercarbia, hypoxia, pain) or decreases the transpulmonary gradient (increased left atrial pressures) can significantly decrease cardiac output. Fontan patients commonly have an elevated CVP (typically in the 10–15 mmHg range), low cardiac output, high systemic vascular resistance and mild but significant hypoxia. The chronically elevated central venous pressures lead to hepatic, renal and pulmonary disease as well as a protein losing enteropathy. Chronic venous hypertension and a low cardiac output promote a pro-coagulant state that is managed with either aspirin and/or warfarin.

Volume management can be challenging. Hypovolemia will decrease cardiac output as these patients cannot compensate to maintain pulmonary flow by increasing heart rate or ejection fraction (there is no right ventricle). Conversely, volume overload can cause increased atrial pressures, particularly in the presence of ventricular dysfunction, and result in decreased venous return.

This chapter is a revision of the original chapter authored by Anila Balakrishnan MD and Dawn Nye DO.

References:


**Review Questions:**

1. Which of the following is the most common reason for hospital admission for patients with adult CHD?
   
   a. Arrhythmias
   
   b. Heart Failure
   
   c. Respiratory distress
   
   d. Myocardial ischemia

2. Which of the following is true?
   
   a. Repaired simple shunts (ASD, VSD, PDA) require specialist care
   
   b. Repaired simple shunts required prophylaxis for bacterial endocarditis
   
   c. Positive pressure ventilation is beneficial for right heart failure
   
   d. In a patient with a modified Blalock-Taussig shunt, blood pressure should be measured in the arm contralateral to the repair.

3. After a Fontan procedure, there may be dysfunction of which of the following organ systems?
   
   a. Hepatic
   
   b. Renal
   
   c. Gastrointestinal tract
   
   d. All of the above
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.

**Key Points:**

- Extracorporeal life support (ECLS) is a comprehensive term that describes all manners 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 PFO or ASD, AI, MS, VSD and ventricular thrombus.

**Patient Case:**
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.
Indications

1. Cardiac failure
   A. Refractory cardiogenic shock
   B. As a bridge to recovery, to heart transplantation or to placement of a long term supportive device

2. Respiratory failure
   A. Severe hypoxemic respiratory failure in patients with ARDS despite the optimization of ventilatory support
   B. Hypercarbic respiratory failure with intractable respiratory acidosis
   C. Bridge to lung transplantation or severe primary graft dysfunction after lung transplantation

3. Combined cardiac and respiratory failure
   A. Failure to wean from cardiopulmonary bypass (CPB) after cardiac surgery
   B. Post cardiac arrest cardiopulmonary support
   C. Acute pulmonary embolism or amniotic fluid embolism

Modes of ECLS

1. Venoarterial (VA ECLS) – Venous-arterial cannulation is used for cardiac failure (tissue hypoxia secondary to hypoperfusion) with or without respiratory failure

2. 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. (1)
1. Vascular access for cannulation

A. 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 1).

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 2).

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 3).

B. 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 4). Central VV ECLS is most commonly from the right atrium to the pulmonary artery.
2. Oxygenator – works as an artificial lung where the blood is saturated with oxygen and CO\textsubscript{2} is removed. Gas is passed in a countercurrent manner allowing exchange across the membranes. 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.

3. Tubing system – length and diameter determine the blood flow resistance (Poiseuille's law).

4. Sweep gas – fresh gas is delivered to the membrane oxygenator to allow for gas exchange. A blender that mixes air with oxygen in desired proportions determines the composition. The gas flow rate determines the CO\textsubscript{2} clearance, and the pump blood flow determines the oxygenation.

5. Driving force (pump)
   A. Roller pump – the roller compresses the tubing and forces the blood forward with each turn. Roller pumps require a reservoir between the venous drainage cannula and the pump and utilize gravity for drainage into the reservoir.
   B. Centrifugal pump – 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 arterial pressure, mixed venous oxygen saturation (SvO\textsubscript{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).

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 hypercapnia with a pH < 7.15 or excessively high inspiratory pressures above 35-40cmH\(_2\)O. (3)
The primary determinants of arterial oxygenation (PaO\textsubscript{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\textsubscript{2} 30%, respiratory rate 5/min, plateau pressures below 20-25cm H\textsubscript{2}O).

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\textsubscript{2} of the gas sample taken before the oxygenator is higher than the PaO\textsubscript{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\textsubscript{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**

1. Clot formation – especially important in VA ECLS, because large and mobile clots in the circuit can result in systemic thrombembolism.

2. 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.

3. 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.

4. 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.

5. Cannulation related complications – bleeding, arterial dissection or pseudoaneurysm, limb ischemia resulting from arterial cannula malposition or venous congestion of the limb resulting from the venous cannula.

6. Nosocomial infection

7. Abdominal compartment syndrome – often due to massive fluid resuscitation in an effort to achieve adequate ECLS flows.

**VENTRICULAR ASSIST DEVICES**

Ventricular Assist Devices (VADs) are used for mechanical cardiac support in patients with acute or chronic heart failure on maximal inotropic support. A device that provides support to the left ventricle is referred to as an LVAD, to the right ventricle as an RVAD and to both ventricles as a BiVAD. VADs can be used as a bridge to recovery, a bridge to heart transplantation or as a permanent support – destination therapy. Increasingly, LVAD therapy has become an accepted intervention for the treatment of late-stage heart failure because of the lack of organ donors.

**Indications** (5)

1. Cardiogenic shock following acute myocardial infarction
2. Cardiogenic shock following cardiac surgery
3. Acute heart failure secondary to myocarditis or acute cardiomyopathy
4. Decompensation or progression of chronic heart failure
5. Primary graft dysfunction after heart transplantation
6. 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).

**Difference between ECLS and VAD**

ECLS and VAD are similar in many ways in terms of function and placement. The main difference is that ECLS has the ability to oxygenate the blood while VADs are circulatory support systems only. Unlike ECLS, many VADs are created to be portable and convenient to live with, especially for patients with VADs used as destination therapy.

**Technical considerations**

1. Cannulation sites
A. 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 5).

B. LVAD – the inflow cannula is placed in left atrium or left ventricular apex; the outflow cannula is placed in the ascending aorta

C. RVAD – the inflow cannula is placed in the right atrium; the outflow cannula is placed in pulmonary artery

2. Position of the device relative to the body

A. Extracorporeal – consist of a bulky machine situated outside the body

B. Intracorporeal – small and light devices, associated with decreased bleeding and infection rate compared with extracorporeal devices.

3. VAD types based on flow pattern

A. Pulsatile flow devices – these devices eject the blood in a pulsatile fashion into the aorta. They are extracorporeal, require the presence of valves, and valve malfunction is common long term.

B. Non-pulsatile or continuous flow devices – these devices are implantable, do not require valves, and use axial or centrifugal pumps creating non-pulsatile (continuous) flow. Non-pulsatile VADs have been demonstrated to offer improved patient survival and device durability in patients requiring long-term hemodynamic support. The majority of durable VADs currently used are non-pulsatile, although there is growing interest in re-establishing pulsatility to VADs since continuous flow results in more endothelial dysfunction and bleeding.

Cardiac conditions that require correction before VAD implantation

1. Intracardiac shunts (e.g. patent foramen ovale or atrial septal defect) – Quiescent intracardiac shunts may become clinically significant once chamber pressures change when VAD support...
is initiated. This imposes risk for right to left shunt and severe hypoxemia.

2. Aortic insufficiency (AI) – results in regurgitant blood flow through the incompetent valve into the LV and then back into the device. This recirculation between the LV and the LVAD leads to increased pump flow, LV distension, and poor forward flow resulting in tissue 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, and can be embolized through the LVAD inflow cannula.

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, with only 30-40% surviving to discharge. Patients who have VADs placed in an elective fashion have more favorable outcomes.

Approximately 30% of patients with LV failure who undergo VAD insertion have concomitant RV failure, but only a small proportion (~10%) of them require RVAD placement. After LVAD implantation, the output of the right ventricle has to increase to match the LVAD work. This leads to increase of RV preload and therefore RV afterload has to be decreased in order to improve compliance. In addition, leftward shift of the intraventricular septum and change in LV motion after LVAD implantation may further impair RV contractility. Optimization of RV function is therefore critical after LVAD placement, and can be achieved through inotropic support and decreasing RV afterload by using agents such as epinephrine, milrinone, epoprostenol and inhaled nitric oxide.

Vigilant monitoring of intravascular volume is important for optimal VAD function. Hypovolemia creates a suction 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. (Table 1)

With non-pulsatil devices, pulse pressure is very narrow and often absent. Noninvasive blood pressure monitoring, using the oscillation method, as well as pulse oximetry are inapplicable. Arterial line monitoring results in a tracing, which reflects the MAP. Due to the lack of pulsatile flow, placement of arterial catheters can be challenging and requires ultrasound guidance.
Table 5.7.1 Etiology of Systemic Hypotension in Patients with LVAD

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Pump Flow</th>
<th>CVP</th>
<th>PCWP</th>
<th>CO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypovolemia</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>RV Failure</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>VAD Failure</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Aortic Insufficiency</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Sepsis</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
</tr>
</tbody>
</table>

CVP: central venous pressure; PCWP: pulmonary capillary wedge pressure; CO: cardiac output

Complications

1. Bleeding – Largely due to systemic anticoagulation.
   Gastrointestinal bleeding is especially common in patients with continuous flow VAD, thought to be related to damage of von Willebrand multimers by the pump, leading to dysfunction in platelet aggregation. In addition, patients with cardiogenic shock often have hepatic congestion and renal dysfunction. Both of these processes lead to problems in platelet function and the coagulation cascade, which can contribute to hemorrhage early after VAD placement.

2. Inflow cannula malposition – May result in obstruction and inadequate drainage

3. Thromboembolic complications – Axial flow pumps are associated with a higher thromboembolic rate. Systemic anticoagulation is of utmost importance.

4. 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.

5. 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.

References:


**Review Questions:**

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

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

3. For which of the following patients is initiation of ECLS most appropriate?
   a. 78 yr old man with lung cancer and obstructive pneumonia with severe hypercapnea and acidemia despite optimized mechanical ventilation
   b. 43 yr old woman with end stage lung disease due to ILD awaiting bilateral lung transplantation
   c. 28 yr old man with idiopathic pulmonary hypertension intubated for severe hypoxemia, whose pulmonary artery pressures responded well to inhaled nitric oxide
   d. 56 yr old woman admitted for large spontaneous intracranial bleeding who sustained cardiac arrest 72 hours after admission.
Chapter 6

Gastroenterology Topics
I. Epidemiology

Gastrointestinal hemorrhage (GIB) is a frequent cause of both Emergency Department visits and Intensive Care Unit admissions with an incidence of approximately 50-100 per 100,000 persons/year. Currently, GIB affects approximately 1.5% of patients in the ICU, although estimates of GIB in ICU patients not receiving prophylaxis range from 5% to 25%. The overall incidence of hospital-acquired GIB appears to be decreasing, presumably due to increased prophylaxis, treatment of Helicobacter pylori (H. pylori), and a clinical practice shift towards early enteral feeding. (1) Mortality rates for patients with massive GIB (defined as GIB with hemodynamic instability) range from 20-39%. (2)

II. Causes

GIB is generally categorized anatomically. Upper GIB is defined as bleeding

Key Points:

- Although decreasing in incidence secondary to prophylaxis, gastrointestinal (GI) bleeding in the ICU occurs and is associated with significant mortality.
- For both upper and lower GI bleeds, endoscopy remains the initial diagnostic and therapeutic intervention of choice.
- Histamine receptor antagonists (H2RA) and proton pump inhibitors (PPI) are effective for prophylaxis, but their use may increase nosocomial pneumonia and Clostridium difficile (C. diff) infections.
- Surgery and/or interventional radiology should be consulted early for refractory bleeding despite endoscopic interventions.

Patient Case:

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.
proximal to the suspensory ligament of the duodenum (“Ligament of Treitz”), located between the third and fourth part of the duodenum. Lower GIB is located distal to the suspensory ligament. Upper GIB is much more common than lower GIB, and is generally further subcategorized as variceal or nonvariceal bleeding. Variceal bleeding most commonly occurs in the setting of hepatic cirrhosis and is associated with higher mortality than most other causes of GIB. Table 1 contains common causes of GIB.

### III. Risk factors

GIB has numerous risk factors, most of which are systemic etiologies that cause overwhelming stress on the GI tract (hypotension, sepsis, surgery, low flow states, etc.). Specific types of GIB often have different predisposing factors (e.g. variceal bleeding and cirrhosis; aortoenteric fistula and previous aortic surgery). Table 2 contains risk factors for GIB.

#### Table 6.1.1 Causes of GI Bleeding

<table>
<thead>
<tr>
<th>Upper</th>
<th>Lower</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peptic ulcer disease (H.pylori, NSAIDs)</td>
<td>Diverticular disease</td>
</tr>
<tr>
<td>Esophageal and gastric varices (liver failure)</td>
<td>Colitis (ischemic, infectious, inflammatory)</td>
</tr>
<tr>
<td>Mallory-Weiss tears (increased abdominal pressure after vomiting)</td>
<td>Hemorrhoids or fissures</td>
</tr>
<tr>
<td>Gastritis (NSAIDs, Crohn’s)</td>
<td>Angiodysplasia/ vascular ectasias</td>
</tr>
<tr>
<td>Esophagitis (GERD)</td>
<td>Polyps/ neoplasms</td>
</tr>
<tr>
<td>Carcinomas</td>
<td>Meckel’s diverticulum</td>
</tr>
<tr>
<td>Stress-related mucosal damage</td>
<td>Colonic tuberculosis</td>
</tr>
<tr>
<td>Vascular malformation (gastric antral vascular ectasia)</td>
<td>Aortoenteric fistula</td>
</tr>
<tr>
<td>Hemobilia (trauma, s/p ERCP, gallstone, inflammation)</td>
<td>Infectious diarrhea (viral, bacterial, parasitic)</td>
</tr>
<tr>
<td>Aortoenteric fistula</td>
<td>Dieulafoy lesion (colonic)</td>
</tr>
<tr>
<td>Pancreatic pseudocyst or pseudoaneurysm</td>
<td></td>
</tr>
<tr>
<td>Hemosuccus (bleeding from pancreatic duct)</td>
<td></td>
</tr>
<tr>
<td>Dieulafoy lesion (gastric)</td>
<td></td>
</tr>
</tbody>
</table>

#### Table 6.1.2 Risk Factors for GI Bleeds

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory failure requiring mechanical ventilation for &gt; 48 hours</td>
<td>Coagulopathy (INR&gt;1.5; plt&lt;50 x 10⁹/L)</td>
</tr>
<tr>
<td>Acute renal insufficiency</td>
<td>Acute hepatic failure</td>
</tr>
<tr>
<td>Sepsis syndrome</td>
<td>Hypotension requiring vasopressors</td>
</tr>
<tr>
<td>Severe head or spinal cord injury (increased ICP increases cholinergic activity)</td>
<td>History of GI bleed</td>
</tr>
<tr>
<td>Low intragastric pH</td>
<td>Thermal injury &gt;35% TBSA</td>
</tr>
<tr>
<td>Major surgery (&gt; 4hours)</td>
<td>High dose corticosteroids (&gt;250 mg/d hydrocortisone or equivalent)</td>
</tr>
<tr>
<td>Acute lung injury</td>
<td>Post-transplant</td>
</tr>
<tr>
<td>Smoking or alcohol use</td>
<td></td>
</tr>
</tbody>
</table>
IV. Prophylaxis

Stress-ulcer prophylaxis (4) has led to a significant decrease in GIB in hospitalized patients. Stress-ulcer prophylaxis should be employed judiciously because complications of usage include an increase risk for hospital-acquired pneumonia, C. diff enterocolitis, interstitial nephritis, central nervous system side effects (elderly), and headaches. Table 3 contains specific high-risk indications for chemical prophylaxis.

Table 6.1.3 Indications for GI Bleeding Prophylaxis

<table>
<thead>
<tr>
<th>Coagulopathy (non-iatrogenic, i.e.: not due to warfarin, etc.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- INR &gt; 1.5</td>
</tr>
<tr>
<td>- Platelets &lt; 50 x 10^9/L</td>
</tr>
<tr>
<td>- Partial thromboplastic time (PTT) &gt; 2 times the control value</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mechanical ventilation &gt; 48 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of GI ulceration or bleed within 1 year</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Trauma</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Traumatic brain injury (TBI) patients</td>
</tr>
<tr>
<td>- Spinal cord injury (SCI) patients</td>
</tr>
<tr>
<td>- Significant burns</td>
</tr>
</tbody>
</table>

2 of the following:
- Sepsis
- ICU stay > 1 week
- Occult GI bleeding in past 6 days
- Steroids (> 250 mg hydrocortisone/week equivalent)

| Neurotrauma (including intracranial bleeding from non-traumatic etiologies) |

Histamine receptor antagonists (H2RA) and proton pump inhibitors (PPI) are generally first line agents. Other potential options include sucralfate, antacids, and prostanoids. H2RAs and PPIs are both available in IV and PO formulations.

H2RAs inhibit H+/K+ ATPase exchange pump by binding to H2 receptors on parietal cells resulting in decreased acid secretion and potassium uptake. Side effects include risk of tachyphylaxis when given intravenously, alterations in drug metabolism (cimetidine interacts with cytochrome P450), thrombocytopenia, impaired liver function, and interstitial nephritis. Elimination is via the kidneys and requires dose adjustment in renal insufficiency. H2RAs are less likely to be effective in patients with neurotrauma as they do not inhibit vagally-induced acid secretion.

PPIs inhibit gastric acid by forming irreversible disulfide bonds with H+/K+ ATPase exchange pumps leading to decreased H+ secretion by the parietal cell. PPIs are generally well tolerated, however long-term usage has been associated with fractures, hypomagnesemia, and hypocalcemia.

In addition to chemical prophylaxis, the rate of stress ulcers can be lowered through several additional modalities. Optimizing the patient’s hemodynamics, splanchnic perfusion, and oxygen delivery decreases the rate of mucosal injury. Enteral nutrition (feed early unless contraindicated) buffers gastric acid, blunts vagal stimulation, and increases secretion of cytoprotective prostaglandins and mucus. Certain medications (i.e.
corticosteroids, slow release enteral potassium, and NSAIDS) have known associations with gastric mucosa damage and should be avoided whenever possible.

Refer to your institutional pharmacy for medications on formulary.

V. Diagnosis

The diagnosis of GIB is generally made with a combination of history, physical examination, and endoscopy. (5) Upper GIB generally causes hematemesis and/or melena, while lower GIB often causes hematochezia. An important exception to this is that a brisk upper GIB may cause hematochezia as blood is a cathartic. Gastric lavage can aid in the diagnosis of GIB, but is unreliable. If positive, gastric lavage indicates an upper GI cause of bleeding, however a negative lavage can provide false reassurance. Gastric lavage is considered negative only if the return is both bilious and non-bloody. False negatives may occur with intermittent upper GIB.

Esophagogastroduodenoscopy (EGD) and colonoscopy are generally considered first line modalities for evaluating GIB. For portions of the bowel inaccessible by EGD or colonoscopy, capsule endoscopy may be used for diagnosis. Other methods of evaluation include double balloon enteroscopy, tagged red cell scans, Meckel's scan, mesenteric arteriography, barium contrast upper GI series with small bowel follow through, and enteroclysis. Arteriography has the benefit of being able to localize brisk bleeds while simultaneously offering definitive intervention/treatment.

VI. Management and Treatment

Management of patients with GIB in the ICU can broadly be categorized as either general resuscitative strategies or strategies aimed at halting the bleeding. (6-8) Initial resuscitation should proceed with airway and hemodynamic stabilization as clinically indicated. Continuous monitoring and frequent reassessment is imperative as an occult GIB can often progress rapidly. It is prudent to mobilize consultants early, including gastroenterology, general surgery, and interventional radiology. In a hospital without these resources available, patient transfer should be arranged expeditiously.

Intravenous (IV) access is extremely important in patients with GIB. Two or more large-bore peripheral IVs (16 gauge or larger), peripheral rapid infusion catheter (RIC), or an 8.5 French (or larger) introducer central venous catheter should be placed as soon as possible. Initial resuscitation should proceed with isotonic crystalloid (or uncrossmatched blood if indicated) to maintain hemodynamic stability while obtaining crossmatched blood products.

Endotracheal intubation should be undertaken in a thoughtful manner, particularly for upper GIB. Given the tenuous hemodynamics of a brisk GI hemorrhage, the patient should be
optimally resuscitated prior to intubation, if possible. The most expert operator available should intubate a patient with a brisk upper GIB. Multiple suction canisters should be available. Eye protection should always be used when intubating patients with upper GIB given the possibility of hematemesis and the potential exposure to blood borne pathogens. Patients with upper GIB should be intubated using rapid-sequence intubation, preferably with an NG tube placed prior to induction to decrease the risk of aspiration.

Administer blood components to maintain a hgb 7g/dL except in patients with signs of hypotension/shock or with ongoing active myocardial ischemia (which may require a hgb of 8g/dL). A conservative transfusion strategy should be employed in hemodynamically stable patients with plans for early endoscopy, as more liberal transfusion strategies are associated with increased mortality. (9) Correct any coagulopathy and maintain platelets > 50 x 10^9/L. A balanced resuscitative strategy for blood products should be employed (PRBC, FFP, platelets).

Prothrombin complex concentrate (PCC) may be considered in anticoagulated patients with massive hemorrhage. Although PCC cost may be prohibitive (when compared to FFP and vitamin K), it provides the benefit of very rapid reversal of warfarin induced coagulopathy with minimal volume. It should be noted, however, that PCC usage may be associated with an increase risk of thrombosis and has not been shown to decrease mortality. Tranexamic acid (TXA) has also been examined in upper GIB as a rapid coagulopathy reversal agent but insufficient data exists for recommendations. Contact your blood bank and initiate your massive transfusion protocol (if available) in times of massive bleeding and exsanguination.

Endoscopy is the mainstay of GIB diagnosis and treatment. An endoscopist may be able to provide definitive therapy via clips, banding, thermocoagulation, laser coagulation, sclerosing agents or epinephrine injection. Bleeding may obscure the operators view in upper endoscopy; therefore the endoscopist may request a promotility agent be given as an adjunct (be aware that most prokinetic agents prolong the QT interval). Balloon tamponade (e.g. Sengstaken Blakemore, Minnesota and Linton-Nichlas) can be considered as an adjunct to temporize variceal bleeding. Endoscopy, however, has widely supplanted the use of balloon tamponade due to the risk of esophageal ischemia and esophageal and gastric perforation.

Antibiotics (generally floroquinolones or cephalosporins) are indicated in variceal bleeding and provide a mortality benefit due to decreasing risk of infection. (10) Octreotide should be considered in variceal bleeding as it decreases portal venous pressure. In non-variceal upper GIB, a PPI bolus followed by an infusion decreases the risk of re-bleeding and “downstages” potential visualized ulcers on endoscopy, but has no overall mortality benefit. (11) Although there is no demonstrated benefit
of PPI prior to endoscopy, it is reasonable for a consultant to request early initiation of a PPI infusion. Unfortunately, the majority of these medications offer little to no benefit in lower GIB.

When bleeding is refractory to endoscopic and maximal medical therapies, interventional radiology (IR) and surgical consultation should be considered. Portosystemic shunts, i.e. transjugular intrahepatic portosystemic shunt (TIPS), may be employed in variceal bleeding refractory to banding. Angiography may be useful in upper and lower GIB as it may be able to localize and embolize a brisk bleed. Laparotomy with intraoperative enteroscopy is a last resort in refractory or life-threatening bleeding. Surgeons may be able to resect the affected bleeding area or oversew a bleeding vessel. Splenectomy may be beneficial in patients with refractory gastric varices. Surgery should only be considered first line when there is a concomitant indication for surgery (i.e. GIB with perforation).

Other considerations for the management of patients with upper GIB include H. pylori screening.

**VII. Outcomes**

Re-bleeding occurs in 10-15% of patients, usually within 48 hours. Endoscopic findings that predict a re-bleed include an actively bleeding vessel and a non-bleeding visible vessel. Ulcers on the lesser curvature of the stomach and the posterior inferior wall of the duodenum have a higher incidence of re-bleeding than ulcers at other locations. In the case of re-bleeding, repeat endoscopy is typically indicated. Alternative treatment modalities (i.e. IR and surgery) should also be considered.

Poor prognostic factors include esophageal varices as an etiology, coagulopathy with INR >1.3, chronic liver or renal disease, thrombocytopenia (plt <150 x 10⁹/L), pre-existing anemia (hgb <10 g/dL), initial systolic blood pressure <100 mmHg, and advanced age. The Rockall scoring system, which includes age, vital signs, comorbidities, etiology of bleeding and endoscopic findings, may aid in prognosis and disposition. (12) Mortality from GIB is between 5 and 10%.

**VIII. Summary**

GIB is a common disease process encountered in the care of the critically ill patient. Patients at risk include those requiring mechanical ventilation, patients with existing coagulopathy, and the TBI/SCI patient. Overall GIB 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 endoscopy remains the most commonly used diagnostic and therapeutic tool. Rational transfusion of blood products, correction of coagulopathy, and guided resuscitation for hemodynamic support are fundamental. The goal of management
is to first restore hemodynamic stability and then proceed with
diagnostic and/or more invasive procedures.

References:

1. Ali T, Harty R: Stress-Induced Ulcer Bleeding in Critically Ill

2. Afessa B: Triage of patients with acute gastrointestinal
   bleeding for intensive care unit admission based on risk factors

3. Quenot JP, Thiery N, Barbar S: When should stress ulcer
   prophylaxis be used in the ICU? Curr Opin Crit Care 2009;
   15(2): 139-43

   prophylaxis in the intensive care unit: is it indicated? A topical

5. Manning-Dimmitt LL, Dimmitt SG, Wilson GR: Diagnosis of
   71:1339-46

   recommendations on the management of patients with
   nonvariceal upper gastrointestinal bleeding. Ann Intern Med
   2010; 152:101-13

   massive upper gastrointestinal bleeding, EM Critical Care,
   volume 3, number 2. Edited by Gogela-Carson, C. EB

   Group: Management of acute upper gastrointestinal bleeding:
   summary of NICE guidance. BMJ 2012; 344:e3412

   368:11-21

10. Lee YY, Tee H-P, Mahadeva S: Role of prophylactic antibiotics
    in cirrhotic patients with variceal bleeding. World Journal of
    Gastroenterology: WJG 2014; 20(7):1790-1796

    a 4-factor prothrombin complex concentrate in patients on
    vitamin K antagonists presenting with major bleeding: a
    randomized, plasma-controlled, phase IIIb study. Circulation
    2013; 128(11):1234-43

12. Rockall TA, Logan RF, Devlin HB, Northfield TC. Risk
    assessment after acute upper gastrointestinal haemorrhage.

Review Questions:
1. Factors resulting in a reduced incidence of stress gastritis in the ICU setting include:
   
a. Increased use of prophylactic agents
b. Early use of enteral feeds
c. Improvement in resuscitation
d. All of the above

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

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 and correction of coagulopathy. 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. Initiation of vasopressin infusion
c. Octreotide bolus followed by an infusion
d. Recombinant factor VIIa

4. A 64-year old man with CHF (EF<15%) on warfarin for atrial fibrillation is admitted to the ICU with a diverticular bleed. The patient is in hemorrhagic shock. His hgb is 6.5 gm/dL, INR is 8.7, and platelets are 155 x 10^9/L. PRBCs are started. Which of the following is indicated to reverse his coagulopathy?
   
a. Hold next dose of warfarin
b. FFP
c. IV vitamin K
d. Prothrombin complex concentrate (PCC)
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 nutrition in the critically ill patient is to improve the outcome by preserving lean body mass and avoiding the negative consequences of malnourishment. Enteral nutrition is always preferred to parenteral nutrition; however, the underlying disease process and the functionality of the GI tract may prohibit its use. The goal of this chapter is to provide a basic framework for critical care nutrition and highlight the challenges that the clinician will face.

1. Malnutrition

   a. Definition

Patient Case:
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 total 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 for the 3 days since his accident. What are your initial nutritional goals for this patient?
Protein Calorie Malnutrition: weight loss of > 10-15% of total body weight or body weight < 90% ideal

Identification of patients at risk

No reliable laboratory method to determine which patients are malnourished or at risk of malnourishment

1. Albumin and pre-albumin are unreliable during critical illness

Patient history is best determination of nutritional status

1. Unintentional weight loss
2. Prolonged NPO status
3. Prolonged critical illness
   a. Patients lose up to 2% per day of muscle mass

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

2. Basic Metabolic Needs

a. There are three basic categories of macronutrients
   i. Carbohydrates: 3.4kcal/g
   ii. Lipids: 9kcal/g
   iii. Protein: 4.1kcal/g

3. Determination of daily caloric need of critically ill patients.

a. Simplified daily caloric estimations can be based on a patient’s weight and estimated stress level.
   i. Maintenance or minimal stress: 25-30 kcal/kg/day
   ii. Moderate stress: 30-35 kcal/kg/day
   iii. Severe stress (e.g. burns): 35-40 kcal/kg/day

b. Metabolic Cart
   i. Gold standard measurement of energy requirements by indirect calorimetry
   ii. Expensive, not commonly performed due to multiple confounding variables (air leaks, supplemental oxygen, vent settings, sedatives, CRRT, etc)

c. Harris-Benedict Equation (HBE)
   i. Based on healthy subjects, oldest, most commonly used
   ii. Calculates basal energy expenditure (B.E.E) in kcal/day
iii. Men: 66 + (13.75 x kg) + (5 x cm) - (6.8 x age)

iv. Women: 655 + (9.6 x kg) + (1.8 x cm) - (4.7 x age)

1. kg=weight in kg, cm=height in cm, age=age in years

d. Ireton-Jones Equation

i. Primarily used in critically ill, mechanically ventilated patients

ii. Total calorie need = 1784- 11(A)+5(kg)+244(M)+239(T) +804(B)

1. A=age in years, M=male gender (1=yes, 0=no)

2. T=trauma (1=yes, 0=no), B=burns (1=yes, 0=no)

e. Mifflin-St. Jeor Equation

i. Men: (10 x kg) + (6.25 x cm) – (5 x A) + 5

ii. Women: (10 x kg) + (6.25 x cm) – (5 x A) -161

1. Calculated with actual body weight in healthy individuals

2. Improved accuracy in obesity and as compared to the HBE

f. Penn State Equation

i. Most accurate in critically ill patient populations (70-75% accuracy)

ii. For patients age≥60 and BMI ≥ 30kg/m²: Mifflin-St. Jeor(0.71) + Tmax(85) + Ve(64) – 3085

iii. All others: Mifflin-St. Jeor(0.96) + Tmax(167) + Ve(31) -6212

1. Tmax=maximum body temperature in last 24 hours in degrees centigrade, Ve=minute ventilation in L/min

g. These formulas may underestimate the metabolic needs of patients with certain underlying disease processes.

i. 25% Increase: peritonitis, long bone fractures, mild/moderate trauma

ii. 50% increase: severe infections, multi-system organ dysfunction, severe trauma

iii. 100% increase: severe burn (>40% total body surface area)

h. Equations vary in accuracy from 40-75% when compared to indirect calorimetry

i. No one equation is shown to be superior

4. Composition of Nutrition Supplementation

a. Step 1: Calculate protein-based calories

i. 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%)
   i. Calories provided from dextrose containing solutions and lipid based medications should be taken into account

d. Step 4: Evaluate nitrogen balance to assess adequacy of protein-based calories. (Limited utility in ICU)
   i. Nitrogen balance = nitrogen intake – nitrogen losses
   ii. If negative, suggests increasing protein-based caloric intake

e. Re-evaluation is often necessary as energy expenditure changes

f. Step 5: Trace Elements, Vitamins, and Other Additives
   i. Trace elements (selenium, zinc and copper) and vitamins (E and C) are associated with lower mortality but showed no effect on length of stay or duration of mechanical ventilation. Little associated harm.

   1. Dose adjustments should be considered in renal dysfunction

   ii. Immune modulating additives have been an active area of nutrition research

1. Fish oils and borage oils have been shown to be efficacious in ALI/ARDS patients (controversial)
   a. Positive studies: decreased incidence of infections and pneumonia
   b. Negative studies: increase in overall mortality

2. Inconsistency of outcomes and diversity in patient populations prevent routine use of glutamine, arginine nucleic acid and other immune modulators in MICU patients.

3. Use of fish oils and arginine is recommended in SICU patients requiring enteral nutrition postoperatively

4. Glutamine has been associated with increased mortality in multi-system organ failure patients (5) and should not be routinely added. It has been shown to reduce mortality in a small cohort of burn 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?

5. Enteral Nutrition

   a. Enteral nutrition (EN) is always preferred to parenteral
nutrition (PN) if no contraindications exist.

b. Enteral nutrition has decreased complication rates
   i. No difference in mortality demonstrated between EN and PN
   ii. Fewer infections and reduced ICU LOS in patients receiving EN vs PN

c. Advantages
   i. Maintenance of structural integrity of GI tract
   ii. Release of endogenous GI substances such as cholecystokinin, gastrin, and bile salts
   iii. Increases blood flow to intra-abdominal viscera
   iv. Preserves villous height and gut derived immune system including gut associated lymphoid tissue (GALT)

d. Contraindications to enteral nutrition
   i. Hemodynamic instability
   ii. High vasopressor requirement
   iii. High-output enteric fistula

e. Access for Enteral Nutrition
   i. Naso-enteric tube most common

1. No difference in complications whether gastric or post pyloric feeding tube
2. Caution advised with gastric feedings in patients at high risk of aspiration or with gastric pathology (ie: gastroparesis, gastric outlet obstruction, gastric fistula)/EN intolerance
3. Post pyloric feeding should be considered in patients with high aspiration risk

ii. Surgical Feeding Tubes
   1. Reserved for patients who require long term enteral access
   2. Percutaneous Gastrostomy Tubes (PEG, G-Tube)
   3. Jejunostomy Tubes (J-Tube)

f. Enteral Nutrition Formulas
   i. Numerous formulas available
   ii. Disease specific formulas
   iii. Typical ICU formula has 1-2 kcal/mL

You decide to proceed with enteral nutrition. 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
   i. Radiographic verification of the feeding tube is absolutely necessary.
   ii. Low nutritional risk patients do not require initiation of EN in first week of ICU stay
   iii. In high nutritional risk patients or patients projected to require at least 72 hours of mechanical ventilation, enteral feedings should be started within 24-48 hours of ICU admission.
   iv. Hemodynamically compromised patients should not receive enteral nutrition until fully resuscitated and stabilized
   v. In ICU, presence or absence of flatus or bowel sounds is not a requirement for initiation of enteral feeding
   vi. Head-of-bed should be elevated to 30-45 degrees for aspiration precautions
   vii. Can consider pro-motility agents if necessary
   viii. EDEN Trial
      1. 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)
      2. No difference in mortality, ventilator free days, or infections
      3. Full feeding group had increased emesis, gastric residuals, use of prokinetic agents, higher glucose, and more constipation
   ix. 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
   i. Patient complaints of pain, gastric distention, vomiting, reduced flatus, radiographic evidence of ileus
   ii. Monitoring gastric residual volume for tolerance of tube feeding is controversial
      1. Not monitoring residual gastric volumes during enteral feeding does not lead to more pneumonia (7), regurgitation or aspiration
      2. In absence of other signs of feeding intolerance, should not hold tube feedings unless gastric residual volume is greater than 500cc (1)
         a. Leads to inadequate nutritional support
6. Total Parenteral Nutrition

a. Advantages of TPN
   i. Ability to provide nutrients to patients who cannot tolerate enteral feeding
   ii. If severe malnutrition and non-functional GI tract, PN should be considered soon after ICU admission as it has been associated with fewer complications and lower mortality

b. Disadvantages
   i. Risk of systemic infection is much higher
   ii. Liver complications include transaminitis, cholestasis, steatosis, steatohepatitis, fibrosis, and cirrhosis
   iii. Hyperglycemia: may be the reason why TPN has higher infection risk
   iv. Need for Central Access
      1. TPN is hypertonic and requires central access
      2. Peripheral parenteral nutrition does exist but requires high volume load
      3. Single lumen dedicated to TPN to help reduce infectious risk

c. Initiation
   i. The appropriate time frame to start parenteral nutrition remains controversial if a patient is not malnourished prior to ICU admission
      1. 2016 ASPEN guidelines recommend delayed initiation of PN for the first 7 days of ICU admission
   ii. Late parenteral nutrition (8 days) has been shown to be associated with fewer complications than early initiation (48 hours). (8)
      1. Fewer infections, less cholestasis, more ventilator free days, and reduced duration of renal replacement therapy
      2. Late TPN group maintained on dextrose containing fluids
   iii. If a patient is expected to be strict NPO for prolonged period of time, it is reasonable to start TPN early
   iv. TPN dependent patients should have therapy continued in absence of bacteremia

d. Monitoring
   i. Electrolytes including calcium, magnesium, and phosphate
      1. Higher risk of refeeding with initiation of PN
After 10 days on the ventilator, he is 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?

7. Nutrition Monitoring
   a. Several nutrition scales used to calculate the nutritional status of patients.
      i. Parameters used include laboratory values (albumin, prealbumin, etc.), BMI, stress level, and amount of weight loss.
   b. Metabolic Cart/Fick equation
      i. The amount of oxygen absorbed is equal to the amount of oxygen consumed
      ii. Extrapolated to the amount of carbon dioxide produced.

iii. Patient must be metabolically stable
   1. Dynamic conditions such as sepsis, trauma, and burns give inaccurate results.
   2. End-tidal carbon dioxide per a given time is measured
   3. Using the Fick equation, the amount of oxygen consumed per minute is calculated.
   4. Respiratory quotient is calculated
      a. \( RQ = \frac{CO_2 \text{ expired}}{O_2 \text{ inspired}} \)
      b. \( RQ \) values <0.67 or >1.3 should raise the question of test validity
      c. Historically used to identify over/underfeeding, \( RQ \) has low sensitivity and specificity for identifying these conditions
   c. Overfeeding leads to difficulty weaning from the ventilator due to increased carbon dioxide production

8. 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
   i. Respiratory failure secondary to diaphragmatic weakness
   ii. Muscle weakness
   iii. Rhabdomyolysis
   iv. Hemolysis
   v. Altered mental status including gait disturbances and paresthesias
   vi. Cardiomyopathy
e. Monitor serum phosphate levels with repletion often necessary

References:
Review Questions:

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 and there are no other signs of feeding intolerance. What is your next step?
   a. Check an abdominal x-ray for evidence of an ileus
   b. Hold tube feeds and re-check gastric residuals in 6 hours
   c. Continue current feeding schedule
   d. Initiate total parenteral nutrition

2. 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

3. After beginning to provide nutritional support to a chronically malnourished patient, he develops confusion and dyspnea. The electrolyte disturbance most likely to be involved is:
   a. Hyperkalemia
   b. Hypokalemia
   c. Hypermagnesemia
   d. Hypophosphatemia
Section 3

Acute Pancreatitis

Lydia Miller MD, Edward A Bittner MD PhD MSEd

Key Points:

- Most patients presenting with acute pancreatitis have mild disease. Early identification of severe disease and triage to an ICU is critical. Severe acute pancreatitis carries a mortality rate of nearly 30%.

- Initial management of acute pancreatitis includes IV fluid resuscitation, analgesia, and nutrition. Enteral nutrition is preferred to parenteral nutrition.

- Infected necrosis usually requires drainage or debridement. Minimally invasive techniques, including percutaneous or endoscopic drainage or video-assisted retroperitoneal pancreatic debridement (VARD), should be attempted before open necrosectomy.

I. Diagnosis: Two out of the following three criteria must be present for diagnosis of acute pancreatitis: 1) acute-onset upper abdominal pain 2) serum lipase and/or amylase greater than three times the upper limit of normal 3) imaging findings, usually contrast-enhanced CT. (1,2) Elevated amylase and lipase are not specific for acute pancreatitis and can be seen in other intra-abdominal conditions (2) and critical illnesses including diabetic ketoacidosis, trauma, intracranial hemorrhage, ruptured abdominal aortic aneurysm, and renal failure. (3) The clinical significance of elevated amylase or lipase in non-pancreatic conditions is often unclear.

Patient Case:
A 54 year-old man with a history of alcohol abuse presents to the emergency department with severe epigastric pain radiating to the back, and 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. An abdominal CT scan shows an enlarged pancreas with a peripancreatic fluid collection. After aggressive fluid resuscitation, the patient remains hypotensive, tachycardic, oliguric, and has altered mental status. ABG shows pH 7.33, PaCO₂ 25, PaO₂ 64 on 6L/min supplemental oxygen, base deficit 6.8 and lactate 3.7. Chest radiograph shows bilateral diffuse opacifications. The patient is intubated and admitted to the ICU.
Diagnosis of acute pancreatitis in ICU patients can be difficult. (3) Serum lipase has higher specificity for acute pancreatitis compared with serum amylase. (2)

**II. Role of imaging:** Contrast-enhanced CT (CECT) is the standard imaging technique for diagnosis of acute pancreatitis. While imaging is not required for diagnosis of acute pancreatitis, CECT at admission may be useful to exclude other etiologies of acute abdominal pain. (1,2) Necrosis appears as areas of non-enhancement of the pancreas (see Figure 1), but may not be detectable on CT for several days after presentation. For this reason, guidelines recommend deferring imaging for at least 72-96 hours after symptoms appear for better assessment of severity. (1) If there is no clinical improvement or deterioration, repeat imaging should be considered to evaluate for necrosis or other local complications. (1) If there are contraindications to CECT (e.g. iodinated contrast allergy, renal insufficiency, pregnancy), MRI with contrast can be used.

**III. Identifying etiology:** Identification of the etiology of acute pancreatitis will guide appropriate treatment and could prevent recurrent episodes. The most common etiologies of acute pancreatitis are gallstones and alcohol use, together accounting for the majority of cases. (2) Transabdominal ultrasonography on admission is recommended for all patients to rule out gallstone pancreatitis. (1,2) Urgent ERCP for gallstone removal is indicated if there is evidence of cholangitis. (1,2)

Rare etiologies of pancreatitis include hypertriglyceridemia, tumor, post-ERCP, and drugs. Many drugs have been implicated in acute pancreatitis; the most well-established are 6-mercaptopurine, azathioprine, and didanosine. Drugs associated with acute pancreatitis that are commonly used in the ICU include propofol, furosemide, erythromycin, metronidazole, and valproic acid. (3)

**IV. Classification:** The Revised 2012 Atlanta Classification defines three categories of acute pancreatitis: mild, moderately severe, and severe. (4) Patients with mild pancreatitis have no
organ failure or systemic or local complications such as necrosis (see **Figure 2**). Mild pancreatitis carries a low mortality rate (0.8%), (5) and patients generally do not require ICU admission. Moderately severe pancreatitis is marked by organ failure lasting less than 48 hours or systemic or local complications. Severe pancreatitis is defined by organ failure lasting more than 48 hours and carries a mortality of nearly 30%. (5) The distinction between moderately severe and severe acute pancreatitis is therefore made retrospectively. Patients with signs of organ failure should be admitted to an ICU.

**V. Predicting severity:** Several scoring systems have been proposed to identify patients at risk of developing severe pancreatitis, including APACHE-II, Harmless Acute Pancreatitis Score (HAPS), and Bedside Index of Severity in Acute Pancreatitis (BISAP). The clinical usefulness of these scoring systems has been questioned, (2) and guidelines recommend close monitoring for hypovolemia and signs of organ failure in lieu of a particular scoring system. Laboratory findings associated with severe pancreatitis include elevated BUN (>20 mg/dl or rising), hematocrit (>44% or rising), and elevated creatinine. (2) Patients with acute pancreatitis and persistent SIRS lasting over 48 hours have significantly higher rates of multi-organ failure and death. (6) Consensus guidelines recommend using persistent SIRS to identify patients at risk for severe acute pancreatitis (1) and admitting patients with persistent SIRS to an ICU. (2)

**VI. Initial management:** Initial management of acute pancreatitis includes appropriate triage, fluid resuscitation, analgesia, and initiation of nutrition.

1) **Fluid resuscitation.** Early IV hydration in the first 12-24 hours of admission is strongly recommended. Hypovolemia in acute pancreatitis results from vomiting, anorexia, third spacing and insensible losses. Guidelines differ in their recommendations for fluid quantity, ranging from 250 cc/hour to up to 10 ml/kg/hour. (1,2) Administration rate should be modified for patients at risk for volume overload (e.g. renal insufficiency or congestive heart
failure). Lactated Ringer’s is preferred to normal saline. Concerns have been raised that overly aggressive fluid administration could be harmful in acute pancreatitis. Resuscitation should be goal-directed; markers to follow include hematocrit, BUN, creatinine, hemodynamics and urine output. For a recent review discussing the complexities of fluid management in acute pancreatitis, see reference 7.

2) Antibiotics. Prophylactic antibiotics to prevent infected necrosis are not recommended in acute pancreatitis. (1,2) Antibiotics should be used only in cases of suspected or confirmed infected pancreatic necrosis or non-pancreatic infections. Infected necrosis should be suspected in patients who don’t improve or deteriorate. Gas in the pancreas on CT indicates infected necrosis. Whether CT-guided FNA should be performed to obtain cultures of pancreatic tissue vs. starting empiric antibiotics is controversial. FNA can have false-negative results and is therefore only recommended for patients who fail to improve and have no imaging evidence of infected necrosis. (1) Antibiotics able to penetrate pancreatic necrosis include carbapenems, quinolones, and metronidazole. (2)

3) Pain management. Abdominal pain is usually severe and requires IV narcotics. There is currently no evidence to recommend a particular analgesic regimen in acute pancreatitis.

4) Nutrition. The theory of needing to “rest” the pancreas by keeping patients NPO and providing nutrition via total parenteral nutrition (TPN) has been abandoned in favor of early enteral nutrition (EN). Enteral nutrition is believed to reduce the risk of infected necrosis by preventing gut bacteria translocation. A Cochrane review of eight RCTs comparing EN and TPN in acute pancreatitis found that EN was associated with significantly decreased mortality, organ failure, need for surgical intervention, and infection. (8) There was a particularly striking reduction in mortality in the subgroup of patients with severe acute pancreatitis where the relative risk of death was 0.18 for EN compared with TPN.

Patients with mild pancreatitis can begin to eat a low-fat solid diet immediately if tolerated. Whether enteral nutrition should be initiated immediately in severe pancreatitis is less clear. A recent RCT compared starting enteral nutrition via NGT within 24 hours of admission to starting enteral nutrition 72 hours after admission in patients at risk for severe pancreatitis. There was no difference in infection or mortality. (9) However, this trial has been criticized, (7) and further studies are needed to investigate optimal timing of enteral nutrition in severe acute pancreatitis. Both nasogastric and nasojejunal feeding are acceptable in severe pancreatitis. (1,2)

VII. Complications of acute pancreatitis:

Necrosis can involve pancreatic and peri-pancreatic tissues. Necrotizing pancreatitis has significantly higher morbidity and mortality. (5)
Local complications are fluid collections that resolve or become walled-off over several weeks. Fluid collections are classified based on the presence or absence of necrosis and an encapsulating wall (see Figure 2). (4)

Infectious complications include infected necrosis and systemic infections such as pneumonia, UTI, cholangitis and bacteremia. In a cohort study of 731 patients with acute pancreatitis, 24% developed an infection. The median time to diagnosis of infection was eight days, (5) with infected necrosis being diagnosed later (median 26 days). Mortality was significantly increased in patients with infections.

ARDS should be suspected if there is rising oxygen requirement and pulmonary infiltrates.

Vascular complications include splenic vein thrombosis and pseudoaneurysms (rare).

Abdominal compartment syndrome has been reported in severe acute pancreatitis. Measurement of bladder pressure should be considered in patients with severe acute pancreatitis who are mechanically ventilated. (1)

VIII. Indications for surgical intervention:

1) Drainage or debridement of infected necrosis. Intervention should be reserved for patients with infected necrosis or rare cases of sterile necrosis causing symptoms (e.g. persistent pain or intestinal obstruction). Options include percutaneous drainage, endoscopic transluminal drainage, minimally invasive necrosectomy, and open necrosectomy. Guidelines recommend a “step-up” approach starting with the least invasive intervention possible (percutaneous or endoscopic transluminal drainage) and proceeding to minimally invasive or open necrosectomy if necessary. (1,2) This step-up approach has been associated with lower risk of major complications and death. (10) Drainage or debridement of infected necrosis should be delayed if possible until the collection becomes walled off, usually at least 4 weeks. Indications for urgent intervention include infected necrosis with clinical deterioration, abdominal compartment syndrome, bleeding, bowel ischemia or obstruction. (1,2)

2) Cholecystectomy for gallstone pancreatitis. Patients admitted with mild acute pancreatitis should undergo cholecystectomy before discharge. Patients with moderately severe or severe acute pancreatitis should not undergo cholecystectomy until fluid collections improve to reduce the risk of infection. (1,2)

References:


**Review Questions:**

1. Recommendation for initial work-up and management of severe acute pancreatitis include all of the following EXCEPT:
   a. Fluid resuscitation with Lactated Ringer’s
   b. Prophylactic broad spectrum antibiotics
   c. Serial measurements of serum BUN, creatinine and hematocrit
   d. Transabdominal ultrasound

2. An indication for urgent surgical intervention in severe acute pancreatitis is:
   a. FNA of acute necrotic collection with positive gram stain
   b. Evidence of pancreatic necrosis on CECT
   c. Bladder pressure of 30 mmHg and rising lactate
   d. Evidence of pseudocyst on CECT

3. Which intervention in severe acute pancreatitis has been shown to have a mortality benefit?
a. Early surgical intervention
b. Prophylactic antibiotics
c. Early enteral nutrition
d. Bowel rest and parenteral nutrition
Section 4

Liver Failure  J Michael Guthrie MD, Andrew J Vardanian MD

Key Points:

- Acute liver failure in the US is usually due to toxicity from medications or supplements. Chronic liver failure is more common and is often associated with alcohol or viral hepatitis but may also be caused by autoimmune disease, metabolic disease and malignancy.

- Liver failure has systemic effects, affecting nearly every organ system of the body.

- Patients with liver failure are prone to acute worsening of clinical status from minor insults and require vigilance and aggressive management in the ICU.

Patient Case:
A 62-year-old man (BMI 34) with cirrhosis from non-alcoholic steatohepatitis (NASH), DM, CKD, and a reducible hernia presents to the ED with symptoms of fever and fatigue. Vital signs are: T: 38.3°C, HR: 110, BP: 82/43 mmHg, SpO₂: 93% on 3L NC. On exam, he is alert and oriented to person and place, with scleral icterus, jaundice, ascites, and lower extremity edema. CBC shows WBC 15.2 x 10⁹/L, Hb 8.3 g/dL, and platelet 63 x 10⁹/L. Other lab data shows serum lactate 6.5 mmol/L, AST 82 IU/L, ALT 33 IU/L, total bilirubin 12.1 mg/dL, albumin 2.1 gm/dL, alkaline phosphatase 81 IU/L, BUN 52 mg/dL, creatinine 2.94 mg/dL, and INR 2.1. Blood and urine cultures are obtained, ceftriaxone is started, and the patient is transferred to the ICU for further management of severe sepsis. A diagnostic paracentesis is done which shows more than 500 neutrophils/μL; cultures from the paracentesis grow gram-negative rods. A CT scan of the abdomen shows a cirrhotic liver, evidence of portal hypertension, and ascites but without a perforated viscus. On hospital day two he is intubated for altered mental status and hypoxic respiratory failure. He progresses to septic shock, requiring norepinephrine and vasopressin to maintain a MAP>60 mmHg. Antibiotic coverage is broadened to vancomycin and piperacillin-tazobactam. Repeat blood cultures are drawn, which show gram-negative rods. Liver transplant evaluation is done. The lactate level is persistently elevated. The patient becomes anuric and requires CRRT for volume overload. The patient requires increasing support on the ventilator and there is worsening intracardiac filling pressures and systemic blood pressure. Given the multi-organ system failure and the patient’s prior wishes, care is withdrawn on hospital day 7.
Introduction

Liver failure is a common presentation in the ICU associated with high mortality, often exceeding 50%. Failure of hepatic function can lead to dysfunction or failure of every other organ in the body. Liver failure can be divided into acute, chronic and acute on chronic with drastic differences in presentation, prognosis, management and physiology. In end stage liver disease, however, transplantation is the only curative option.

Acute Liver Failure

Acute liver failure (ALF) is severe but potentially reversible with onset of hepatic encephalopathy (HE) within eight weeks of symptom onset. ALF is much less common than chronic liver failure. In ALF, a sudden insult causes hepatocellular death resulting in abnormal liver function. Unlike chronic liver failure, however, recovery is possible, as cirrhosis and fibrosis have not yet developed. A rapid disease progression from the onset of jaundice to encephalopathy and coagulopathy is characteristic, and the timing of this progression can affect outcome. ALF is more common in developing countries due to the higher incidence of viral hepatitis. In the United States, drug induced ALF is more common. Other causes include ischemia/hypoxia following severe shock or cardiac arrest, malignancy, toxin ingestion, vascular causes (i.e. Budd-Chiari syndrome), autoimmune hepatitis, and metabolic disease (i.e. Wilson’s disease).

With supportive care and targeted therapy such as N-acetylcysteine for acetaminophen toxicity, there may be recovery of hepatocellular function. Without recovery, however, mortality approaches 100%. The only cure for fulminant hepatic failure in the acute setting is liver transplantation. Scoring systems are designed to predict patients with poor prognosis without liver transplant. In the United States, the King’s College criteria are commonly used. The criteria include: cause of liver failure (acetaminophen versus other cause), degree of encephalopathy, degree of liver dysfunction as defined by coagulopathy and hyperbilirubinemia, patient age, duration of jaundice before encephalopathy and renal function.

Organ Specific Complications of Acute Liver Failure

Neurologic

Hepatic encephalopathy is a state of altered mental status associated with decreased metabolism of circulating toxins and decreased degradation of ammonia to urea due to hepatocellular dysfunction. In the brain, ammonia is metabolized to glutamine, which alters neurotransmitter synthesis and causes cerebral edema contributing to encephalopathy. Unrecognized or untreated cerebral edema in ALF or acute on chronic liver failure may lead to permanent brain injury, brainstem herniation, and death.

The role of therapies used for chronic hepatic encephalopathy
such as non-absorbable antibiotics and lactulose are unclear in acute liver failure. Treatment is focused on preventing or treating intracranial hypertension. Goals include decreasing ammonia uptake and metabolism, dialysis for hyperammonemia, avoidance and treatment of fever, and treatment of metabolic derangements such as hypo- or hypernatremia, hypercapnia, and acidosis. Many centers utilize invasive ICP monitoring.

Cardiac

Cardiovascular dysfunction is not uncommon in acute liver failure and is often multifactoral. Its work up and treatment should mirror that of other critically ill patients. The particular circulatory derangements such as portal hypertension and varices seen in end stage liver disease are not common with acute liver failure.

Renal

Renal dysfunction may occur in half of all cases of acute liver failure, but is more common with elderly patients, diabetics, or those with acetaminophen toxicity. In most cases, renal dysfunction will resolve with improvement in hepatic function. Renal replacement therapy (RRT) may be necessary in the interim for supportive care. RRT may also be used to control hyperammonemia and acid base disturbances seen in acute liver failure.

Hematologic

Coagulopathy is expected with ALF. Abnormalities in fibrinogen, INR, and platelet number are seen. At some institutions, Factor V and Factor VII levels are used to further assess hepatic synthetic function and recovery. Acute, spontaneous bleeding is not common.

Metabolic

Patients with acute liver failure are prone to hypoglycemia and electrolyte abnormalities such as hyponatremia and hypomagnesemia.

Chronic Liver Failure

Chronic liver failure (CLF) is the result of continuous hepatic injury over many years most commonly due to viral hepatitis, alcohol or non-alcoholic steatohepatitis. Other causes include, primary sclerosing cholangitis, primary biliary cirrhosis, hemochromatosis, alpha-1 antitrypsin deficiency, vascular problems, malignancy, autoimmune hepatitis, and Wilson’s disease. Regardless of the cause, liver cirrhosis occurs. The replacement of normal hepatic tissue with fibrotic tissue results in declining liver function. New vasculature causes portal hypertension and portosystemic shunts that result in vasoactive compounds reaching end organs. These phenomena are responsible for multi-organ complications associated with end stage liver disease (ESLD).

Patients with ESLD admitted to the ICU have a very high mortality, ranging from 50% to 100%. The Model in End Stage
Liver Disease (MELD) score predicts mortality in ESLD and is used in the allocation process for liver transplant recipients. Patients with higher scores have an increased chance of death and are prioritized for transplant. The MELD score was originally designed to predict three-month mortality in ESLD patients undergoing TIPS. MELD underestimates mortality in diseases such as HCC and portopulmonary hypertension as well as for patients with acute on chronic liver failure. MELD scores range from 0 to 40, with a score of 40 associated with a roughly 70 percent mortality at three months. Originally the MELD variables were creatinine or dialysis, INR, and bilirubin. Recently it was recognized that hyponatremia is associated with worsened mortality and sodium was added to the MELD score.

Organ Specific Complications of Chronic Liver Failure

Neurologic: Hepatic Encephalopathy

In CLF, there is decreased metabolism of ammonia by the liver as well as portosystemic shunting, both of which increase the amount of ammonia reaching the brain. Acute worsening in the context of chronic hepatic encephalopathy is due to precipitating factors such as infection, GI bleeding, or interventions such as transjugular intrahepatic portosystemic shunting (TIPS) which further increase portosystemic shunting. The primary treatment goal is to resolve the initiating factor. Lactulose is used to increase bowel movement frequency, to acidify bowel content, and to promote bowel lactobacillus over urease-producing bacteria (which decreases ammonia production), all of which help decrease net ammonia absorption. Rifaximin, sodium benzoate, and bromocriptine are other agents used to decrease ammonia levels. CLF patients in the ICU with acute on chronic encephalopathy are at high risk for aspiration and appropriate precautions should be employed.

Cardiovascular

Circulation in ESLD is hyperdynamic with a vasodilatory state manifested clinically by low resting blood pressure and high cardiac output. Patients may demonstrate cardiomyopathy characterized by inadequate response to physiologic stress, impaired systolic and diastolic function, and conduction abnormalities. Volume overload predisposes patients to elevated pulmonary artery systolic pressures. Autonomic function is impaired leading to orthostasis and diminished responsiveness to both endogenous and exogenous vasoconstrictors. The cardiovascular system is prone to decompensation from minor stress. The clinician must remain vigilant regarding hypotension and signs of inadequate end organ perfusion, such as high lactate or worsening renal function.

Pulmonary

Patients with CLF commonly have volume overload due to liver dysfunction and renal failure. There are additional pulmonary complications associated with CLF. Hepatopulmonary syndrome
manifests as hypoxia due to intrapulmonary vasodilation, shunting and ventilation/perfusion mismatching. The physiology is exacerbated in the upright position causing hypoxia and shortness of breath. Patients are treated with supplemental oxygen and the disease is reversible with liver transplantation.

Portopulmonary hypertension develops due to portal hypertension and shunting resulting in vasoactive compounds reaching the lungs and causing pulmonary arterial hypertension and right ventricular dysfunction. Portopulmonary hypertension increases the risk of graft failure after transplant. Treatment is with pulmonary vasodilators. Following transplant, pulmonary hypertension may improve somewhat. However, due to vascular remodeling, pulmonary hypertension and right ventricular dysfunction may persist and contribute to a poor outcome. Careful consideration is necessary in patients with CLF with HPS or PPH with regards to candidacy for liver transplantation.

In hepatohydrothorax, small defects in the diaphragm allow ascites to communicate and accumulate in the right pleural space. These collections may become infected. Treatment is primarily with aggressive and sustained diuresis. TIPS may improve hepatohydrothorax. Chest tube drainage is controversial and the condition resolves with transplantation.

Gastrointestinal

Portal hypertension in CLF frequently leads to portal gastropathy and esophageal varices and bleeding. Acute management for upper GI bleeding includes large bore IV access, intubation for airway protection, if appropriate, and urgent endoscopy to control bleeding with banding, clipping, or cautery. Octreotide is commonly used to decrease portal pressure. TIPS may be necessary. Gastric acid suppression with proton pump inhibitors is a mainstay of therapy.

Renal

Hepatorenal syndrome (HRS) is renal dysfunction in patients with end stage liver disease and ascites not explained by another cause. Patients with HRS have a median survival time of 3 months without liver transplantation. In type 1 HRS, onset is rapid (within 2 weeks) with the creatinine increasing by 100% or > 2.5mg/dL. Type 2 HRS patients have a more indolent decline in renal function and do not fulfill type 1 criteria. Treatment is aimed at increasing preload and MAP through albumin and splanchnic vasoconstriction with octreotide and midodrine.

Infection

CLF patients are susceptible to infection and are prone to rapid decompensation from infection with characteristic systemic inflammation. Outcomes from infection are much worse than with the general population. Due to the high mortality associated with decompensated liver disease, clinicians must have a low threshold to evaluate and aggressively treat infection including
those of the bloodstream, lung, urinary tract, and peritoneum.

**Hematologic**

Considerations for hematologic derangements in chronic liver disease are similar to those discussed in the acute liver failure section, with worsening coagulopathy and thrombocytopenia. Patients often have anemia of chronic disease. Portal hypertension and the presence of esophageal varices, portal gastropathy, or vascular malformations predispose patients to gastrointestinal bleeding. The effects on the coagulation system are complex, with imbalances in pro- and anticoagulant proteins. The INR does not reliably predict bleeding complications and patients may be at increased risk of thrombotic complications including venous thromboembolism.

**Metabolic**

Metabolic abnormalities in chronic liver failure are similar to those discussed with acute liver failure. These patients are often malnourished at baseline.

**Acute on Chronic Liver Failure**

Acute on chronic liver failure (ACLF) is a distinct clinical state from chronic decompensated liver disease and acute liver failure. It is a syndrome in patients with chronic liver disease, with or without cirrhosis, characterized by acute hepatic decompensation such as jaundice and prolonged INR plus one or more extrahepatic organ failures, such as renal or cardiovascular failure. ACLF is associated with increased mortality. Common precipitating causes are infection, bleeding, and surgery. In as many as 40% of cases, the precipitant is not determined.

Various scoring systems have been designed to predict survival and are used for organ allocation (like MELD). The Chronic Liver Failure Consortium (CLIF-C) organ failure score was combined with 2 other independent predictors of mortality (age and white cell count) into a new score, the CLIF-C Acute-on-Chronic Liver Failure (ACLF) score. This has been shown to discriminate survivors from non-survivors better than MELD and the Child-Pugh score. It incorporates markers of liver failure plus markers of extrahepatic organ failure. Treatment considerations for ACLF are similar to decompensated chronic liver failure.

This chapter is a revision of the original chapter authored by C. Patrick Henson DO.

**References:**


**Review Questions:**

1. Which of the following may occur with chronic liver failure but not acute liver failure?
   - a. Coagulopathy
   - b. Altered mental status
   - c. Portopulmonary syndrome
   - d. Hyponatremia

2. Which is a common cause of hepatic encephalopathy?
   - a. Increased intracranial pressure
   - b. Hyperglycemia
   - c. Increased ammonia
   - d. Hypoxia

3. Which of the following is the most likely precipitant for decompensation in this patient?
   - a. Upper GI bleeding
   - b. Incarcerated umbilical hernia
   - c. Spontaneous bacterial peritonitis
   - d. Hepatorenal syndrome

4. This patient’s presentation was most consistent with:
   - a. Chronic liver failure
   - b. Acute liver failure
   - c. Acute on chronic liver failure
   - d. None of the above
Renal System Topics
The healthy kidney provides filtration of the blood plasma and excretion of waste, maintains electrolyte concentrations, controls blood acidity, and helps regulate blood pressure. Even when injured due to chronic conditions such as diabetes mellitus or hypertension, the renal system is typically able to continue functioning well enough to avoid serious complications. The systemic involvement of critical ill patients is at risk for the development of AKI.

Contrast-induced AKI can be attenuated by aggressive IV hydration. Oral N-acetylcysteine and statin therapy may also be useful in prevention.

Cardiorenal syndrome is a common cause of AKI in the critically ill patient. Treatment should be directed at restoring cardiac function and normalizing volume status.

**Patient Case:**
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 in the following table.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>17 gm/dL</td>
</tr>
<tr>
<td>Na⁺</td>
<td>144 mmol/L</td>
</tr>
<tr>
<td>INR</td>
<td>1.5</td>
</tr>
<tr>
<td>K⁺</td>
<td>5.4 mmol/L</td>
</tr>
<tr>
<td>WBC</td>
<td>30.2 x 10⁹/L</td>
</tr>
<tr>
<td>BUN</td>
<td>44 mg/dL</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.4 mg/dL</td>
</tr>
</tbody>
</table>
illness places the kidney at extremely high risk of acute injury, 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 primarily dependent on one major physiologic principle with two components: the delivery of an adequate volume of blood at an appropriate perfusion pressure. Filtration of the plasma is primarily a mechanical process, reliant upon interactions between hydrostatic and oncotic pressures at the glomerulus, and affected by alterations in systemic and regional blood pressure. Additionally, nephrotoxic drugs and inflammatory mediators may impair renal processes through injury to the glomerular membrane or via disruption of intrarenal pressure gradients. Acute kidney injury (AKI) may occur as a result of derangements in these physiologic processes and result in rapidly progressive deterioration of renal function leading to difficulties in regulation of intravascular volume, pH and electrolyte abnormalities. The presence of AKI has been directly related to negative outcomes such as prolonged ICU stay and in-hospital mortality. (3)

Long-term renal complications in outpatients are typically due to changes in vascular health related to chronic hypertension and diabetes, but periods of acute hypotension are likely to be more of a concern in the critically ill patient with AKI. At a mean arterial pressure (MAP) below 65 mmHg, autoregulatory compensation fails and blood flow becomes pressure dependent. Intrarenal perfusion falls off dramatically with corresponding decreases in renal artery blood flow, which may occur in various shock states. While MAP is a good indicator of organ perfusion in the euvoletic 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. Thus, even with a “normal” MAP of 65 mmHg, the critically ill patient likely has deficits in perfusion that may be difficult to assess. Systemic shock of any kind is the biggest single risk factor associated with the development of AKI.

In the face of any renal insult, it is important to optimize perfusion by maintaining pressure and flow. In addition to the shock states, other factors associated with critical illness, such as sepsis, use of vasopressors, vascular embolic events, mechanical ventilation, and nephrotoxic medications, significantly increase the risk of AKI. 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, AKIN and KDIGO criteria provide a quick bedside tool to assess for the presence and severity of AKI, although they provide little insight into the mechanism (Figure 1). All three 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. KDIGO criteria are nearly identical to the AKIN model, but they emphasize the importance of time course. (1) The early stages of AKI in all three sets of criteria suggest less severe injury, but progression to the later stages is nearly 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 (urine output and serum creatinine) that have high variability in patients, especially those with critical illness. Total body water, diuretic use, nutritional status and body mass all confound one or both of these values, which can lead to 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. Increases in creatinine may 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. (6) The critical care physician must rely on clinical suspicion (duration and severity of illness) and data (urine output, creatinine, BUN:creatinine ratio), to identify patients with AKI. (5)

AKI can be classified as prerenal, postrenal, or intrinsic. This helps guide the critical care physician toward appropriate management. Fractional excretion of either sodium (FeNa) or urea (FeUrea) (Figure 2) can be calculated. While FeNa has long been the standard, FeUrea may have more accuracy in patients with critical illness and those on diuretic therapy. FeNa < 1% and FeUrea < 35% suggest decreased effective 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.

Obstruction to urinary flow and elevated backpressure should be considered in patients with AKI or oliguria, 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. While congestive heart
failure and hepatorenal syndrome may generate urine studies consistent with prerenal azotemia, they require quite different treatments. In most cases, cost-effective choices such as balanced salt solutions are preferable to colloid solutions, such as human albumin, while 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. (4)

Along with replacing 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 MAP greater than 75 mmHg may be necessary for prevention of AKI, especially in patients with underlying chronic hypertension. (8) Even though vasopressor use is a risk factor for the development and worsening of AKI, this association is likely multifactorial and, the benefits of treating systemic hypotension may outweigh the theoretical risks. Norepinephrine infusion should be considered the gold standard vasopressor in patients with critical illness, while supplemental 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.

The cardiorenal syndrome is a pathologic process associated with acute or chronic heart failure and renal dysfunction. Greater than 50% of patients with significant heart failure will have concomitant renal dysfunction. The physiologic changes involve not just decreased forward flow by the failing heart, but also hormonally mediated changes in intrarenal hemodynamics and venous congestion from increased right atrial pressures. Cardiac filling pressures such as CVP and LVEDP are static indicators of circulating volume that may be useful in management, although they are not reliable measures of cardiac preload. Aggressive management of the underlying heart failure and diuresis, even in the face of worsening renal function, may improve long-term outcomes. (10)

In patients with decreased cardiac output and critical illness, especially those with reduced oxygen delivery, inotropic support with milrinone, epinephrine, or dobutamine may be useful for cardiac support, and help to improve blood flow to the kidneys. Dopamine is a potent vasoactive agent with vasopressor and inotropic effects at low doses, and it also acts as a diuretic. Despite this, studies have shown that low-dose, or “renal-dose” dopamine, is not protective to the kidney and may increase mortality. Vasodilator therapy to reduce afterload may also help the failing heart and improve blood flow to peripheral organs, but should be used cautiously.

Many well-known nephrotoxins are currently in use in ICUs
around the world. Mechanisms of injury include disruption of intrarenal hemodynamics, crystal formation, and direct tubular injury. Antibiotics such as aminoglycosides, fluoroquinolones, penicillins, and vancomycin 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 commonly associated with these injuries and eosinophils may 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, such as cardiac catheterizations and CT scans. The risk of serious renal 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 significantly more likely to require these studies 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. (2)

The goal in prevention of CI-AKI is twofold: maintain adequate circulating volume and minimize exposure. The clinician should consider alternative imaging studies in patients with AKI or with significant risk factors, and also avoid repeating contrast doses. The use of iso-osmolar or 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. Balanced salt solutions are ideal, and isotonic sodium bicarbonate solution, which has been shown to have some benefit in high-risk patients, may also be considered as an infusion. (11) The known free radical scavenger N-acetylcysteine has a relatively benign risk profile and has been shown to maybe be beneficial in emergent situations. Its use may be considered in patients at high risk for CI-AKI in addition to aggressive hydration. Pooled data suggests that pre-intervention statin use may be associated with reduced risk of CI-AKI in patients with or without renal impairment at baseline. (9)

Ultimately, a percentage of patients will progress to require renal replacement therapy (dialysis), either in the short or long term. Continuous renal replacement therapy (CRRT) may be better tolerated in the critically ill patient over conventional intermittent hemodialysis (HD), but randomized trials have not shown a difference in mortality between the 2 interventions. CRRT allows for a more controlled ultrafiltration and volume removal, whereas HD is likely better for rapid correction of electrolyte abnormalities. (7) Overall it seems that the dialysis dose is the more important factor as opposed to method of dialysis.
References:


6. Ricci Z, Cruz DN, Ronco, C: Classification and staging of acute kidney injury: beyond the RIFLE and AKIN criteria. Nat Rev Nephrol 2011; 7:201-8


Review Questions:

1. In reference to the patient case, administration of which of the following intravenous fluids is preferred for resuscitation?
a. Packed red blood cells
b. Hextend
c. Lactated Ringer’s solution
d. Fresh frozen plasma

2. 48 hours later, he is in septic shock, requiring large doses of vasopressors and ventilatory support. He is oliguric, making < 10 cc/hr of urine. Which of the following would not be considered indications for urgent hemodialysis?

a. ECG changes with K+ > 6.0 mmol/L following appropriate medical therapy
b. pH < 7.1 and minute ventilation of 20 L/min
c. Altered mental status and BUN of 125 mg/dL
d. All of the above would be indications

3. A contrast CT is ordered to evaluate for pulmonary embolism. Which of the following statements is true regarding contrast induced AKI?

a. Furosemide diuresis before and after contrast administration is protective
b. Statin therapy may be associated with a protective effect
c. Incidence of CI-AKI is similar in patient groups, regardless of baseline renal function
d. Hyperosmolar contrast solutions are preferred in patients with renal dysfunction

4. The patient develops hyperkalemia and acidosis with signs of volume overload. Continuous renal replacement therapy is initiated. Urine output is minimal for the previous 6 hours. Serum creatinine is 3.1 mg/dL, up from a baseline of 1.4 mg/dL. Which of the following parameters is diagnostic of AKI using AKIN criteria?

a. Creatinine elevated to 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

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.
Overview:

The extracellular fluid (20% of total body water) contains 40 nmol/L of H⁺ and is regulated within a narrow range by metabolic, renal, and respiratory buffering mechanisms. In the absence of disease, these mechanisms are very effective at maintaining pH in the normal range (7.4 ± 0.02). Many patients in the Intensive Care Unit (ICU) will have chronic acid/base disorders in addition to those associated with their acute illness. Additionally, many therapies used in the setting of critical illness cause acid/base disturbances. For instance, treatment with diuretics and administration of specific intravenous fluids can directly impact acid/base balance and may require counter therapies until normal compensatory mechanisms can restore balance.

Acids, bases and buffering mechanisms

Acidosis or alkalosis imply the process by which the pH changes from the neutral point (pH 7.4). Each may lead to acidemia (pH < 7.35) or alkalemia (pH > 7.45), respectively. Despite the different meanings of “osis” and “emia”, many clinicians use the two terms interchangeably. While acid/base disturbances occur in all body compartments (plasma, extracellular fluid, intracellular fluid), we will focus on the plasma component.

Key Points:

- Acid/base homeostasis is critical to enzymatic function and metabolism. Hydrogen ion (H⁺) concentrations affect protein configuration that can affect critical metabolic pathways and alter the ionization of many compounds that affect cell membrane transport.
- The human body has a vast capacity to buffer hydrogen ion and maintain a normal pH. Significant acid/base disturbances are only observed when those reserves are depleted. Most acid/base disturbances are mild and inconsequential. However, they provide insight into disease processes that might otherwise be missed.
- Acid/base disturbances can be complex and may result from multiple metabolic derangements. Distinguishing the primary disorder is critical to the proper management of patients in the OR and ICU.
Carbonic acid is a weak acid that is critical to understanding the basic acid/base balance. It rapidly and easily dissociates to generate $H^+$, $HCO_3^-$ and $CO_2$, which makes it a versatile compound that allows both the lungs ($CO_2$ elimination) and kidneys ($HCO_3^-$ formation and reabsorption) to contribute to acid/base balance.

While the lungs and kidneys play a critical role in buffering through carbonic acid, other, less modifiable, intracellular systems also contribute to the body’s buffering capacity. Those include phosphate buffers, intracellular proteins, hemoglobin, and bone (up to 40% of acute acid load buffering).

**Acid/base analysis:**

The two major approaches to acid/base interpretation are the traditional Bicarbonate Approach and Strong Ion Difference (SID). While some believe SID may be more sensitive in detecting acid/base disturbances in a few rare occasions, it offers little, if any, advantage over the bicarbonate approach. In this chapter, we will use the bicarbonate-centered analysis as it is a simple, accurate method of assessing and treating acid/base disturbances for most clinical purposes.

Typically, acid/base analysis is performed using an arterial blood sample which provides measurements of pH, $PaCO_2$, $PaO_2$ and base excess (BE). In addition, most arterial blood gas (ABG) equipment will also measure basic electrolytes ($Na^+$, $K^+$, $Ca^{++}$) and hemoglobin. It is important to recognize that the $HCO_3^-$ value provided by the ABG is a calculated value and not directly measured. Hence, $HCO_3^-$ levels provided by direct electrolyte analysis (e.g. basic metabolic panel) should be used when available.

When analyzing an ABG, one should answer the following questions:

1. What type of disorder exists? Acidosis/acidemia or alkalosis/alkalemia?
2. What is the primary disorder? Metabolic or respiratory?
3. Is the primary disorder acute or chronic?
4. Are there compensatory mechanisms in play and if so, are they appropriate?
5. Are there other independent disorders?
The following 6-step approach was developed to answer the above questions in an easy and systematic manner.

Step 1: Is the patient acidemic or alkalemic?

Step 2: Is the primary disturbance respiratory or metabolic?

Step 3: For respiratory disturbances, is it acute or chronic?

Step 4: If metabolic acidosis exists, determine whether an anion gap (AG) is present.

Step 5: Determine if a secondary metabolic disturbance co-exists with an AG acidosis.

Step 6: Assess the degree of compensation by the respiratory system for the primary metabolic disturbance.

It is always prudent to verify the accuracy of numbers reported on the ABG by comparing the $H^+$ from the modified Henderson equation. A quick method uses the two digits after the decimal point of the pH. By subtracting the two digits from 80, the resulting number should equal the results from $24(PaCO_2/HCO_3^-)$.

Example:
ABG: 7.24/49/21/120
$H^+ = 80-24 = 56$
$H^+ = 24(PaCO_2/HCO_3^-) = 24(49/21) = 55.9$
This confirms that the reported numbers are correct per Henderson's equation.

Step 1: Is the patient acidemic or alkalemic?
The ABG pH deviation from the neutral point (7.40 ± 2) identifies the disorder as alkalemic or academic (Figure 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 $\text{HCO}_3^- < 22$, metabolic acidosis is present, go to step 4. If $\text{HCO}_3^- > 26$, a metabolic alkalosis is present, and the next question is whether the respiratory compensation is adequate? Go to step 6.

**Step 3: For a respiratory disturbance, is it acute or chronic?**

In acute respiratory acidosis, $\text{CO}_2$ retention occurs with the onset of hypercarbic respiratory failure. $\text{CO}_2$ retention will result in a pH reduction of 0.08 for every 10 mmHg rise of $\text{PaCO}_2$. However, in chronic respiratory acidosis, increased $\text{HCO}_3^-$ mediated by the kidneys results in a pH reduction of only 0.03 per 10 mmHg rise of $\text{PaCO}_2$. Respiratory alkalosis results from hyperventilation due to multitude of reasons (see below) and the same rules apply to pH changes but in the opposite direction. While respiratory compensation for metabolic disturbances is rapid, renal compensation for respiratory acid/base changes is more on the order of days. It is also worth noting that renal compensation will correct the pH toward normal but never completely. Thus, the pH will always indicate the direction of the primary disturbance unless a complex or mixed disorder exists.

Step 4: For a metabolic acidosis, determine whether an anion gap is present.

The normal anion gap is 12 mEq/L. The anion gap is the calculated difference between positively charged (cation) and negatively charged (anion) electrolytes, which are measured in routine serum assays.

$$\text{Anion gap} = \text{Na}^+ - (\text{Cl}^- + \text{HCO}_3^-)$$

Since the anions and cations are always in balance to maintain electrical neutrality, the anion gap reflects the unmeasured anion

<table>
<thead>
<tr>
<th>Unmeasured Anion</th>
<th>Unmeasured Cations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteins, mostly albumin 15 mEq/L</td>
<td>Calcium 5 mEq/L</td>
</tr>
<tr>
<td>Organic acids 5 mEq/L</td>
<td>Potassium 4.5 mEq/L</td>
</tr>
<tr>
<td>Phosphates 2 mEq/L</td>
<td>Magnesium 1.5 mEq/L</td>
</tr>
<tr>
<td>Sulfates 1 mEq/L</td>
<td></td>
</tr>
<tr>
<td><strong>Totals: 23 mEq/L</strong></td>
<td><strong>Totals: 11 mEq/L</strong></td>
</tr>
</tbody>
</table>

**Summary:**

<table>
<thead>
<tr>
<th>Acute respiratory acidosis: pH decrease</th>
<th>$0.08 \times (\text{PaCO}_2 - 40)/10$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic respiratory acidosis: pH decrease</td>
<td>$0.03 \times (\text{PaCO}_2 - 40)/10$</td>
</tr>
<tr>
<td>Acute respiratory alkalosis: pH increase</td>
<td>$0.08 \times (40 - \text{PaCO}_2)/10$</td>
</tr>
<tr>
<td>Chronic respiratory alkalosis pH increase</td>
<td>$0.03 \times (40 - \text{PaCO}_2)/10$</td>
</tr>
</tbody>
</table>
concentration (Table 1). Because there are more unmeasured anions than cations, there is a normal difference expressed by the above equation.

The causes of an anion gap acidosis differ from those of a non-anion gap acidosis (see common acid/base disturbances). The anion gap determination is usually an excellent tool for narrowing the list of potential causes of a metabolic acidosis, but there are limitations to its use. For example, hypoalbuminemia (e.g. cirrhosis, nephrotic syndrome) can reduce the normal anion gap and make patients with an anion gap metabolic acidosis appear to have a normal anion gap.

**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 additional variation in HCO$_3^-$ exists. If no other metabolic disturbance exists, then the corrected bicarbonate would be 24.

**Corrected HCO$_3^-$ = measured HCO$_3^-$ + (anion gap - 12)**

If the corrected HCO$_3^-$ varies significantly from 24, then a mixed metabolic disturbance exists. Specifically, 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 2).

**Step 6. Assess the normal compensation by the respiratory system for a metabolic disturbance.**

The respiratory system responds quickly to a metabolic acidosis with a linear reduction in PaCO$_2$. The Winter’s formula predicts the expected PaCO$_2$ in response to changes in HCO$_3^-$.  

**Expected PaCO$_2 = (1.5 \times \text{HCO}_3^-) + (8 \pm 2)**
In a simple metabolic acidosis, the measured PaCO$_2$ will fall within the range predicted by Winter’s formula. However, if the expected PaCO$_2$ falls outside the range, one should suspect a mixed acid/base disturbance, usually respiratory in origin. For example:

1. If the measured PaCO$_2$ is less than the Winter’s expected range, the patient must have a respiratory alkalosis in addition to the metabolic acidosis.  

2. If the measured PaCO$_2$ is more than the Winter’s expected range, the patient must have a respiratory acidosis in addition to the metabolic acidosis (Figure 3).

It is important to recognize that Winter's formula does not reliably predict the respiratory response to a metabolic alkalosis. While hypoventilation is the natural compensatory response to a metabolic alkalosis, the PaCO$_2$ does not increase linearly with HCO$_3^-$: There are two general rules one can count on to predict the respiratory response to a metabolic alkalosis:

1. PaCO$_2$ will not usually increase to more than 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. If the pH is < 7.38, an additional respiratory acidosis exists.

**Common acid/base disturbances:**

1. Respiratory acidosis:

Respiratory acidosis is usually from hypoventilation, which results in an elevated PaCO$_2$ and reduced pH.

Examples:

a. Central nervous system depression (sedatives, central hypoventilation syndrome, obesity)
2. Respiratory alkalosis:

Respiratory alkalosis is usually from hyperventilation, which results in decreased PaCO$_2$ and increased pH.

Examples:

a. Catastrophic CNS event (CNS hemorrhage)

b. Drugs (salicylates, progesterone)

c. Pregnancy (especially the 3rd trimester)

d. Decreased lung compliance (interstitial lung disease)

e. Liver cirrhosis

f. Anxiety and/or pain

3. Anion Gap Acidosis

An anion gap acidosis results from the accumulation of metabolic acids and the consumption of HCO$_3^-$ (low HCO$_3^-$) in the presence of an anion gap (>12).

Examples:

a. Renal failure

b. Ketoacidosis (diabetic ketoacidosis, EtOH withdrawal)

c. Alcohol poisoning or drug intoxication (methanol, ethylene glycol, paraldehyde, salicylates)

d. Lactic acidosis (sepsis, heart failure)

4. Non-Anion Gap Acidosis

Non-anion gap acidosis results from the loss of HCO$_3^-$ or external acid infusion and is manifested by a low HCO$_3^-$. The anion gap is $<12$.

Examples:

a. GI loss of HCO$_3^-$ (diarrhea)

b. Renal loss of HCO$_3^-$

c. Compensation for respiratory alkalosis

d. Carbonic anhydrase inhibitor (acetazolamide)

e. Renal tubular acidosis

f. Ureteral diversion

g. Other causes: HCl or NH$_4$Cl infusion, parenteral nutrition
5. Metabolic Alkalosis

Metabolic alkalosis is a common acid/base disturbance in the ICU and results from elevation of serum bicarbonate.

Examples:

a. Volume contraction (vomiting, excessive diuresis, ascites)

b. Hypokalemia (H$^+$ exchange with K$^+$)

c. Alkali ingestion (bicarbonate)

d. Excess gluco- or mineralocorticoids

e. Massive resuscitation with hyperchloremic intravenous fluids (0.9% NS)

6. Mixed and complex disorders

It is rare to find simple acid/base disorders in critically ill patients, because critical illness often affects patients with pre-existing co-morbidities and baseline acid/base disturbances. Furthermore, many therapies, whether it be sedatives/analgesics, intravenous fluids, diuretics, or gastric suctioning, can further alter the acid/base state. While one may find a simple primary disorder early in the course of critical illness, the disorder becomes more complex with disease progression and subsequent treatment.

It is often difficult to understand the complex acid/base states.

For example, patients can have an anion gap and non-anion gap acidosis at the same time or a chronic respiratory acidosis and acute metabolic alkalosis. A patient may have had vomiting due to intestinal obstruction (causes metabolic alkalosis) and subsequently developed sepsis with hypoperfusion and lactic acidosis (anion gap acidosis). Another patient may have COPD with chronic respiratory acidosis and metabolic compensation (elevated HCO$_3^-$). When he is placed on mechanical ventilation with normalization of PaCO$_2$, his ABG will show an elevated HCO$_3^-$ (metabolic compensation for chronic respiratory acidosis) and normal PaCO$_2$. This will lead us to the diagnosis of metabolic alkalosis if we are unaware of his COPD with chronic CO$_2$ retention history. Thus the medical history is crucial to understanding complex acid base disorder, and in the formulation of clinical diagnoses and treatment plans.

Treatment

It is very rare for a clinician to be compelled to treat acid/base disorders directly. Most patients need treatment for the inciting pathology rather than manipulating the acid/base derangement directly. For example, a patient with an anion gap metabolic acidosis from severe sepsis should be treated for septic shock by restoring perfusion and obtaining source control. The metabolic acidosis should then resolve without further intervention.

However, it is not uncommon to resort to manipulating the acid/base state directly as a temporizing measure while the inciting
pathology is being treated. A few important points of such therapy are outlined below.

1. Most mild and moderate acid/base disturbances are self-limited and resolve with treatment of the underlying disease. Apart from severe, acute disorders, treatment should focus on the inciting pathology.

2. Utilize and augment the normal compensatory mechanism when possible. For example, in severe metabolic acidosis, one can facilitate respiratory compensation by augmenting ventilation prior to giving buffering agents.

3. Mild acidosis in patients under stress is beneficial and rarely of any harm, as it augments oxygen unloading from hemoglobin and into tissues. There is no need to normalize HCO$_3^-$ and/or pH with mild derangements.

4. It is rarely beneficial to administer HCO$_3^-$ to patients with a level > 10 mEq/L. The pH can be kept near normal with hyperventilation until HCO$_3^-$ levels drop to a single digit.

5. In rare situations when the pH drops below 7.2, administration of HCO$_3^-$ is indicated as a temporizing measure. It is important to make sure CO$_2$ elimination is effective during administration of HCO$_3^-$.

6. Severe alkalosis (metabolic or respiratory, pH > 7.5) is as harmful as acidosis and acute treatment may be indicated. While correcting the primary pathology, metabolic alkalosis may be treated with a carbonic anhydrase inhibitor (acetazolamide) for 24-48 hours. Conversely, respiratory alkalosis may be difficult to treat. This is especially true 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. In neonates and children, who are sensitive to large changes in intravascular volume, intracranial hemorrhage can occur with rapid administration of NaHCO$_3$. Furthermore, patients with chronic hyponatremia can experience osmotic demyelination.

---

**Figure 7.2.4 Intracellular Acidosis**

![Figure 4](image_url)

- **Figure 4**
- **NaHCO$_3$** + H$^+$ → H$_2$CO$_3$ → H$_2$O + CO$_2$
- **Cell** intracellular acidemia

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syndrome with the acute hypernatremia from NaHCO$_3$ administration.

8. THAM (Trome Thamine) solution is another H$^+$ acceptor and could be used to correct a metabolic acidosis when hypernatremia is contraindicated. While it is a weak buffer compared to NaHCO$_3$, it is less hypertonic. It generates NH$_3^+$ and HCO$_3^-$ without generating CO$_2$, so may be useful when CO$_2$ elimination is impaired. Since it is eliminated by the kidneys, it should not be used in patients who are anuric. Currently, the manufacturer has stopped production of THAM.

References:


Review Questions:

1. A 52 year-old man with a history of renal failure has the following ABG: pH 7.33, PaCO$_2$ 33, HCO$_3$ 17. What is the most appropriate response?
   a. This is inaccurate report, please repeat
   b. Administer 100 mEq of NaHCO$_3$
   c. Schedule patient for hemodialysis ASAP
   d. Initiate BiPAP to assist ventilation
   e. Do nothing, no intervention is needed

2. A 66 year-old woman, who is admitted with fever and leukocytosis, was found to have urosepsis. An ABG is obtained for tachypnea and shows: pH 7.34, PaCO$_2$ 35, HCO$_3$ 291
18, PaO₂ 78, Na 141, Cl 105. The most appropriate response(s) after initiating antibiotics is:

a. Intubate and initiate mechanical ventilation

b. Check lactic acid, it is likely elevated

c. Administer 50 mEq of NaHCO₃

d. Increase IV fluids and monitor urine output

e. Both B & D

3. A 22 year-old man sustains multiple trauma after a motor vehicle accident. Chest x-ray shows multiple rib fractures on the left with a small pneumothorax. His neurologic exam is intact, but he is noted to have tachypnea and requires 2L per nasal cannula to maintain SpO₂ > 95%. His ABG is: pH 7.47, PCO₂ 31, HCO₃ 22, PaO₂ 81 on 2L NC. What is the next best step?

a. Do nothing

b. Initiate acetazolamide therapy

c. Administer morphine to control pain and anxiety

d. Place large bore IV and give 1L of 0.9 NS

e. Perform left thoracostomy to drain pneumothorax
Sodium

Sodium is the main extracellular cation and therefore the main determinant of extracellular solute concentration. It reflects total body water and is mainly regulated by thirst and ADH.

Hypernatremia

Hypernatremia is defined as [Na\(^+\)] greater than 145 mEq/L. Incidence in ICU patients is up to 25% with mortality up to 70%. Symptoms include confusion and lethargy that can progress to seizures, coma, and death. (Table 1)

1. Free water deficit = [0.6 x total body weight] x [(measured [Na\(^+\)]/140) -1]

Patient Case:

A 30 year old male with type I diabetes mellitus (DM) presents to the emergency room with lethargy and abdominal pain. His roommate states that he had been vomiting for the past day. On further questioning, the patient admits he has not been compliant with his insulin regimen. His labs are remarkable for a glucose of 523 mg/dL, sodium of 125 mEq/L, and potassium of 5.4 mEq/L. He is diagnosed with diabetic ketoacidosis and treatment is initiated with insulin and normal saline.
Table 7.3.1: Causes of Hypernatremia

<table>
<thead>
<tr>
<th>Type</th>
<th>Cause(s)</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypovolemic</td>
<td>Urine sodium &gt; 20 mmol/L indicates renal losses such as diuretics and intrinsic renal disease</td>
<td>Provide volume resuscitation with isotonic solutions. Correct free water deficit (only after resuscitation)</td>
</tr>
<tr>
<td></td>
<td>Urine sodium &lt; 20 mmol/L indicates extra-renal losses such as sweating, burns, diarrhea, fistulas</td>
<td></td>
</tr>
<tr>
<td>Euvolemic</td>
<td>Renal losses such as diabetes insipidus (DI) or hypodipsia</td>
<td>Correct free water deficit</td>
</tr>
<tr>
<td></td>
<td>Extra-renal losses such as insensible losses (respiratory, dermal)</td>
<td>Give desmopressin for central DI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treat nephrogenic DI with thiazides, NSAIDs, amiloride.</td>
</tr>
<tr>
<td>Hypervolemic</td>
<td>Sodium intake (i.e. hypertonic saline, sodium tablets, sodium bicarbonate administration),</td>
<td>Remove excess sodium and volume</td>
</tr>
<tr>
<td></td>
<td>primary hyperaldosteronism, Cushing’s syndrome, hypertonic dialysis</td>
<td>May require hemodialysis (HD) for renal failure</td>
</tr>
</tbody>
</table>

2. Symptomatic hypernatremia should be treated with repletion of free water deficit:
   A. Goal is to decrease [Na⁺] to 145 mEq/L
   B. 3 mL/kg of electrolyte-free water should decrease plasma [Na⁺] by 1 mEq/L
   C. Replace half of free water deficit in first 12-24 hours and the rest over the next 48 hours
   D. Correction should be monitored closely to avoid the risk of cerebral edema

   1) For acute cases (less than 2 days), do not correct [Na⁺] more than 2 mEq/L/hr
   2) For chronic cases (more than 2 days), do not correct [Na⁺] more than 0.5 mEq/L/hr

Hyponatremia

Hyponatremia is defined as [Na⁺] less than 135 mEq/L. It is the most common electrolyte abnormality, present in up to 40-50% of ICU patients. Mortality can be as high as 50% in acute hyponatremia and 10-15% in chronic hyponatremia. Symptoms include nausea, vomiting, lethargy, confusion, coma, seizures, and herniation (due to cerebral edema) which can lead to death. (Table 2)

1. It is important to correct symptomatic or severe hyponatremia ([Na⁺] less than 120 mEq/L), however caution should be used when correcting hyponatremia in order to avoid osmotic demyelination syndrome
   A. 1 mL/kg of 3% saline should increase plasma [Na⁺] by 1 mEq/L

2. Correction of symptomatic hyponatremia should be determined by onset
   A. Acute cases (less than 2 days)
      i. Increase [Na⁺] by 4-6 mEq/L in the first 6 hours
<table>
<thead>
<tr>
<th>Types</th>
<th>Causes</th>
<th>Treatment</th>
</tr>
</thead>
</table>
| Hypovolemic hypotonic hyponatremia | - Urine sodium > 20 mmol/L indicates renal losses, such as excess diuretics, renal tubular acidosis, mineralocorticoid deficiency, cerebral salt wasting  
- Urine sodium < 20 mmol/L indicates extra-renal losses, such as vomiting, diarrhea, third spacing (burns, pancreatitis, trauma) | - Address underlying cause of hypovolemia and use isotonic volume resuscitation  
- Cerebral salt wasting needs aggressive volume resuscitation |
| Euvolemic hypotonic hyponatremia | - Glucocorticoid deficiency, hypothyroidism, psychogenic polydipsia, medications that mimic or increase vasopressin activity, psychotropic medications (i.e. haloperidol, amitriptyline)  
- Syndrome of inappropriate ADH secretion (SIADH) is a diagnosis of exclusion: 1. Plasma osmolality < 270 mOsm/kg H2O  
2. Urine osmolality > 100 mOsm/kg H2O  
3. Urine sodium > 20 mEq/L  
4. Euvolemia  
5. No adrenal, thyroid, pituitary, or renal insufficiency  
6. Lack of diuretic use | - Address underlying cause and initiate free water restriction  
- With elevated urine sodium, can also consider loop diuretics, demeclocycline, or salt  
- With SIADH, do not treat with isotonic solutions as volume expansion will result in increased excretion of urinary sodium. This will worsen hyponatremia |
| Hypervolemic hypotonic hyponatremia | - Urine sodium > 20 mmol/L indicates renal failure  
- Urine sodium < 20 mmol/L indicates nephrotic syndrome, hepatic cirrhosis, or congestive heart failure (CHF) | - Manage underlying cause, initiate salt and water restriction  
- Can also use loop diuretics or vaptans in refractory patients |
| Pseudohyponatremia (normal serum osmolality) | - Hyperproteinemia > 12-15 g/dL (like multiple myeloma, IVIG treatments) and hyperlipidemia > 1500 mg/dL can influence lab measurements | - Manage underlying cause |
| Translocational hyponatremia (hyperosmolality) | - Hyperglycemia  
- [Na+] decreases between 1.6-2.4 mEq/L for every 100 mg/dL increase in plasma glucose above 100 mg/dL  
- Less commonly with hypertonic sodium-free solutions such as mannitol, glycine, or maltose | - Treat hyperglycemia and provide volume resuscitation |

### Potassium

Potassium is the most common intracellular cation and is integral to determining the membrane potential in neural, cardiac and muscular cells.

### Hyperkalemia

Hyperkalemia is defined as [K+] greater than 5.5 mEq/L. The most concerning symptoms are EKG changes such as peaked T-waves, widening of the QRS complex, atrioventricular conduction blocks, and sine waves which can progress to ventricular fibrillation and asystole. Other symptoms include paresthesia and weakness, which can progress to flaccid paralysis that spares the cranial nerves. (Table 3)

### Hypokalemia

Hypokalemia is defined by [K+] less than 3.5 mEq/L. It has an incidence of up to 20% in hospitalized patients. Hypokalemia can cause the following symptoms: (Table 4)
Table 7.3.3: Causes of Hyperkalemia

<table>
<thead>
<tr>
<th>Causes</th>
<th>Examples</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excessive intake</td>
<td></td>
<td>Treat emergently for ([K^+] &gt; 6.5) mEq/L or EKG changes</td>
</tr>
<tr>
<td>Impaired excretion</td>
<td>- Renal failure&lt;br&gt;- Mineralocorticoid deficiency (i.e. Type 4 RTA, Addison's disease, hereditary enzyme deficiencies)&lt;br&gt;- Drugs (i.e. potassium-sparing diuretics, ACE-inhibitors, ARBs, NSAIDs)&lt;br&gt;- Pseudohypoaldosteronism (i.e. CKD with DM)&lt;br&gt;- Uretojejunostomy</td>
<td>- Stop potassium sources (TPN, supplementation, medications)&lt;br&gt;- Stabilize cardiac membrane (calcium chloride or gluconate)&lt;br&gt;- Shift intracellularly (regular insulin and glucose, beta-agonist, or treat acidosis)&lt;br&gt;- Renal excretion (potassium-wasting diuretic like furosemide)&lt;br&gt;- GI excretion (sodium polystyrene sulfonate)&lt;br&gt;- Extracorporeal removal (HD or continuous renal replacement therapy)</td>
</tr>
<tr>
<td>Extracellular shifts</td>
<td>- Hypertonicity&lt;br&gt;- Tissue destruction (trauma, burns, rhabdomyolysis)&lt;br&gt;- Cellular destruction (tumor lysis, acute intravascular hemolysis)&lt;br&gt;- Insulin deficiency or resistance&lt;br&gt;- Drugs (like beta-blockers, digoxin, succinylcholine)</td>
<td>Treat emergently for ([K^+] &gt; 6.5) mEq/L or EKG changes&lt;br&gt;- Stop potassium sources (TPN, supplementation, medications)&lt;br&gt;- Stabilize cardiac membrane (calcium chloride or gluconate)&lt;br&gt;- Shift intracellularly (regular insulin and glucose, beta-agonist, or treat acidosis)&lt;br&gt;- Renal excretion (potassium-wasting diuretic like furosemide)&lt;br&gt;- GI excretion (sodium polystyrene sulfonate)&lt;br&gt;- Extracorporeal removal (HD or continuous renal replacement therapy)</td>
</tr>
</tbody>
</table>

1. Cardiac – ventricular arrhythmias and EKG changes (flattened T waves, ST-depression, U waves, QT prolongation)
2. Musculoskeletal – generalized weakness that can progress to muscle necrosis, rhabdomyolysis and then respiratory failure and arrest
3. Gastrointestinal – constipation or ileus with severe hypokalemia
4. Neurologic – encephalopathy
5. Renal – polyuria

Table 7.3.4: Causes of Hypokalemia

<table>
<thead>
<tr>
<th>Causes</th>
<th>Examples</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased intake</td>
<td></td>
<td>Address underlying causes such as drugs causing intracellular shifts or treating concurrent hypomagnesemia</td>
</tr>
<tr>
<td>Increased excretion</td>
<td>Renal losses such as diuretics, metabolic alkalosis, osmotic diuresis (hyperglycemia), renal tubular acidosis, excess mineralocorticoids (congenital adrenal hyperplasia, primary aldosteronism), hypomagnesemia, high-dose glucocorticoids, penicillin or derivatives</td>
<td>Supplement with potassium chloride or potassium phosphate</td>
</tr>
<tr>
<td>Intracellular shifts</td>
<td>Beta-agonism&lt;br&gt;- Drugs (bronchodilators, dobutamine, decongestants, tocolytics)&lt;br&gt;- Physiologic causes (hypothyroidism, delirium tremens, familial hypokalemic periodic paralysis)</td>
<td>Other causes include insulin, theophylline, caffeine, barium poisoning, refeeding syndrome</td>
</tr>
</tbody>
</table>

**Magnesium**

Magnesium is a very important cofactor in reactions involving adenosine triphosphate (ATP). It is also integral to the regulation of sodium, potassium, and calcium.

**Hypermagnesemia**

Hypermagnesemia is defined as \([Mg^{2+}] > 2.3\) mEq/L. Incidence has been reported up to 5% in hospitalized patients.
Table 7.3.5: Causes of Hypermagnesemia

<table>
<thead>
<tr>
<th>Causes</th>
<th>Examples</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased intake</td>
<td></td>
<td>IV calcium for hemodynamic instability</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Renal excretion with diuretics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HD for renal failure or acute intoxication</td>
</tr>
<tr>
<td>Decreased excretion</td>
<td>Renal failure</td>
<td>IV calcium for hemodynamic instability</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Renal excretion with diuretics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HD for renal failure or acute intoxication</td>
</tr>
</tbody>
</table>

Hypermagnesemia can cause the following symptoms: (Table 5)

1. Neurologic – lethargy, somnolence, coma
2. Musculoskeletal – decreased deep tendon reflexes that can progress to muscle paralysis
3. Cardiac
   A. Bradycardia, hypotension
   B. EKG changes - prolonged QRS, PR and QT intervals, complete heart block, cardiac arrest

Hypomagnesemia

Hypomagnesemia is defined as [Mg2+] less than 1.8 mEq/L and its incidence in ICU patients is up to 65%. Hypomagnesemia can cause the following symptoms: (Table 6)

1. Cardiac EKG changes – flattened T-waves, U waves, QT prolongation, widened QRS complex, arrhythmias (i.e. atrial fibrillation, ventricular tachycardia [characteristic torsade de pointes pattern])
2. Neurologic – seizures, lethargy, coma
3. Musculoskeletal – loss of deep tendon reflexes, tetany

Table 7.3.6: Causes of Hypomagnesemia

<table>
<thead>
<tr>
<th>Causes</th>
<th>Examples</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased intake</td>
<td>Short bowel syndrome</td>
<td>Address underlying cause IV repletion</td>
</tr>
<tr>
<td>Renal losses</td>
<td>Diuretics</td>
<td>Bolus for acute symptoms such as seizures, tetany, arrhythmias (like torsade de pointes)</td>
</tr>
<tr>
<td></td>
<td>Alcohol abuse</td>
<td>Care and reduce dose when treating patients with renal failure</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acute tubular necrosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other drugs such as aminoglycosides, amphotericin, cyclosporine, cisplatin, digoxin</td>
<td></td>
</tr>
<tr>
<td>GI losses</td>
<td>Vomiting</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nasogastric suction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pancreatitis</td>
<td></td>
</tr>
<tr>
<td>Intracellular shifting</td>
<td>Refeeding (glucose, amino acids)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Insulin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Excess catecholamines</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Metabolic acidosis</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Burns</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Massive blood transfusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cardiopulmonary bypass</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Liver transplant</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe sepsis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dilution from volume resuscitation</td>
<td></td>
</tr>
</tbody>
</table>

Calcium

Calcium is involved in smooth muscle contraction, neuromuscular signaling, and coagulation. It is the most abundant electrolyte in the body and the majority of it is stored in bone.
**Hypercalcemia**

Hypercalcemia is defined as a total body $[\text{Ca}^{2+}]$ greater than 10.4 mg/dL. The incidence in ICU patients is less than 15%.

Symptoms of hypercalcemia include: (Table 7)

1. Neurologic – confusion, delirium, psychosis, coma
2. Gastrointestinal – nausea, vomiting, constipation, abdominal pain, ileus, pancreatitis
3. Cardiovascular – hypotension, hypovolemia, EKG changes (shortened QT interval)
4. Musculoskeletal - weakness, fatigue

**Table 7.3.7: Causes of Hypercalcemia**

<table>
<thead>
<tr>
<th>Causes</th>
<th>Examples</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excessive bone resorption</td>
<td>Hyperparathyroidism</td>
<td>- Address underlying cause (such as chloroquine for sarcoidosis)</td>
</tr>
<tr>
<td></td>
<td>Paraneoplastic syndrome (most commonly parathyroid hormone-related peptide)</td>
<td>- Hydration</td>
</tr>
<tr>
<td></td>
<td>Prolonged immobility</td>
<td>- Renal excretion (diuretics like furosemide)</td>
</tr>
<tr>
<td>Medications</td>
<td>Thiazides</td>
<td>- Inhibit bone resorption (calcitonin, bisphosphonates)</td>
</tr>
<tr>
<td>Increased intestinal intake</td>
<td>Milk-alkali syndrome</td>
<td>- Corticosteroids (reduces intestinal absorption and production of calcitriol)</td>
</tr>
<tr>
<td></td>
<td>Increased vitamin D</td>
<td>- Hemodialysis</td>
</tr>
<tr>
<td></td>
<td>Calcipotriol</td>
<td>- Parathyroidectomy if medical therapy fails</td>
</tr>
<tr>
<td>Endogenous calcitriol production</td>
<td>Chronic granulomatous disorders (such as sarcoidosis or tuberculosis)</td>
<td></td>
</tr>
</tbody>
</table>

5. Renal - nephrolithiasis, renal insufficiency

**Hypocalcemia**

Hypocalcemia is defined as total body $[\text{Ca}^{2+}]$ less than 8.5 mg/dL or ionized $[\text{Ca}^{2+}]$ less than 1.0 mg/dL. The incidence in ICU patients varies based on the type of testing. It can range from 15-50% when measuring ionized calcium to 70-90% when measuring total serum calcium. This difference is likely due to hypoalbuminemia in ICU patients. Hypocalcemia can cause a variety of symptoms: (Table 8)

1. Cardiovascular
   A. Decreased cardiac output
   B. Refractory hypotension to volume and vasopressors
   C. EKG changes – bradycardia, QT prolongation, T-wave inversion, heart block, ventricular tachycardia

2. Neurologic – paresthesia, seizures

3. Musculoskeletal – muscle spasms, tetany
   A. Chvostek’s sign – twitching of facial muscles with tapping of facial nerve
   B. Trousseau’s sign – carpopedal spasm with decreased blood flow to hand (from inflating blood pressure cuff to 20 mmHg for 3 minutes)
4. Psychiatric – dementia, psychosis, depression

**Table 7.3.8: Causes of Hypocalcemia**

<table>
<thead>
<tr>
<th>Causes</th>
<th>Examples</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired parathyroid hormone</td>
<td>Primary hypoparathyroidism (impaired secretion)</td>
<td>Address underlying cause (such as vitamin D repletion or phosphate binders)</td>
</tr>
<tr>
<td></td>
<td>Secondary hypoparathyroidism (impaired action)</td>
<td></td>
</tr>
<tr>
<td>Vitamin D deficiency</td>
<td>Decreased intake, malnutrition SIRS, sepsis Hepatic or renal disease Hypomagnesemia</td>
<td>Treat for severe ionized (&lt;0.8 mg/dL) and symptomatic IV repletion with calcium chloride (preferred because immediately physiologically available) or gluconate</td>
</tr>
<tr>
<td>Chelation or precipitation</td>
<td>Hyperphosphatemia Citrate (in massive transfusion) Pancreatitis Rhabdomyolysis Ethylene glycol Alkalosis</td>
<td>Address underlying cause (such as vitamin D repletion or phosphate binders)</td>
</tr>
<tr>
<td>Impaired bone mobilization</td>
<td>Hypothyroidism Excess calcitonin Cisplatin Diphenosphonate Mithramycin Phosphate</td>
<td>Address underlying cause (such as vitamin D repletion or phosphate binders)</td>
</tr>
</tbody>
</table>

**Phosphorus**

Phosphorus plays an important role in the formation of ATP and phospholipids in cell membranes.

**Hyperphosphatemia**

Hyperphosphatemia is defined as phosphate level greater than 4.5 mg/dL. Symptoms of hyperphosphatemia include: (Table 9)

1. Similar to hypocalcemia (see above)

2. Metastatic calcification

3. Renal – acute renal failure

4. Cardiovascular – arrhythmias

**Table 7.3.9: Causes of Hyperphosphatemia**

<table>
<thead>
<tr>
<th>Causes</th>
<th>Examples</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased renal resorption</td>
<td>Hypoparathyroidism Thyrotoxicosis</td>
<td>Address underlying cause</td>
</tr>
<tr>
<td>Increased intake</td>
<td>Vitamin D toxicity</td>
<td>Increase renal excretion</td>
</tr>
<tr>
<td>Cell damage</td>
<td>Rhabdomyolysis Tumor lysis syndrome Hemolysis</td>
<td>- IV fluids - Diuretics (acetazolamide)</td>
</tr>
<tr>
<td>Other</td>
<td>Laxative abuse Bisphosphonate use</td>
<td>Phosphate binder (renal failure)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hemodialysis</td>
</tr>
</tbody>
</table>

**Hypophosphatemia**

Hypophosphatemia is defined as phosphate level less than 3.0 mg/dL. The incidence in ICU patients is 10-30%. Symptoms of hypophosphatemia include: (Table 10)

1. Musculoskeletal – weakness (including respiratory muscle weakness leading to difficulty weaning from ventilator), rhabdomyolysis, bone demineralization

2. Neurologic – confusion, lethargy, gait disturbance, paresthesia, seizures, coma
3. Hematologic – acute hemolytic anemia, leukocyte dysfunction

4. Cardiovascular – acute left ventricular dysfunction, reversible dilated cardiomyopathy

5. Gastrointestinal – ileus

Table 7.3.10: Causes of Hypophosphatemia

<table>
<thead>
<tr>
<th>Causes</th>
<th>Examples</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transcellular shifts</td>
<td>Refeeding syndrome</td>
<td>Address underlying cause</td>
</tr>
<tr>
<td></td>
<td>Insulin</td>
<td>Repletion with IV sodium phosphate or potassium phosphate</td>
</tr>
<tr>
<td></td>
<td>Respiratory alkalosis</td>
<td></td>
</tr>
<tr>
<td>Renal losses</td>
<td>Diuretics (like acetazolamide)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Osmotic diuresis (like with diabetic ketoacidosis)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hyperparathyroidism</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Proximal renal tubular dysfunction (like Fanconi's syndrome)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alcoholism</td>
<td></td>
</tr>
<tr>
<td>Decreased intestinal absorption</td>
<td>Malnutrition</td>
<td>Address underlying cause</td>
</tr>
<tr>
<td></td>
<td>Phosphate-binding antacids</td>
<td>Repletion with IV sodium phosphate or potassium phosphate</td>
</tr>
<tr>
<td></td>
<td>Vitamin D deficiency</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chronic diarrhea, malabsorption</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nasogastric suction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Corticosteroids</td>
<td></td>
</tr>
<tr>
<td>Extreme catabolic states</td>
<td>Burns</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sepsis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trauma</td>
<td></td>
</tr>
</tbody>
</table>

References:


Review Questions:

1. A patient is found to have a \([K^+]\) of 6.0 mEq/L, you should do all of the following EXCEPT
   a. Check for hemolysis in the sample
   b. Order a 12 lead EKG
   c. Administer acetazolamide
   d. Order sodium polystyrene sulfonate

This chapter is a revision of the prior chapter authored by Anna M. Allred, MD and Sheena M. Weaver, MD
2. During morning rounds, you decide to initiate fluid restriction on a patient with [Na\(^+\)] of 131 mEq/L. Based on your decision for treatment, your differential includes all of the following EXCEPT

a. Congestive heart failure

b. Pancreatitis

c. Renal failure

d. Hepatic cirrhosis

3. One of your patients develops hypotension overnight so you decide to order IV fluids as well as a norepinephrine infusion. A few hours later, you notice that your interventions have not been successful. Which of the following lab results is consistent with this picture?

a. [Na\(^+\)] = 130 mEq/L

b. [K\(^+\)] = 3.0 mEq/L

c. [Mg\(^{2+}\)] = 1.5 mg/dL

d. Ionized [Ca\(^{2+}\)] = 0.9 mmol/L
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 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.

Key Points:

- Total body water (TBW) is related to lean body mass; men and women are estimated to be 60% and 50% water, respectively.
- Hydrostatic pressure is the primary force driving the distribution of fluid between compartments.
- Clinical evaluation of volume status is challenging; vital signs, serum electrolytes and markers of renal function are of most diagnostic value.
- The selection of fluids used in resuscitation should be tailored to each patient’s illness or injury.
- The Surviving Sepsis Guidelines and ATLS guidelines provide recommendations for fluid management in severe sepsis/septic shock and traumatic hemorrhagic shock.

Patient Case:

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. His vital signs and pertinent laboratory data are below.

| Temp (C) | 38.6 | WBC (x10⁹/L): 22 |
| HR (bpm)| 128  | Hgb (g/dL): 9     |
| RR (bpm)| 24   | Na⁺ (mEq/L): 140  |
| BP (mmHg)| 74/53| K⁺ (mEq/L): 4.2   |
| O₂Sat (%)| 98   | Cr (mg/dL): 2.0   |
|         |      | Lactate (mmol/L): 6.8 |
Although rarely termed this way, the intracellular and extracellular compartments represent the “first” and “second” spaces.

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:

\[(\text{Na}^+ [\text{mEq/L}] \times 2) + (\text{glucose} [\text{mg/dL}] / 18) + (\text{BUN} [\text{mg/dL}] / 2.3)\]

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?

Fluids used to restore the intravascular circulating volume 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 in the

*In the average 70-kg man: TBW=42 kg, Extracellular Water= 14 kg, Intracellular water = 28 kg, Interstitial fluid = 10.5 kg, and plasma = 3.5 kg.
intravascular space. It has been traditionally taught that three to four times as much crystalloid as colloid is required for equal intravascular volume expansion. This, however, has not been shown to be true under actual clinical circumstances and is more on the order of less than or equal to 2:1. 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 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 (INR 1.5) can be transfused contemporaneously in an attempt to approximate transfusion of whole blood. The Pragmatic, Randomized Optimal Platelet and Plasma Ratio (PROPPR) Trial (2015) demonstrated no significant difference in 24 hour or 30 day mortality between a 1:1:1 and a 1:1:2 ratio of plasma, platelets, and red blood cells in trauma patients requiring massive transfusion. However, deaths due to bleeding at these time points were significantly lower in the 1:1:1 cohort, leading to a suggested target for resuscitation between plasma and PRBC of 1:2 and 1:1. (2)

**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. (3) 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. (4) 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. Colloids have not been shown to improve outcomes and may be detrimental in critically ill patients. When a colloid solution is indicated, human

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**Table 7.4.1: Composition of Commonly Used Crystalloids and Colloids**

<table>
<thead>
<tr>
<th>Solution</th>
<th>Na (mEq/L)</th>
<th>K (mEq/L)</th>
<th>Cl (mEq/L)</th>
<th>Other Ions</th>
<th>Calculated Osmolarity (mOsm/L)</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS</td>
<td>154</td>
<td>0</td>
<td>154</td>
<td></td>
<td>308</td>
<td>4.5-7.0</td>
</tr>
<tr>
<td>LR</td>
<td>130</td>
<td>4</td>
<td>109</td>
<td>Lactate, calcium</td>
<td>274</td>
<td>6.0-7.5</td>
</tr>
<tr>
<td>Plasmalyte</td>
<td>140</td>
<td>5</td>
<td>98</td>
<td>Magnesium, Acetate, Gluconate</td>
<td>294</td>
<td>6.5-7.6</td>
</tr>
<tr>
<td>D5W</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Dextrose (50 mg/L)</td>
<td>278</td>
<td>5.0</td>
</tr>
<tr>
<td>Albumin 5%</td>
<td>145</td>
<td>&lt;1</td>
<td>145</td>
<td>Albumin (50 gm/L)</td>
<td>310</td>
<td>6.9</td>
</tr>
<tr>
<td>Albumin 25%</td>
<td>145</td>
<td>&lt;1</td>
<td>145</td>
<td>Albumin (250 gm/L)</td>
<td>308</td>
<td>6.9</td>
</tr>
<tr>
<td>HES 130/0.4</td>
<td>154</td>
<td>0</td>
<td>154</td>
<td></td>
<td>308</td>
<td>4.0-5.5</td>
</tr>
<tr>
<td>(Voluven®)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5.9</td>
</tr>
<tr>
<td>HES 450/0.7</td>
<td>154</td>
<td>0</td>
<td>154</td>
<td></td>
<td>310</td>
<td>5.9</td>
</tr>
</tbody>
</table>
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. (5-7)

**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, hyperlacticemia, 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 2.

**Table 7.4.2: Findings Differentiating the 4 Classic Categories of Shock**

<table>
<thead>
<tr>
<th>Type</th>
<th>Mean RAP (Neck veins)</th>
<th>Mean LAP (Lungs)</th>
<th>Stroke Volume (Pulse Volume)</th>
<th>SVR (Skin)</th>
<th>Mixed Venous O₂%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypovolemic</td>
<td>↓, flat</td>
<td>↓, clear</td>
<td>↓</td>
<td>↑, cool/mottled</td>
<td>↓</td>
</tr>
<tr>
<td>Cardiogenic</td>
<td>↑</td>
<td>↑, rales</td>
<td>↓</td>
<td>↑, cool/mottled</td>
<td>↓</td>
</tr>
<tr>
<td>Distributive</td>
<td>↓, flat</td>
<td>↓, clear</td>
<td>↑↑</td>
<td>↓, warm/diaphoretic</td>
<td>↑</td>
</tr>
<tr>
<td>Obstructive*</td>
<td>↑</td>
<td>↓, clear</td>
<td>↓</td>
<td>↑, cool/mottled</td>
<td>↓</td>
</tr>
</tbody>
</table>

*Classic findings of a massive pulmonary embolism. Findings vary if the etiology is tension pneumothorax or cardiac tamponade.

Hypovolemic shock can occur from a variety of causes including hemorrhage, profound diarrhea, or severe dehydration. Regardless of its 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 catheter, control of bleeding, and a 2 liter fluid challenge. Transient and non-responders need blood products for volume and to control coagulopathy. Ultimately, source control is the most important intervention in traumatic hemorrhagic shock. (8)

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 their 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 resuscitation be started with crystalloids with a challenge of at least 2 liters or 30 mL/kg within the first 3 hours. Additional fluids should be guided by frequent reassessment of hemodynamic status. Albumin may have a role only after substantial amounts of crystalloids have been given. Synthetic colloids are contraindicated in these patients. Barring other indications for transfusion, a target hemoglobin of 7-9 g/dL is adequate and FFP is not indicated, except in the presence of bleeding or planned procedures. (9)

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.

**Case Discussion**

This patient is in septic shock. Hemodynamic resuscitation goals described by the Surviving Sepsis Campaign guidelines should be targeted. Hypotension and tachycardia have further resulted in demand ischemia. Other etiologies of 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 the patient’s hypotension and tachycardia, a vasopressor should be started to maintain the mean arterial pressure greater than 65 mmHg. Although his hemoglobin is greater than 7 g/dL, a packed red cell transfusion may be appropriate after other hemodynamic goals have been achieved. Aggressive resuscitation, in conjunction with treatment of the underlying systemic infection, gives this patient his best chance at survival and optimal recovery.

**References:**


**Review Questions:**

1. Which of the following is most correct regarding the use of colloid solutions for volume resuscitation in the critically ill?
   a. Colloid solutions help maintain lower intracranial pressure in patients with traumatic brain injury
   b. Colloids limit ascites in patients with acute pancreatitis
   c. Colloids are associated with improved mortality in patients with septic shock
   d. The total volume of colloids administered to achieve hemodynamic goals is less than that required for resuscitation with crystalloid solutions

2. In which of the following patients would you most expect to find an elevated mixed-venous oxygen saturation (ScVO$_2$)?
   a. An 81-year old female with a history of worsening fatigue who is admitted with uremic encephalopathy. BP: 84/52, HR: 136, T: 35.3, SpO$_2$ 96%
b. A 63-year old male with a history of dyschezia (painful defecation) who is admitted with severe left flank pain. BP: 78/50, HR: 144, T: 40.2, SpO₂ 90%.

c. A 48-year old male with a history of hypertension who was found down at home. BP: 74/48, HR: 133, T: 36.0, SpO₂ 84%, JVP 11 cm.

d. A 70-year old female who complained of hemoptysis status post right total knee replacement. BP: 60/30, HR 160, T: 37.9, SpO₂ 70%.

3. When measured or observed correctly, which physical exam finding is most indicative of a depleted extracellular fluid volume (hypovolemia) due to severe diarrhea in a 40-year old woman?

a. Capillary refill equal to 5 seconds

b. Supine blood pressure 90/58

c. Dry mucous membranes with poor skin turgor

d. Postural increase in heart rate greater than 30 beats per minute on standing
Introduction

Acute kidney injury (AKI) is a common problem in the Intensive Care Unit (ICU), occurring in up to 57% of ICU patients. (1) With worsening renal injury, therapeutic options become limited and renal replacement therapy (RRT) becomes the mainstay of treatment. Up to 13% of patients admitted to the ICU will require RRT.

Principles of Renal Replacement Therapy

All forms of RRT utilize a semipermeable membrane across which three basic processes occur to allow for exchange of solutes and water: ultrafiltration, diffusion, and convection. Ultrafiltration is a process by which water moves across a semipermeable membrane due to a trans-membrane pressure gradient. This is

Patient Case:
A 72 year-old man is admitted to the ICU after open repair of a thoracoabdominal 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 venovenous 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.

Key Points:

- Renal replacement therapy (RRT) is a common therapy in the ICU.
- RRT can be performed in an intermittent (IHD) or continuous (CRRT) fashion; 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 resource availability.
- In RRT, three processes by which solute and water exchange occur are ultrafiltration, diffusion, and convection.
how RRT rids the blood of water: the blood compartment is pressurized and forces water across the membrane, leaving behind the other blood components. Solute exchange across the semipermeable membrane occurs by either diffusion or convection. Diffusion is the movement of solutes from an area of high concentration to low concentration. Convection refers to the movement of solutes across a semipermeable membrane driven by the movement of a solvent across the membrane (i.e. solutes are “dragged” across the membrane by water). The membrane pore diameter limits the size of solutes that are able to cross. Low-flux (cellulose-based) membranes have low water permeability and limit the size of solutes to less than 500 Daltons (small proteins and electrolytes). High-flux (synthetic-based) membranes have high water permeability and allow larger molecules (5,000-50,000 Daltons) to cross.

**Indications for Renal Replacement Therapy**

Common indications for RRT are listed in Table 1. Less common uses of RRT include immunomodulation in sepsis, rhabdomyolysis, severe hypothermia, increased intracranial pressure, other electrolyte abnormalities (dysnatremia). In the setting of AKI, RRT has the following goals: 1) maintain fluid, electrolyte, and acid-base balance; 2) limit additional kidney injury; 3) promote kidney recovery; and, 4) aid in other supportive measures (i.e., urea clearance in the setting of protein-rich nutritional support). (2)

**Initiation of Renal Replacement Therapy**

Life-threatening conditions such as severe fluid, electrolyte, and acid-base abnormalities necessitate emergent initiation of RRT. Aside from these instances, the decision of when to start RRT is controversial. Studies have explored the effects of early and delayed initiation of RRT with mixed results. Current guidelines suggest using the overall clinical picture as opposed to lab values (i.e BUN, creatinine) in considering when to start RRT. (2) Once the decision to commence RRT is made, the essential

**Table 7.5.1 Indications for RRT**

<table>
<thead>
<tr>
<th>Primary</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol and drug intoxications</td>
<td>Endotoxic shock</td>
</tr>
<tr>
<td>Fluid management for oliguria/anuria</td>
<td>Acute hepatic failure</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>Plasmapheresis (in lieu of)</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>Severe dysnatremia</td>
</tr>
<tr>
<td>Metabolic acidosis (pH &lt; 7.1)</td>
<td>Severe rhabdomyolysis</td>
</tr>
<tr>
<td>Rapidly climbing urea/ creatinine</td>
<td></td>
</tr>
<tr>
<td>Refractory fluid overload</td>
<td></td>
</tr>
<tr>
<td>Uremia with acute signs of pericarditis, neuropathy, mental status changes, or refractory bleeding</td>
<td></td>
</tr>
</tbody>
</table>
components of the RRT prescription include the modality, anticoagulation, intensity of treatment, composition and rate of replacement or dialysate fluid, and net fluid goal.

**Modalities of Renal Replacement Therapy**

Current RRT modalities include intermittent hemodialysis (IHD), continuous renal replacement therapy (CRRT), peritoneal dialysis (PD), and more novel hybrid techniques, such as extended duration dialysis (EDD) and sustained low-efficiency dialysis (SLED). Depending upon the type of RRT, solute and fluid removal can be achieved by different mechanisms: hemodialysis, hemofiltration, hemodiafiltration, and ultrafiltration (Figure 1).

*Hemodialysis* utilizes the concept of diffusion to rid the blood of unwanted solutes. During hemodialysis, blood is pumped through an extracorporeal membrane where it is physically separated from a crystalloid solution (dialysate) by a semipermeable membrane. Solutes move across the membrane, down their concentration gradient, according to Fick’s laws of diffusion. For example, bicarbonate moves from the dialysate to the blood (higher concentration in the dialysate) while urea and potassium move from the blood to the dialysate (lower concentration in the dialysate). The dialysate travels in a countercurrent direction to the blood; this maintains the solute concentration gradients and maximizes the efficiency of solute exchange. Hemodialysis typically employs low-flux membranes that have lower water permeability and allow small molecules and electrolytes to cross. With application of hydrostatic pressure to the blood-side of the membrane, some degree of ultrafiltration occurs, allowing for fluid removal into the dialysate; however, this is not as efficient as with other RRT modalities.

*Hemofiltration* employs the concepts of ultrafiltration and convection. With hemofiltration, blood is pumped through an extracorporeal system incorporating a semipermeable membrane. Hydrostatic pressure is created on the blood-side of the
membrane thereby driving fluid across the membrane (ultrafiltration). During this process, molecules small enough to pass through the membrane are dragged across the membrane along with the water molecules (convection). Fluid crossing the membrane is called ultrafiltrate and is discarded. This is replaced by replacement fluid, which is adjustable in volume and composition, but usually consists of glucose, electrolytes, and a buffer (bicarbonate, citrate, lactate, etc). Typically, high-flux membranes are used in hemofiltration. These membranes are more permeable to water and have larger pores allowing large molecules (5,000-50,000 Daltons) to cross.

Hemodiafiltration exploits concepts common to both hemofiltration and hemodialysis with benefits of each; however, to a lesser extent than when the individual techniques are used alone. In hemodiafiltration, blood is pumped through a extracorporeal system where it is separated from a dialysate solution by a semipermeable membrane. The dialysate flows by a countercurrent mechanism similar to hemodialysis. Hydrostatic pressure is applied to the blood-side of the membrane, forcing water into the dialysate/ultrafiltrate as in hemofiltration. Replacement fluid can be added to the blood if desired.

Slow-continuous ultrafiltration is used when only water removal is the objective. During ultrafiltration, hydrostatic pressure is applied to the blood-side of the membrane (or negative pressure is applied to the opposite side of the membrane) and water transverses the membrane. Unlike hemofiltration, very little convection (solute transfer) occurs. In addition, replacement solution is not added.

Traditionally, severe AKI has been managed with IHD that is delivered over 3-5 hours per session with 3-6 sessions per week. Decisions regarding dialysis session duration and frequency are based upon the patient’s metabolic control, volume status, and hemodynamic stability. A major advantage of IHD is rapid solute and volume removal. In addition, IHD 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 hemodynamic instability associated with rapid electrolyte and solute removal. Rapid solute removal from the intravascular space can result in cerebral edema limiting this modality for patients with head trauma or hepatic encephalopathy. With CRRT, on the other hand, the patient is continuously being dialyzed via an extracorporeal system, allowing for slower flow rates and less rapid removal of fluid and solutes. This generally translates into less hemodynamic disturbances and more gradual changes in osmolarity. CRRT requires continuous anticoagulation and is more expensive than IHD. Forms of CRRT include continuous veno-venous hemodialysis (CVVHD), hemofiltration (CVVH), and hemodiafiltration (CVVHDF).

Studies comparing IHD and CRRT have failed to demonstrate any
survival advantage; however, these studies have been limited by issues related to study design, such as exclusion of patients with hemodynamic instability, improper randomization, and differences in baseline characteristics. 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 patients’ changing needs. When deciding between different forms of CRRT, the primary considerations are resource availability and provider preference. Because CVVH utilizes high-flux membranes with larger pores, it may allow clearance of large molecules, such as cytokines, and thus may help to downregulate the systemic inflammatory response seen in sepsis.

Other forms of renal replacement therapy include Peritoneal Dialysis (PD), Sustained-Low Efficiency Dialysis (SLED), and Extended Day Dialysis (EDD). PD is rarely used in the ICU to treat AKI. During PD, dialysate is injected into the peritoneal cavity via a catheter. The peritoneum serves as a membrane across which fluid and solutes are exchanged. Dialysate solution, which consists of an osmotic agent, buffer, and electrolytes, is periodically removed and replaced.

SLED and EDD are dialytic modalities that use conventional hemodialysis machines, but provide reduced blood 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, allowing time for diagnostic and therapeutic procedures to be done that are often required in critically ill patients.

**Anticoagulation**

As blood passes through the extracorporeal dialysis circuit, the clotting cascade is activated as blood comes in contact with foreign surfaces, particularly the dialysis membrane. Thus, anticoagulation is commonly required. With IHD, unfractionated heparin is typically used, while in CRRT, either citrate or unfractionated heparin can be employed. For patients at increased risk of bleeding, patients may receive RRT without anticoagulation; however, there is increased risk of clotting. When no anti-coagulation is used, methods to avoid clotting include short dialysis sessions (<2 hours), increasing flow rates (stagnant blood clots faster), adding replacement fluids prior to the filter (diluted blood clots less), regional heparinization, and regional citrate. With regional heparinization, heparin is added to the circuit before the filter, while protamine is added to the circuit after the filter to reverse the effects of heparin. This is no longer recommended due to the side effects of protamine (anaphylaxis, hypotension, thrombocytopenia, etc). With regional citrate anticoagulation, citrate is added prior to the filter, while systemic
calcium is simultaneously administered to the patient.

In patients with *heparin-induced thrombocytopenia (HIT)*, heparin is contraindicated and the dialysis system must be heparin-free. Alternatives for anticoagulation include regional citrate anticoagulation, direct thrombin inhibitors (argatroban), and Factor Xa inhibitors (fondaparinux). When systemic anticoagulation is needed, argatroban is recommended. Argatroban is hepatically-metabolized and safe in patients with intact hepatic function. Argatroban has a half-life of 35 minutes and is monitored using activated clotting time (ACT) or activated partial thromboplastin time (aPTT).

**Dosing of Renal Replacement Therapy**

The dose or amount of renal replacement therapy prescribed is equal to the amount of blood “purified” per unit time. This is commonly measured using the clearance of a specific marker molecule (i.e. volume of blood cleared of a substance per unit time) such as urea (BUN) or creatinine. In practice, the effluent (ultrafiltrate and/or spent dialysate) flow rate is used as a surrogate of clearance and is expressed in milliliters per kilogram of body weight per hour (mL/kg/hr). Typical doses of CRRT in AKI are 20-25 mL/kg/hr. Occasionally, higher doses are used (25-30 mL/kg/hr) to account for the decreased efficiency of the filter with increased use and downtime if clotting occurs. Although more intense dosing was initially thought to decrease mortality; it is now generally accepted that doses above 25-30 mL/kg/hr have no additional benefit.

**Vascular Access**

Vascular access is required for RRT. In the ICU, *venous-venous RRT* is most commonly used to treat AKI in either an intermittent (IHD) or continuous (CRRT) fashion. This is performed via a double-lumen (11-14 French) central venous catheter placed percutaneously. The catheter has two ports corresponding to each lumen; the proximal port removes blood from the patient, while the distal port returns blood from the dialysis machine. In order of preference, the catheter is placed in the right internal jugular, femoral, or left internal jugular veins. The subclavian sites are usually avoided because thrombosis or stenosis of the vein could compromise future AV fistula sites if long-term dialysis becomes necessary. When longer duration of RRT is anticipated, a tunneled venous cannula can be placed, which is associated with a lower thrombosis and infection risk.

*Arterio-venous RRT* can be performed intermittently or continuously. With continuous arterio-venous RRT, a central artery and vein are cannulated, with the femoral site being most common. The arterial cannula removes blood from the patient, while blood is returned via the venous cannula. Unlike venous-venous RRT, an extracorporeal pump is not required and blood flow rate is dependent upon the gradient between the mean systemic arterial and venous pressures; thus low blood pressure
decreases flow rate. Continuous arterio-venous RRT has largely been replaced by continuous venous-venous RRT given the higher risk of vascular complications. Intermittent arterio-venous RRT is most commonly performed in the setting of end-stage renal disease via an arterio-venous fistula (AV fistula) or graft (AV graft), which are surgically-created communications between an artery and vein. Unlike an AV fistula, an AV graft contains a synthetic conduit connecting an artery and vein, which is more prone to thrombosis and infection. Intermittent arterio-venous RRT is performed by placing two large bore needles in the conduit or venous portion of the AV graft or fistula, respectively. The needle nearest the artery diverts blood to the dialysis machine, while the other needle returns blood to the patient. AV fistulas and AV grafts are not used for CRRT given concern of needle dislodgement and thrombosis with prolonged dialysis sessions.

**Discontinuation of Renal Replacement Therapy**

Standardized criteria for discontinuation of RRT do not exist; thus, the decision to transition off RRT is based upon some indicator of improvement in intrinsic renal function, which is usually an improvement in urine output. As renal function improves, patients on CRRT are commonly transition to IHD, which serves two roles. First, native kidney function can be assessed by evaluating clearance of BUN and creatinine during interdialytic periods; and second, patients can be “weaned” off RRT by spacing out dialysis sessions as renal function gradually improves.

**Other Considerations**

*Hemodynamic instability* is common to patients admitted to the ICU. When available, CRRT is preferred over IHD because it causes less hemodynamic disturbance; this is related to the more gradual fluid and solute removal. RRT may help to improve hemodynamic stability with the correction of metabolic disturbances.

*Cerebral edema or intracranial hypertension* are other clinical scenarios where CRRT is preferred over IHD for the treatment of AKI. In addition to allowing better control of cerebral perfusion pressure with fewer hemodynamic disturbances, CRRT allows for more gradual changes in serum osmolarity and better control over cerebral edema. *Traumatic brain injury (TBI)* with risk of intracranial bleed is one instance where CRRT should be used with caution. In this scenario, it may be best to use CRRT without anticoagulation.

*Osmotic demyelination syndrome* is a neurologic disorder caused by damage to the myelin sheath of neurons (particularly in the brainstem) from rapid correction of hyponatremia. This can occur with RRT if chronic hyponatremia is corrected too quickly. Adjustment of dialysate or replacement fluids with lower sodium...
concentration as well as frequent monitoring of sodium levels is warranted.

**Acute liver failure** is frequently associated with hyponatremia, cerebral edema, increased intracranial pressure, and acute or chronic kidney disease (hepatorenal syndrome). CRRT is preferred in this setting with special attention given to hemodynamic stability, maintenance of cerebral perfusion pressure, and limiting abrupt changes in serum sodium concentrations.

**Dialysis disequilibrium syndrome** is a neurologic disorder characterized by nausea, headache, and mental status changes that is thought to be secondary to abrupt changes in serum osmolarity resulting in cerebral edema. The mechanism is likely due to rapid serum clearance of urea during dialysis with slower equilibration of intracerebral urea concentration promoting influx of free water. This occurs more frequently with higher baseline BUN levels (> 175 mg/dL). Preventive measures include decreasing the dose of dialysis, slowing treatment time, and initiation of ultrafiltration prior to dialysis.

Both AKI and RRT affect drug clearance. Water-soluble drugs as well as drugs that are not highly protein bound are more readily cleared. The dosing of many medications, particularly antibiotics, will need to be adjusted depending upon the choice of RRT, frequency of RRT, and degree of native renal function. During IHD, it is important to remember that renally-cleared medications may not be cleared until the subsequent hemodialysis session. Common medications cleared by RRT are listed in Table 2.

### Table 7.5.2 Drugs Cleared by RRT

<p>| | |</p>
<table>
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<tr>
<td>Barbiturates</td>
<td>Aminoglycosides</td>
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<tr>
<td>Ethylene glycol</td>
<td>Carbapenems</td>
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<tr>
<td>Lithium</td>
<td>Cephalosporins</td>
</tr>
<tr>
<td>Metformin</td>
<td>Metronidazole</td>
</tr>
<tr>
<td>Methanol</td>
<td>Penicillins</td>
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<tr>
<td>Salicylates</td>
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**Contrast-induced nephropathy (CIN)** is a common concern of ICU patients undergoing radiographic imaging, particularly when there is preexisting renal dysfunction. Hemodialysis can remove contrast media from the bloodstream with a single IHD session removing 60-90% of contrast media. Nonetheless, the prophylactic use of IHD or hemofiltration for the prevention of CIN has not shown benefit over standard volume resuscitation and is not recommended; in fact, it may cause harm.

### Complications

Adverse events of RRT vary in nature, but complications can be classified as those relating to vascular access, the extracorporeal circuit, or the therapy, itself (Table 3).
Table 7.5.3 Complications of RRT

<table>
<thead>
<tr>
<th>Complication</th>
<th>Vascular Access</th>
<th>Use of Anticoagulation</th>
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<tbody>
<tr>
<td>Air emboli</td>
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<td>Altered drug kinetics</td>
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<td>Blood loss</td>
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<td>Electrolyte imbalances</td>
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<tr>
<td>Hemodynamic instability</td>
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<td>Hypothermia</td>
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Catheter-related: Bleeding, Infection, Line disconnection, Pain, Pneumothorax, Thrombosis

Use of anticoagulation: Bleeding, HIT

Review Questions:

1. The following statement 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 in using CRRT versus IHD
   d. CRRT is preferred in patients who have an unstable cardiovascular status

2. The following statements regarding RRT are true, except:
   a. Internal jugular or femoral vein central access is preferred over the subclavian veins for dialysis catheter placement
   b. Water-soluble drugs are more easily removed by RRT than protein-bound drugs

References:

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

3. The following statements comparing hemodialysis with hemofiltration are true, except:

a. Hemofiltration is more effective than hemodialysis at removing water

b. A low-flux membrane is typically used for hemofiltration and a high-flux membrane is typically used for dialysis

c. Hemofiltration is more effective than hemodialysis at removing cytokines, and hemodialysis is more effective at removing small molecules

d. Hemofiltration depends primarily on convection, while hemodialysis depends on diffusion.
Chapter 8

Hematology Topics
INTRODUCTION

Venous thromboembolism (VTE) is 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 900,000 people in the United States are affected.

**Patient Case:**
A 32-year-old woman is admitted to the ICU status post a craniotomy for tumor resection. Three days after admission, she becomes tachycardic and complains of SOB. Her physical exam, CXR, and ABG are unremarkable. Later that day, she develops sudden respiratory distress with mild hypotension and hypoxia. Sequential compression devices have been in use, but SQ heparin had not been started due to her intracranial tumor resection. An EKG shows an S1Q3T3 pattern and a bedside TTE is concerning for right heart strain. She is stabilized with an IV infusion of norepinephrine for hypotension and milrinone for her right heart strain. A helical computed tomography (CT) scan reveals a pulmonary embolus. Risks of treatment options are discussed with her neurosurgeon. It is decided to start a heparin infusion with a PTT goal of 60-80, but without a heparin bolus in the context of her recent intracranial surgery. Over the next 24 hours, her oxygen requirement improves, and the norepinephrine infusion is weaned off as her hemodynamics stabilize.
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. (1-3) Many of the deaths related to PE are preventable as the outcome is not due to a failure of anticoagulation therapies, but is related to a missed diagnosis. (1,2) 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. (1-3)

**EPIDEMIOLOGY**

The exact incidence of venous thromboembolism (VTE) is unknown but studies estimate the number cases in the US each year exceed 900,000. (3) The majority of VTE deaths are caused by pulmonary embolus (PE), but VTEs have significant morbidity as well. Sudden death is the initial clinical presentation of PE in approximately 20% of all cases. Mortality of untreated PE is approximately 30%, but once diagnosed and treated, mortality decreases to 2.5%, illustrating the importance of prompt diagnosis and initiation of treatment. (2)

Taking into account patient risk factors in the context of the clinical presentation can assist in diagnosis. Risk factors for VTE include history of VTE, age greater than 40 years, acute postoperative period, prolonged immobility (recent travel, or condition resulting in becoming sedentary), cerebrovascular accident, congestive heart failure, malignancy, trauma, obesity, pregnancy or recent delivery, estrogen therapy, inflammatory bowel disease, inherited or acquired defects in blood coagulation factors. (2)

**PATHOPHYSIOLOGY**

Certain physiologic conditions allow for supranormal clot formation and have been given the eponym, Virchow’s triad, which includes venous stasis, hypercoagulable state, and vascular endothelial injury. (4) Approximately 50% of patients with a VTE will have more than one risk factor. (2) Venous stasis leads to a decreased oxygen tension in blood flowing through those regions and stimulates coagulation by signaling leukocytes, platelets, and endothelial cells to trigger hypoxia responses. (4) Hypercoagulable states include pregnancy, malignancy, inflammatory bowel disease, and inherited coagulation defects. States such as malignancy and inflammatory bowel disease can lead to the upregulation of tissue factor and other coagulation factors, potentiating clot formation. (4) Trauma, and inflammatory vascular diseases directly disrupt the endothelium and can expose von Willebrand factor, collagen, and tissue factor which adhere to platelets and initiate the coagulation cascade leading to clot formation. (4)

**PROPHYLAXIS**
Due to the high incidence and significant morbidity and mortality of VTE, prophylaxis is recommended for all hospitalized patients. Pharmacologic options for VTE prophylaxis include heparins, vitamin K antagonists, and direct oral anticoagulants. Mechanical options also exist for those unable to tolerate anticoagulation. One advantage of unfractionated heparin or low molecular weight heparin (LMWH) is that laboratory value monitoring is not needed for prophylactic dosing. A recent meta-analysis has shown LMWH to be superior to unfractionated heparin in preventing PE. Complications include bleeding, thrombocytopenia, paradoxical arterial thrombosis, and resistance to heparin (antithrombin III deficiency). Thrombocytopenia due to heparin (heparin-induced thrombocytopenia or HIT) is secondary to an IgG-mediated immune response, which then may lead to arterial thrombosis. Osteoporosis also occurs in approximately 30% of patients treated with long-term unfractionated heparin therapy. Vitamin K antagonist therapy, or warfarin, is also associated with complications including bleeding and skin necrosis due to protein C or S deficiency.

Mechanical options available for VTE prophylaxis include early ambulation, leg elevation, physiotherapy, graduated compression stockings, and intermittent pneumatic compression, or sequential compression devices. If anticoagulation is contraindicated or a patient has a VTE despite adequate anticoagulation, an IVC filter may be placed.

**DIAGNOSIS**

Clinical presentation of VTE and PE can be extremely varied, ranging from asymptomatic to limb pain to severe hypoxia and hemodynamic collapse. For VTE, the most common presentations are limb edema/pain, differential limb circumference, Homan’s sign (calf pain with foot dorsiflexion), distended collateral veins, and fever in the absence of infection. For PE, symptoms include dyspnea, pleuritic chest pain, tachypnea, tachycardia, hypoxemia, hypocarbia, hemoptysis, infiltrate on CXR, or sustained hypotension without an obvious alternative cause. Due to this varied and non-specific presentation, clinical probability assessment is used based on signs, symptoms, and risk factors. Clinical judgment is heavily weighted in most diagnostic algorithms. Clinical probability tools such as the Wells Criteria, Geneva Score and Pulmonary Embolism Severity Index (PESI) help stratify patients based on the probability of PE.

Diagnostic workup for PE is first stratified by whether the patient is hemodynamically stable or unstable, then by degree of clinical suspicion. For patients who are hemodynamically stable and the clinician has a low or intermediate clinical suspicion, it is recommended to start by checking a D-Dimer (usually omitted in hospitalized patients because specificity is reduced in this population). If the D-dimer is normal, PE is ruled out. If the D-Dimer is elevated, CT angiogram (CTA) should be obtained to...
either rule out or confirm the diagnosis. If CTA is not available, the patient has chronic kidney disease, or the patient has an allergy to contrast dye, then ventilation-perfusion scanning is an acceptable alternative. Importantly, if the patient is hemodynamically stable, but the clinician feels there is a high probability of PE, then CTA should be done first without collecting a D-dimer. (1,6)

If the patient is hemodynamically unstable but is safe to transport, CTA should be obtained. Echocardiography is acceptable if CTA is not available. If the patient is unsafe to transport and there is a high clinical probability of PE, transthoracic or transesophageal echocardiography should be obtained to evaluate for right ventricular (RV) dysfunction to either rule out or confirm the diagnosis of PE. RV function is evaluated since only rarely can a thrombus be visualized within the pulmonary arteries or RV. (1,6,7)

There are multiple diagnostic options available. Pulmonary angiography is considered the gold standard but is rarely performed today since it requires expertise to perform and interpret, is invasive, and has associated risks. Therefore, it is usually reserved for patients with chronic thromboembolic pulmonary hypertension. Alternatively, contrast enhanced helical CT scans have a reported sensitivity ranging from 57-100% and specificity ranging from 78-100%. (2) 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. A normal CT scan may indicate a substantially reduced likelihood of embolism but the negative predictive value is lower than with a negative ventilation perfusion (V/Q) scan. (2)

Ventilation perfusion (V/Q) scans previously had a central role in the diagnosis of PE and still can be a valuable tool when CTA is contraindicated and when paired with clinical judgment. A normal scan rules out the diagnosis of embolism with a negative predictive value of 97%, and a high probability V/Q scan result is strongly suggestive of embolism with a positive predictive value of 85 to 90%. (1) Large trials have demonstrated that most patients with suspected PE who undergo a V/Q scan do not have findings that are considered definitive, which limits the use of this test but paired with clinical suspicion, the results of a V/Q scan can be more meaningful. To obtain a V/Q scan, patients must have a normal chest radiograph and normal ventilation patterns. Magnetic Resonance Angiography/Venography (MRA/MRV) has been shown to have insufficient sensitivity and a high rate of technically inadequate images when used for diagnosing PE (PIOPED III) so is not used in many institutions. (8)

Echocardiography is another useful tool in the diagnosis of PE. 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. (8) According to the International Cooperative Pulmonary Embolism
Registry, RV hypokinesis predicted an increased risk of death within 14 days and 3 months in patients with SBP < 90mm Hg. At 14 days after a PE, mortality rates in patients with or without RV hypokinesis were 21% and 11% respectively, and at 3 months were 29% and 16% respectively. (7) The quality of the echocardiogram is dependent on the proceduralist.

Other diagnostic workup includes electrocardiography, chest x-rays, arterial blood gases, D-dimer levels, troponin levels, and BNP levels. (3,8) An electrocardiogram in the setting of PE may show the classic S1Q3T3 pattern, which is a deep S-wave in lead I, Q-wave in lead III, and inverted T-wave in lead III. This S1Q3T3 pattern suggests right heart strain and should prompt consideration for PE work up, but is neither sensitive nor specific for PE and is only seen in a small percentage of patients with a PE. (3) A chest x-ray may show ipsilateral elevation of the diaphragm, wedge-shaped infiltrate, focal oligemia, or an enlarged right descending pulmonary artery but these findings are neither sensitive nor specific. (3)

For laboratory values, obtaining an arterial blood gas may rule out other causes of symptoms or confirm hypoxia, but previous studies have shown that a PE cannot be excluded with a normal alveolar-arterial gradient. (3) D-dimer is an endogenous marker for fibrinolysis. As previously discussed, a D-dimer level is a highly sensitive but nonspecific screening test for suspected VTE. Elevated levels are present in nearly all patients with VTE but can also be elevated with advanced age, pregnancy, trauma, recent surgery, inflammation, or cancer. (2,3) An elevated troponin level is not specific for PE, but in the presence of known PE, an elevated troponin level correlates with worse RV function. A normal troponin level in the setting of PE has a 97-100% negative predictive value for in-hospital mortality. (3) Brain natriuretic Peptide (BNP) is released from cardiac ventricular cells in response to high ventricular filling pressures, and is an indicator of myocardial wall stress and hypoxia. In one series, the negative predictive value of a normal serum BNP level reached 100%. (1,3)

Diagnostic workup of DVT includes contrast venography, impedance plethysmography (IPG), and ultrasonography with color Doppler flow. Contrast venography is the gold standard for the diagnosis of VTE but is invasive and rarely performed for this indication. A noninvasive option is impedance plethysmography (IPG). IPG has an overall sensitivity and specificity of 93% and 95% respectively, but has false positive results with tensing of the leg muscles. (9) Ultrasonography with color Doppler flow (duplex scan) has a sensitivity for DVT of 94% and specificity of 97%. However, duplex scans will not identify deep pelvic DVTs, and cannot distinguish between occlusion from external pressure versus thrombosis. This modality is also less sensitive in identifying asymptomatic, isolated calf vein, and recurrent thrombosis but the predictive value is greater than that of IPG. (9)

TREATMENT
Treatment for VTE centers around anticoagulation, but local measures such as, elevation of extremity and warm compresses, can be used as adjunctive measures.

Anticoagulation therapy should begin before diagnostic studies if a PE is ‘intermediate’ or ‘high probability’ based on clinical criteria. The typical sequence of treatment for inpatients is to first initiate an unfractionated heparin infusion and adjust dose to keep PTT ≥1.5 - 2.0 times control. PTT is checked in 6-8 hour intervals while the infusion is continued to ensure therapeutic dosing. Warfarin is initiated within 24 hours and INR is measured daily until it reaches a therapeutic level. Once warfarin is therapeutic, the heparin infusion is discontinued, and warfarin is continued for at least 3 months with INR monitoring. Another option for anticoagulation is a fixed dose of LMWH administered subcutaneously (SC). LMWH regimens have been proven to be effective treatment for VTE and PE and usually do not require monitoring. (1,5) A third option is initiation of a direct thrombin inhibitor. This treatment is usually reserved for patients with heparin induced thrombocytopenia (HIT) as unfractionated heparin and LMWH both are contraindicated in HIT. Direct thrombin inhibitors can have unpredictable anticoagulation, require intensive lab monitoring, and have potential drug-drug interactions. (10)

Insertion of an inferior vena cava (IVC) filter is reserved for patients who have contraindications to anticoagulant therapy or an inability to be adequately anticoagulated. This is associated with higher long term incidence of DVT but lower risk of PE. Use of retrievable IVC filters should be considered and they should be removed as soon as possible to avoid endothelialization. (1)

For patients with evidence of RV impairment or are deteriorating despite aggressive medical therapy, thrombolytic therapy may be considered. Available agents include streptokinase, urokinase, and alteplase. If thrombolysis is contraindicated, a pulmonary embolectomy can be performed. Catheter-directed thrombolysis is emerging as another therapeutic alternative which may be associated with lower risk compared to systemic thrombolytic therapy or pulmonary embolectomy.

CONCLUSIONS and RECOMMENDATIONS

VTE can be difficult to diagnose due to its varied clinical presentation. Stable critically ill patients with suspected PE should receive a CTA as a diagnostic intervention, unless contraindicated. If a patient is unstable, urgent echocardiography should be considered to rule out right ventricular strain. If clinical suspicion is high, empiric anticoagulation should be initiated while the diagnostic workup is completed. Thrombolytic therapy should be considered in patients with PE and hemodynamic deterioration. Pulmonary embolectomy is reserved for unstable patients in whom thrombolysis is contraindicated.

References:


**Review Questions:**

1. A 76 year-old man is 5 days post intracranial hemorrhage and develops dyspnea and pleuritic chest pain. Vitals: T=38.6 C, BP=82/48 mmHg, P=125 bpm. CXR and ECG are unrevealing. ABG on RA shows: pH=7.48, PaCO$_2$ = 32, PaO$_2$ = 72. Which of the following is the most appropriate next step in his care?

   a. IV heparin and no further diagnostic testing

   b. IV heparin followed by thrombectomy

   c. Echocardiogram followed by possible embolectomy

   d. CTA followed by IV heparin
2. A 58-year-old woman with renal failure develops acute dyspnea 7 days after hip replacement surgery. She has a 90 pack-year smoking history and has received heparin 5000U 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 V/Q scan, then anticoagulate if scan is high probability

c. Anticoagulate with IV heparin, then start warfarin in 5 to 7 days

d. Obtain a CTA, then anticoagulate if PE is present

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. CTA is considered the gold standard for diagnostic testing of PE

c. Hormone replacement therapy in postmenopausal women is a risk factor for venous thromboembolism

d. Patients with clinically significant PE have characteristic manifestations that suggest its presence.
Coagulopathies in the ICU  Nicholas Pesa MD, John C 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.

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 (see Chapter 8.1) and transfusion (see Chapter 8.3) are discussed separately in this manual.

Patient Case:
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 placement of an intra-aortic balloon pump. 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 PRBCs 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.
I. Physiology of Coagulation

As Figure 1 demonstrates, coagulation is a complex interplay of multiple variables, initially triggered by tissue injury. 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.

I. 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.

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.

5. Pregnancy

Pregnancy can result in a pathological state of HELLP (hemolysis, elevated liver enzymes, low platelets) that can cause spontaneous hepatic hemorrhage and even maternal death.

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).

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, thrombotic thrombocytopenic purpura/ hemolytic uremic syndrome (TTP/HUS), nephrotic syndrome, and antiphospholipid antibody syndrome are other important hypercoagulable states.

II. 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, recombinant factor VII 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 hypercoagulability.

IV. Antithrombotic Agents

A. Unfractionated Heparin (UFH)

UFH forms a complex with antithrombin causing inhibition of factor II (prothrombin) 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 a smaller molecule produced from UFH 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 the intravenous DTIs. 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. Idarucizumab is a monoclonal antibody designed for the reversal of the anticoagulant effects of dabigatran.

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. Direct Factor Xa Inhibitors

Direct factor Xa (fXa) inhibitors prevent factor Xa from cleaving prothrombin to thrombin. They bind directly to factor Xa. Several oral agents are available, including rivaroxaban, apixaban, and edoxaban. Routine monitoring of coagulation times is not necessary with these agents. In the event of life-threatening hemorrhage, hemodialysis is unlikely to be effective because fXa inhibitors have a high degree of protein binding. Activated charcoal may be useful, but there is no clinical data to support this. Only PCCs and antifibrinolytic agents may be of use to reverse the effects of the drug. Specific reversal agents (andexanet alfa) are being developed, but no FDA approved reversal agents is currently available for the direct factor Xa inhibitors.

V. Antiplatelet Agents

A. 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.

B. Glycoprotein IIb/IIIa Inhibitors

The GPIIb/IIIa inhibitors 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.

C. Platelet ADP Receptor Antagonists

Clopidogrel, ticlopidine, prasugrel and ticagrelor 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.

Ticlopidine 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.

Ticagrelor is a reversible oral direct-acting inhibitor of the ADP P2Y12 receptor with more rapid onset and increased platelet inhibition compared to clopidogrel.

D. 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.

VI. 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](http://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 fibrinolysis. They are used extensively in cardiac surgery with the use of cardiopulmonary bypass.

C. Desmopressin (DDAVP)

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.

E. Prothrombin Complex Concentrates (PCC)

PCCs are formulations containing varying amounts of coagulation factors (factor II, VII, IX, and X) as well as one or more types of anticoagulant (protein C or S). Most of the factors are administered in the inactive state, which is supposed to decrease the thrombogenic risks. PCCs are now the drug of choice for emergent reversal of oral anticoagulants in place of rFVIIa or FFP.

References:

1. Villalba MR, Schreiber MA: Coagulopathies, Thrombotic Disorders, and Blood Component Therapy, Comprehensive Critical Care: Adult. Edited by Roberts PR, Todd SR. 2012, pp 551-569


2002; 4:465–473


Review Questions:

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

2. A 24 year-old man is shot in the abdomen multiple times. He arrives at your hospital's trauma bay with a palpable but faint pulse and multiple entry/exit wounds in his abdomen. Ten units of non-cross matched PRBC are available and given in the ED. In the OR, he is noted to have injuries to his aorta, superior mesenteric artery, right kidney, and spleen. What additional blood component administration, in addition to surgical control, is appropriate to best achieve hemostasis?
   a. FFP administration based on labs such as PT or INR
   b. PRBC:FFP:platelets in a maintained 1:1:1 ratio throughout resuscitation
   c. Single-dose factor Vlla
   d. FFP to be transfused only once surgical hemostasis is achieved
3. A patient with urosepsis is admitted and treated in the ICU. On HD 4, his BP is stable, and he is being weaned from vasopressors. His hemoglobin is 8.5 g/dL, platelets are 36 x 10⁹/L, PT is 19 seconds, and PTT is 41 seconds. Which of the following blood products should be transfused at this time?

a. Fresh frozen plasma
b. No blood products
c. Red blood cells only
d. Platelets only
Overview

Allogeneic blood product administration is a common procedure in the intensive care unit. Donor-derived blood products frequently transfused include packed red blood cells (pRBC), fresh frozen plasma (FFP), cryoprecipitate, and platelet suspensions. Current practice entails separation of donor whole blood into each of these components to allow for targeted use of this limited resource to correct the specific blood component deficiency in the individual patient. Generally speaking, there are three primary indications for blood component therapy:

1. Insufficient oxygen carrying capacity/delivery thought to be at least partially due to inadequate total red blood cell mass.

2. Replacement of coagulation cascade constituents to correct severe coagulopathy, and inadequate quantity and/or dysfunction of platelets.

Patient Case:
A 56-year old man with atrial fibrillation on warfarin therapy is admitted with melena. He has received 2 L of crystalloid, and is hemodynamically stable. Most recent laboratory results include a hemoglobin concentration of 5.6 g/dL, platelet count of 125 x 10^9/L, INR of 4.2, partial thromboplastin time of 38 seconds, and fibrinogen concentration of 165 mg/dL.
coagulopathy.

3. Inadequate quantity and/or dysfunction of platelets

The aim of this chapter is to discuss the indications for each of the commonly transfused blood components as well as other considerations including storage, safety, and complications of transfusion.

Specific Blood Components

Whole Blood

Unfractionated whole blood is, as its name implies, equivalent to circulating blood: erythrocytes, leukocytes, plasma (including clotting factors), and platelets are present in their normal ratios. Whole blood has a shorter storage life and higher risk of donor-recipient interactions, and has largely been phased out in favor of targeted blood component therapies. Its use in trauma and acute bleeding, to replace shed whole blood, is a subject of renewed interest.

Packed Red Blood Cells

PRBCs are the most common blood component therapy transfused. A typical unit of pRBCs consists of 200-250 mL of centrifuged erythrocytes (hematocrit of approximately 60-70%) suspended in an anticoagulant storage solution. Most centers in the United States routinely filter leukocytes from donated blood (leukoreduction) to reduce the risk of febrile non-hemolytic transfusion reactions and alloimmunization. Units of cytomegalovirus-negative or irradiated pRBCs may be indicated for certain immunocompromised patients. Transfusion of a single unit of pRBCs is classically expected to increase the concentration of hemoglobin by 1 g/dL in the absence of ongoing blood loss.

The only indication for transfusion of pRBCs is to increase the oxygen carrying capacity of blood, which may be impaired due to anemia of insufficient production, excessive erythrocyte consumption, or replacement of shed blood with non-oxygen carrying solutions leading to a dilutional anemia. The threshold at which anemia necessitates transfusion has been examined in several large, prospective, randomized, controlled trials. They have shown, nearly universally, that there is no benefit, and may be harm, from transfusion thresholds above 7-8 g/dL. Possible exceptions are patients with ongoing blood loss (see later) or active ischemia, although prospective studies in high-risk populations such as post-cardiac surgical and active, non-exsanguinating upper gastrointestinal bleeding patients have generally supported restrictive erythrocyte transfusions. Ultimately, all pRBC transfusions should be individualized to the patient and situation at hand.

Fresh Frozen Plasma

FFP, the supernatant of centrifuged whole blood, contains all of
the acellular components of whole blood. These include all endogenous pro- and anti-coagulant factors, fibrinogen, albumin, and immunoglobulins. Each unit is usually 250-350 mL in volume and can be stored frozen for up to a year.

The primary indication for transfusion of FFP is correction of coagulopathy associated with deficiency of multiple clotting factors. This may occur in the setting of blood loss due to a combination of consumption and/or dilution of clotting factors by replacement fluids, acute or chronic organ failure with deficient production, unregulated consumption (sepsis, disseminated intravascular coagulation, medications, etc.), or genetic deficiencies in factor production (hemophilia, von Willibrand disease, etc.). While FFP contains all proteins necessary to correct the above deficiencies, their relatively low concentrations make correction of specific factor deficiencies inefficient from a volume perspective. In these cases, primarily genetic deficiencies, it is usually preferable to replace only the needed factors with human-derived or recombinant factor concentrates. Factors II, VII, VIII, IX, and X as well as von Willibrand factor and proteins C and S are available as concentrates. They are expensive and carry the risk of pro-thrombotic sequelae, so the risks and benefits must be weighed before their use.

Transfusion of FFP has not been studied as extensively as that of pRBCs, and much of the usage falls outside of the realm of high-quality evidence-based medicine. In clinical practice, the administration of FFP is most often driven by prolongation of bleeding tests to greater than 1.5 times the upper limit of normal: these may include PT/INR, PTT, or the initial clot formation times of functional tests such as thromboelastography or thromboelastometry. FFP is also frequently administered as part of a massive transfusion protocol (see below).

Cryoprecipitate

When frozen plasma is slowly thawed, a semi-solid precipitate is formed, called cryoprecipitate (cryo). Each unit of FFP produces about 10-20 mL of cryo, which contains concentrated quantities of fibrinogen, factor VIII, factor XIII, von Willibrand factor, and fibronectin. Cryo is typically transfused as pooled units. Previously referred to as “cryoprecipitated antihemophilic factor” for its use in hemophilia A and von Willibrand disease, in the modern era, the primary indication for the use of cryo is hypofibrinoginemia, as purified factor concentrates have largely replaced its use in genetic single-factor deficiencies. The development of fibrinogen concentrate could potentially reduce the use of cryo for this indication. Fibrinogen concentrates are available in a lyophilized form which can quickly be reconstituted. Fibrinogen concentrates are currently only available as a human-derived, heat-treated preparation and the relative advantages and disadvantages of cryo versus fibrinogen concentrate are currently under investigation.

Platelets
Traditionally obtained by separation from donated whole blood and transfused as pooled units (a “six-pack”), single-donor units of platelets obtained by apheresis have become more common. Both types contain a similar quantity of platelets, and classically increase the platelet count by approximately \(50 \times 10^9/L\). Unique among blood products, platelets are stored at room temperature to prevent denaturation of proteins, and this limits their storage life to 5 days. The storage requirements may also be responsible for the higher incidence of bacterial contamination.

The indications for platelet transfusion vary by clinical circumstance to a greater degree than other blood products, but have also not been examined in high-quality randomized clinical trials. Spontaneous hemorrhage may occur with severe thrombocytopenia (less than \(5-10 \times 10^9/L\)). In the setting of current, recent, or anticipated bleeding, higher levels are generally indicated: \(50 \times 10^9/L\) is a broadly-accepted lower limit, although clinical practices vary tremendously and higher levels are frequently achieved prophylactically prior to invasive procedures. Platelet dysfunction is a second indication for transfusion, and may occur in many clinical settings including the recent use of antiplatelet agents, uremia, renal or liver disease, and following cardiopulmonary bypass. This can be evaluated using platelet function assays, but often transfusions are given empirically when faced with bleeding in a patient at risk for platelet dysfunction.

Safety

Although the majority of blood product transfusions are well tolerated, blood component therapy exposes the patient to risk of both acute and long-term complications. Recognition of such complications has led to wider acceptance of more restrictive transfusion approaches as described above.

Donor Screening and Testing of Donated Blood

Prospective donors are screened to determine if they are in good health and to identify known risk factors for transmissible diseases. Donated blood then goes through testing to determine the blood type (ABO group) and Rh status (positive or negative). These results predict which major plasma antibodies are present in the donor blood (Table 1). Additionally, donor blood is screened against a panel of well-known antibodies to further establish an appropriate cross-match. Risk of disease transmission is reduced by routine laboratory testing including bacterial culture and detection of hepatitis B, hepatitis C, human immunodeficiency virus (HIV), human T-lymphotropic virus (HTLV), \(T. pallidum\), West Nile virus (WNV), and more recently, Zika virus. Testing for other specific pathogens can be done on an as-needed basis for special populations.

Transfusion Reactions

These can occur in up to 1% of transfusions. Fortunately, fatal reactions are exceedingly rare. General management of transfusion reactions includes careful documentation of the
nature of the reaction including symptoms and vital sign abnormalities. The transfusion should be stopped and supportive care started to ensure respiratory and circulatory stability. The blood product label and patient identification should be rechecked to ensure the correct product was given to the correct patient. In case of reactions causing more than minor discomfort or cutaneous symptoms, a new patient blood sample and the partially transfused product should be returned to the blood bank for further analysis. Some important transfusion reactions to be aware of include the following:

1. **Allergic** (100/100,000 units) / **anaphylactic** (8/100,000) transfusion reactions: Usually occur within 4 hours of transfusion, most often related to platelet transfusion (300 per 100,000 platelet units). Often mediated by histamine release. Most are mild and limited to rash, pruritis, hives which can be managed with antihistamines. Often the transfusion can resume under close supervision. Severe cases can progress to respiratory distress and hypotension.

2. **Acute hemolytic transfusion reactions** (2.5-8/100,000): Most often due to failure of patient identification at either specimen collection or transfusion. Immune-mediated hemolysis results in rapid destruction of donor RBCs related to ABO incompatibility that can occur at the time of transfusion or up to 24 hours after. Symptoms include fever, pain, hypotension, dyspnea, and hemoglobinuria. These reactions can result in kidney failure, disseminated intravascular coagulation (DIC), shock and death.

3. **Delayed hemolytic transfusion reaction** (40/100,000): Increasing titers of recipient antibodies to donor antigens develop between 1-28 days after a transfusion, often due to an amnestic immune response. Symptoms include dark urine or jaundice, fever, pain, hypertension, and progressive anemia due to ongoing hemolysis. Development of new antibodies against donor erythrocytes without hemolysis is termed delayed serologic transfusion reaction.

4. **Febrile non-hemolytic transfusion reactions** (1000-3000/100,000): This is the most common reported transfusion reaction and is caused by pro-inflammatory cytokines or recipient antibodies encountering donor antigen.
Patients develop fever and/or chills in the absence of hemolysis within four hours of transfusion. These reactions are generally mild and respond well to conservative treatment. This is a diagnosis of exclusion; patients should be closely monitored to rule out hemolysis or infection.

5. **Septic transfusion reaction (0.03-3.3/100,000)**: Onset usually within 4 hours of transfusion. Bacterial contamination of platelets is most common due to room temperature storage. Symptoms include fever, rigors, and hypotension. Definitive diagnosis requires culture of same pathogen from blood product and patient.

6. **Transfusion related infection**: 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 risk has been achieved by improvements in awareness and employment of efficient nucleic acid screening technology. 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.

7. **Transfusion associated circulatory overload (TACO) (11/100,000)**: As the name implies, TACO is hypervolemia resulting from the volume of transfused blood product. There is no consensus for diagnostic criteria, but symptoms can include respiratory distress, elevated brain natriuretic peptide (BNP), increased CVP, left heart failure, positive fluid balance, and pulmonary edema developing within 6 hours of transfusion. TACO can be related to a high infusion rate as well as large overall volume given. Patient risk factors include older age, renal dysfunction, heart failure, and pre-existing fluid overload. Management is with respiratory support as needed and diuresis.

8. **Transfusion-related acute lung injury (TRALI) (0.4-1/100,000, varies by component)**: This is a rare but serious reaction leading to alveolar congestion and hypoxemia that is not related to other potential causes such as volume overload, pneumonia, trauma, or heart failure. TRALI is currently the leading cause of transfusion-related death in the United States. TRALI can occur with even relatively small volume transfusions. The mechanism is thought to be mediated by recipient immune response to donor antigens. It is commonly associated with FFP (1:5000 units), but can also occur with platelets or whole blood. The incidence of TRALI has decreased somewhat with the avoidance of multiparous female plasma donors. Although mortality is estimated at 5%, most patients recover within 2-4 days with supportive therapy.

**Procedure for 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.
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.

Massive Transfusion

The loss of large volumes of whole blood requires a different
approach from the targeted therapy typically preferred. An
exsanguinating patient requires replacement of both the oxygen-
carrying and coagulant components of blood to maintain oxygen
delivery and achieve hemostasis. Definitions of massive
transfusion vary, but examples include: a blood loss rate >150
mL/min, transfusion of 50% of a patient’s total blood volume over
3 hours, or more than 10 units of pRBC transfused over 24 hours.
Historically, massive transfusions involved administration of whole
blood to replace lost whole blood, an approach which has
garnered renewed interest recently. Best studied in the trauma
population, current recommendations are to essentially
reconstitute whole blood with transfusion of products at a ratio of
red blood cells, plasma, and platelets of 1:1:1 (due to pooling of
platelets this is generally applied as 1 unit of pooled or apheresis
platelets for every 6 units of pRBCs and FFP) until control of
hemorrhage is achieved, at which time targeted blood therapies
should resume. Administration of crystalloid or colloid solutions
can continue simultaneously, but the advantages of rapid volume
expansion must be weighed against the risk of dilutional anemia
and coagulopathy. In circumstances where massive transfusion is
not anticipated but develops gradually with repeated erythrocyte
administration, empiric 1:1:1 transfusion should be considered
after approximately 4-6 units of pRBCs due to the high likelihood
of dilutional coagulopathy. Fibrinogen replacement is also
frequently indicated in these circumstances, and either evaluation
for or empiric treatment of hypofibrinogenemia should be
considered. Further risks related to massive transfusion include
citrate toxicity and associated hypocalcemia, hyperkalemia, and
hypothermia. It cannot be overemphasized that administration of
any blood product should be individualized to the patient and
circumstance at hand, and be given the same consideration as
any other risk-bearing therapy.

Summary

Allogeneic blood product transfusion is a very common
procedure in critically ill patients. Classically thought to be a
relatively simple decision, contemporary practice regarding when
to transfuse reflects increasing awareness of potential
drawbacks, including transfusion reactions, infectious risks, and
potential longer term sequelae such as immune modulation and
adverse long-term outcomes. This coupled with limited blood
product supplies has led to a growing culture of blood
conservation. The above discussion aims to provide a basic outline of the considerations regarding this complex clinical decision.

This chapter is a revision of the prior chapter authored by Michael C Grant MD and Steven M Frank MD.

References:


Review Questions:

1. A 56-year old man with atrial fibrillation on warfarin therapy is admitted with melena. He has received 2 L of crystalloid, and is hemodynamically stable. Most recent laboratory results include a hemoglobin concentration of 5.6 g/dL, platelet count of 125 x10⁹/L, international normalized ratio (INR) of 3.2, activated
partial thromboplastin time (aPTT) of 38 seconds, and fibrinogen concentration of 165 mg/dL. What is the primary indication for transfusion of pRBC to this patient?

a. Lower gastrointestinal bleed
b. Hypovolemic shock
c. History of cardiac disease (atrial fibrillation)
d. Severe anemia

2. Which blood component is best able to correct this patient’s coagulopathy?

a. Whole blood
b. FFP
c. Platelets
d. Cryoprecipitate

3. If the patient is found to be ABO type A-positive, which blood components are NOT acceptable for transfusion, if further transfusion is indicated?

a. Type O-negative whole blood
b. AB-negative pRBCs
c. AB-positive FFP
d. O-positive platelets

4. After transfusion of 4 total units of appropriately selected blood components, the patient develops dyspnea, hypoxemia, and bilateral pulmonary infiltrates. He is urgently intubated. Which of the following is the most likely diagnosis?

a. Acute hemolytic transfusion reaction
b. Delayed serologic transfusion reaction
c. Septic transfusion reactions
d. Transfusion-associated lung injury
Chapter 9

Infectious Disease Topics
**Introduction**

Sepsis can be defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, while septic shock is a subset of sepsis in which profound circulatory, cellular and metabolic abnormalities are associated.

**Patient Case:**
A 46-year-old male is admitted to the intensive care unit with fever, altered mental status, tachycardia, and hypotension. A family member at the bedside states that his only medical history is insulin dependent diabetes for which he rarely checks his blood sugars and frequently forgets to take his insulin as directed. In addition to hypotension and tachycardia, you note a small wound on the plantar surface of his foot with erythema spreading up the leg. A CBC shows leukocytosis and a mild normocytic anemia and additional blood work shows a serum lactate of 6.0 mmol/L. Blood and urine cultures are sent prior to administration of broad-spectrum antibiotics. After administration of 30ml/kg of lactated ringers, he remains hypotensive and has minimal urine output. The decision is made to place an arterial catheter and central line for infusion of norepinephrine. Over the next 24 hours, the patient’s blood pressure improves and blood cultures return with a growth of S. Aureus and the antibiotics are narrowed according to susceptibilities.
with a greater risk of mortality than with sepsis alone. These terms have recently been redefined based on current understanding of sepsis-induced changes in organ function, morphology, cell biology, biochemistry, immunology, and circulation. The previous definition that relied on two or more SIRS criteria along with the presence of infection did not fully identify the complexity of organ dysfunction that exists with sepsis.

Sepsis and septic shock remain one of the leading causes of mortality and critical illness worldwide. It is estimated that it accounts for more than $20 billion (5.2%) of total US hospital costs in 2011, and the incidence is increasing with aging populations with more comorbidities.

The European Society of Intensive Care Medicine and the Society of Critical Care Medicine have helped redefine sepsis and clarify guidelines for treatment that are also endorsed by the Surviving Sepsis Campaign. They provided and rated statements on management and resuscitation of patients in sepsis or septic shock as “strong”, “weak”, or “best-practice”. All of these are outlined in this chapter.

**Diagnosis and Initial Resuscitation, Antimicrobials**

Traditionally, the SIRS criteria along with an identified or suspected infection have been used to diagnose sepsis. More recently the SIRS criteria which include changes in white blood cell count, temperature, respiratory rate, and heart rate, were thought to be less helpful in indicating a severely dysregulated, life-threatening response. They are nonspecific criteria that may help aid in the general diagnosis of infections but more is needed to assess severity. It is recommended that patients suspected of having sepsis have blood cultures drawn before initiation of antibiotics if clinically appropriate and possible, along with imaging studies to help confirm a potential source of infection. Additionally, organ dysfunction can be identified by using the Sequential Organ Failure Assessment Score (SOFA). This score takes into account abnormality by organ system along with specific lab values: PaO$_2$, platelet count, bilirubin level and creatinine level. (Table 1). In healthy patients the baseline SOFA score is assumed to be zero and a score of 2 or more has been shown to be associated with increased mortality. A quick bedside assessment qSOFA (for quick SOFA) can also be used for non-ICU patients. qSOFA takes into account tachypnea, hypotension (SBP<100) and altered mentation, and if abnormal these should prompt further investigations for organ dysfunction and potentially closer monitoring. (Table 2)

Patients meeting the sepsis criteria and demonstrating signs of acute organ dysfunction need to be resuscitated and treated with antibiotics promptly. The Surviving Sepsis Campaign recently released 2016 guidelines for the management of sepsis and septic shock. These guidelines take into account the recent evidence of three trials (Process, ARISE, PRoMIS) that
Table 9.1.1: SOFA Score

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<td>3.4-4.9</td>
</tr>
<tr>
<td></td>
<td>Urine output (ml/day)</td>
<td></td>
<td></td>
<td></td>
<td>500ml/day</td>
</tr>
<tr>
<td>Liver</td>
<td>Bilirubin (mg/dL)</td>
<td>&lt;1.2</td>
<td>1.2-1.9</td>
<td>2.0-5.9</td>
<td>6.0-11.9</td>
</tr>
<tr>
<td>Coagulation</td>
<td>Platelets count x10^9/L</td>
<td>&gt;150</td>
<td>&lt;150</td>
<td>&lt;100</td>
<td>&lt;50</td>
</tr>
</tbody>
</table>

compared traditional early goal-directed therapy (EGDT) with a less aggressive management approach. Based on these studies, placement of a central line (CVC) to monitor central venous pressure (CVP) and central venous oxygen saturation (SVO₂) in all patients with sepsis did not demonstrate a mortality benefit.

Table 9.1.2: qSOFA Score

<table>
<thead>
<tr>
<th>Criteria</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory Rate &gt;22 /min</td>
<td></td>
</tr>
<tr>
<td>Altered Mentation</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure &lt;100mmHg</td>
<td></td>
</tr>
</tbody>
</table>

Summary of Recommended Initial Resuscitation:

a. For sepsis induced hypoperfusion, at least 30 ml/kg of IV crystalloid fluid should be given within the first 3 hours.

b. Additional fluids should be guided by frequent reassessment of hemodynamic status with dynamic variables (versus static measurements) used to predict fluid responsiveness.

c. Application of vasopressors for hypotension unresponsive to initial fluid resuscitation, to maintain mean arterial pressure (MAP) ≥ 65 mmHg.

d. Use lactate as a guide to resuscitation.

e. Blood cultures prior to administration of antibiotics.

f. Administration of broad-spectrum antibiotics.

These goals are simply guidelines and individual patient histories must be taken into account, as well. For example, patients with long-standing hypertension may require a MAP goal > 65 mmHg to maintain adequate end organ perfusion.

Once the diagnosis of sepsis has been made or is strongly suspected, a search for the source must be further pursued. This should include cultures (blood, respiratory, urine if appropriate) imaging studies and specific lab values such as 1,3 beta-D-glucan if an invasive fungal infection is suspected. Blood cultures should be drawn from peripheral IVs as well as any central access.
sites, especially if they were placed > 48 hours prior to diagnosis. Most importantly, antimicrobial therapy should be initiated promptly and not be delayed for culture collection if it is expected to take > 45 minutes. Ideally, the goal is to administer antibiotics within 1 hour of recognition of the signs of sepsis.

Some of the most frequently encountered pathogens in sepsis are listed in Table 3, along with the first-line antimicrobials for treatment. However, these are often variable in each community and it’s important to be familiar with your own unit’s antimicrobial profile.

Equally as important as initiating broad spectrum antibiotics with suspected sepsis, is the daily re-evaluation and potential de-escalation of antibiotics once susceptibilities are known. In general, a total of 7-10 days of targeted treatment is sufficient to treat most infections. However, immunocompromised patients may require further treatment.

Finally, source control should not be overlooked as a definitive treatment. Once a specific source is identified, intervention to remove that source should occur as soon as possible.

**Support of Failing Circulation in Septic Shock**

Crystalloid is the recommended resuscitation fluid but albumin can be considered in patients requiring large amounts of crystalloid. In patients presenting with hypotension, an initial crystalloid challenge of 30ml/kg should be given, and a repeat

<table>
<thead>
<tr>
<th>Source</th>
<th>Likely Pathogen</th>
<th>First Line Empiric Therapy</th>
<th>Alternate Empiric Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Abdominal</strong></td>
<td>GNRs Enterobacter Enterococci Bacteroides</td>
<td>Piperacillin-Tazobactam Ertapenem</td>
<td>Combo Fluoroquinolone plus Metronidazole Tigecycline</td>
</tr>
<tr>
<td></td>
<td>Severe, life-threatening peritonitis</td>
<td>Imipenem Meropenem Doripenem</td>
<td>Combo Ampicillin plus Metronidazole plus Fluoroquinolone or Aminoglycoside</td>
</tr>
<tr>
<td><strong>Kidney/Bladder</strong></td>
<td>Enterococci Enterobacter Pseudomonas</td>
<td>Piperacillin-Tazobactam Combo Ampicillin plus Gentamycin</td>
<td>Fluoroquinolone Cefepime</td>
</tr>
<tr>
<td><strong>Lung</strong></td>
<td>S. Pneumoniae H. Influenzae GNRs</td>
<td>Fluoroquinolone</td>
<td>Combo Ceftriaxone plus Azithromycin</td>
</tr>
<tr>
<td></td>
<td>If recent viral influenza, cover S. Aureus</td>
<td>Combo Vancomycin plus Fluoroquinolone</td>
<td>Combo Linezolid plus Fluoroquinolone</td>
</tr>
<tr>
<td></td>
<td>If Pseudomonas suspected</td>
<td>Combo Piperacillin-Tazobactam + Fluoroquinolone</td>
<td>Combo Aztreonam plus Fluoroquinolone Combo Aztreonam plus Aminoglycoside plus Azithromycin</td>
</tr>
<tr>
<td><strong>Central Line</strong></td>
<td>S. Epidermidis S. Aureus</td>
<td>Vancomycin</td>
<td>Daptomycin if no response to Vancomycin</td>
</tr>
<tr>
<td><strong>VAP</strong></td>
<td></td>
<td>Imipenem Meropenem</td>
<td></td>
</tr>
</tbody>
</table>
bolus may be administered when patients demonstrate hemodynamic improvement with the fluid administration. Although the use of albumin has not been shown to be superior in the resuscitation of septic shock, in patients who present with severe septic shock, the use of albumin may be beneficial. (8) On the other hand, the use of starch-based colloids is not recommended in sepsis due to the increased incidence of renal failure. (9)

After adequate fluid resuscitation, if a patient remains hypotensive, vasopressors should be added to maintain adequate blood pressure. For septic shock, the recommended initial treatment remains norepinephrine. Studies comparing low dose vasopressin and dopamine as first line agents compared to norepinephrine did not show a mortality benefit but they may be considered in refractory septic shock or as second line agents. Placement of an arterial catheter may aid in more accurate administration and titration of these agents.

Phenylephrine is not routinely recommended in the treatment of septic shock except in the circumstance where norepinephrine may be associated with serious arrhythmias, or cardiac output is known to be high and the blood pressure remains low.

In patients who continue to demonstrate tissue hypoperfusion or decreased cardiac output after appropriate volume resuscitation and the addition of vasopressors, the possibility of cardiac dysfunction must be considered. Up to 20% of patients with sepsis develop septic cardiomyopathy. Cardiac ultrasound may help aid in making this diagnosis. Invasive monitoring may also help demonstrate increased cardiac filling pressures and decreased cardiac output (i.e. cardiogenic shock). In these cases, inotropic agents such as dobutamine or epinephrine may be helpful.

Finally, in patients who have not responded to fluid resuscitation and vasopressor therapy, steroid administration may be considered. Although the data on steroid administration in sepsis has varied and failed to prove a true mortality benefit, a short course of intravenous steroids should be considered the next line of treatment as it may aid in the reversal of shock.

**Adjunct Therapies in Sepsis**

Patients with sepsis often have failure of other organ systems. Patients with respiratory failure will frequently require mechanical ventilation. In patients meeting the Berlin definition of acute respiratory distress syndrome, a lung-protective ventilation strategy should be employed.

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. Additionally, erythropoietin does not have a role nor does FFP to correct lab abnormalities in the absence of bleeding or planned procedures. Platelet counts often fall in the septic patient. In the absence of
bleeding, platelet counts of $\geq 20 \times 10^9$/L are accepted in patients without significant risk factors for bleeding. Platelet counts $\geq 50 \times 10^9$/L are suggested for active bleeding, surgery, or if invasive procedures are planned. Additionally, platelets are suggested prophylactically when counts drop to $\leq 10 \times 10^9$/L even in the absence of bleeding.

Sedation and analgesia should target specific titration endpoints. Neuromuscular blocking agents should be withheld in patients without ARDS. If they must be used, train-of-four monitoring should be used and should not be used for a prolonged period.

In those with kidney injury, renal replacement therapies are often required. Continuous and intermittent hemodialysis are equivalent, but continuous therapy is often tolerated better from a hemodynamic standpoint.

Blood glucose is often elevated in response to the systemic inflammation of sepsis. Blood glucose should be treated to maintain blood glucose $< 180$ mg/dL. Hypoglycemia should be avoided and aggressively treated when present.

Patients with sepsis or septic shock who have risk factors should receive stress-ulcer prophylaxis with either an H2-blocker or proton pump inhibitor.

Many clinicians use bicarbonate therapy to correct the acidemia from lactic acidosis despite a lack of evidence-based medicine to support this practice. The surviving sepsis guidelines recommend not using sodium bicarbonate for the purpose of improving hemodynamics or reducing vasopressor requirements with a pH $\geq 7.15$.

Patients should receive daily pharmacoprophylaxis for venous thromboembolism or a combination of pharmacoprophylaxis plus compression devices unless there is an absolute contraindication to these such as active bleeding or acute DVT.

Current nutrition recommendations suggest that enteral nutrition should be initiated within 24-48 hours following the onset of critical illness, and advanced to a goal of full nutritional support within one week. It is also recommended that steps be taken to reduce the risk of aspiration and improve tolerance to gastric feeding by elevating the head of the bed and the use of prokinetic agents if needed.

**Summary**

Sepsis is associated with high morbidity and mortality in critically ill patients and is a continuum of disease caused by an infection that can affect multiple systems resulting in organ dysfunction. There is still much to be learned about sepsis and it remains a topic of ongoing debate in terms of optimal treatment. As for now, the updated definitions and guidelines presented in this chapter provide some consensus from which to direct care.

*This chapter is a revision of the prior chapter authored by Judson Mehl DO and Deborah Rohner MD.*
References:

2. Surviving Sepsis Campaign Guidelines: [http://www.survivingsepsis.org/guidelines/Pages/default.aspx](http://www.survivingsepsis.org/guidelines/Pages/default.aspx)


Review Questions:

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

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

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

4. Which of the following accurately describe the elements of the qSOFA score:

a. WBC > 10 x 10⁹/L, tachycardia, tachypnea

b. Urine output of 0.5 ml/kg/hr, tachycardia, fever

c. Hypotension, tachypnea, altered mental status

d. Mean arterial pressure < 65 mmHg, fever, tachycardia
Initial evaluation and management of sepsis (1,2)

The Surviving Sepsis Campaign recommends the following for identifying, controlling and treating infections: measure lactate level, obtain blood cultures prior to antimicrobial administration, administer broad spectrum antimicrobials, and source control.

1. Obtaining cultures

Draw blood and other cultures (e.g., respiratory, urine, cerebral spinal fluid, wound, body fluids) before administering antimicrobials because pre-antimicrobial culture
and susceptibility results help determine definitive therapy and de-escalation. The yield after starting antimicrobials is much lower. Two sets of blood cultures are necessary, one from a sterile peripheral site and one from a recently placed (<48 hours) vascular catheter or other sterile peripheral site. Do not delay antimicrobial administration if cultures cannot be obtained.

2. Source control

Antimicrobial penetration to tissues and organs can vary. Penetration into abscesses and loculated fluid collections is limited increasing the risk of clinical failure. Source control through drainage, debridement, or definitive management is vital to the successful management of infections. Patient risk factors, comorbidities, severity of illness, area of infection and clinical status will determine which method for source control is most appropriate.

Antimicrobial pharmacokinetic and pharmacodynamics considerations in patients with sepsis

1. Pharmacokinetic alterations of antimicrobials

Appropriate concentrations of antimicrobials should be attained quickly in order to optimize outcomes while minimizing risk for adverse effects. Increases in volume of distribution caused by third spacing and large-volume fluid resuscitation may necessitate aggressive loading and maintenance doses of hydrophilic antimicrobials (e.g., β-lactams, aminoglycosides, vancomycin, linezolid, polymyxins, daptomycin); renal impairment will reduce clearance of hydrophilic drugs while hepatic impairment will reduce clearance of lipophilic drugs (fluoroquinolones, macrolides, tigecycline, tetracyclines, metronidazole); changes in albumin and α₁-acid glycoprotein will impact free drug concentrations. Trauma and burn patients are at risk for enhanced clearance of drugs. Other factors such as extracorporeal devices and body habitus - including being under- and over-weight - will also impact dosing.

2. Pharmacodynamic properties of antimicrobials

The pharmacodynamic properties of antimicrobials can be classified into 3 groups: time dependent, concentration dependent, and a combination of concentration and time dependent killing. With concentration dependent antimicrobials, optimal killing occurs when the concentration of the drug exceeds the MIC (minimum inhibitory concentration) of the organism (Cmax/MIC). In contrast, optimal killing by time dependent antimicrobials occurs when the maximal concentration at the site of infection exceeds that of the organism’s MIC for most of the dosing interval (T>MIC). Many antimicrobials that display concentration-dependent killing also display a post-antibiotic effect where bactericidal activity is still occurring despite concentrations lower than the MIC of the organism. Pharmacodynamic properties of common antimicrobial classes are located in Table 1. Antimicrobials must be dosed
appropriately in order to maximize these pharmacodynamic properties.

Table 9.2.1 Pharmacodynamic Properties of Antimicrobials

<table>
<thead>
<tr>
<th>Time Dependent (T&gt;MIC)</th>
<th>Concentration-Dependent (Cmax/MIC)</th>
<th>Both Properties (AUC/MIC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbapenems</td>
<td>Aminoglycosides</td>
<td>Fluoroquinolones</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>Daptomycin</td>
<td>Linezolid</td>
</tr>
<tr>
<td>Penicillins</td>
<td>Metronidazole</td>
<td>Macrolides</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Polymyxins</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tetracyclines</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tigecycline</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vancomycin</td>
</tr>
</tbody>
</table>

Empiric antimicrobial therapy

1. Timing of antimicrobials

The Surviving Sepsis Campaign recommends that appropriate antimicrobials be administered within 1 hour of recognition of sepsis. Many studies have observed a linear relationship with mortality and delayed antimicrobial administration in patients with sepsis. One study showed a decrease in survival by 7.6% in patients with septic shock with every 1 hour delay in administration. (4) When multiple antimicrobials are prescribed, timing of administration depends on drug compatibility, type of access, recommended infusion duration, type of infection, likely organism(s) and clinical status of the patient.

2. Determining empiric antimicrobials regimens

Since time to administration of appropriate antimicrobials can impact outcomes in patients with sepsis, determining the source of infection and choosing a regimen that will cover likely pathogens is important. Aerobic gram-negative and gram-positive bacteria will be the causative organisms in most infections, but fungal and viral pathogens should also be considered in patients who have risk factors. While respiratory, intra-abdominal and urinary tract infections are the most common, other infections such as bloodstream, surgical site, and central nervous system infections can be commonly found in patients at risk. Initial antimicrobials must have good penetration to the site of infection and recently used antimicrobials should be avoided. Risk factors for MDR organisms include: length of hospitalization, antimicrobial use within 90 days, hospitalization within the past 3 months, inadequate treatment of a recent infection, immunosuppression, residence in a nursing home or long term care facility, indwelling devices, local resistance patterns and antimicrobial sensitivities as indicated by hospital antibiograms. Every effort should be made to determine past culture history,
recent antimicrobial exposure, and intolerances or allergies to specific agents. Antimicrobials that will cover gram-positive and gram-negative organisms should be chosen in patients with sepsis. Patients with risk factors for multi-drug resistant (MDR) organisms should have even broader coverage of gram-positive and gram-negative organisms.

Broad-spectrum penicillins with a β-lactamase inhibitor (e.g., piperacillin-tazobactam), 3rd and 4th generation cephalosporins (e.g., ceftriaxone, cefepime), carbapenems (e.g., imipenem, doripenem, ertapenem, meropenem) are commonly used for gram-negative and non-methicillin resistant Staphylococcus aureus (MRSA) coverage. Double coverage with either a fluoroquinolone or preferably an aminoglycoside can be considered when MDR gram-negative bacteria are suspected. Intravenous vancomycin should be used for MRSA or penicillin-resistant pneumococcus coverage and either daptomycin or linezolid should be used for vancomycin resistant Enterococcus (VRE) spp. coverage in those at risk. The use of multiple β-lactams should be avoided to minimize the risk for toxicity. Using antimicrobials with different mechanisms of action is preferred to optimize therapeutic effects. Antimicrobial spectrum and clinical considerations of common antimicrobials are listed in Tables 2 and 3.

### Management of commonly encountered infections

1. Ventilator / hospital-acquired pneumonia (5)

| Table 9.2.2 Commonly Used Drugs Active Against MSSA, MRSA, VRE and *Pseudomonas* spp. |
|-----------------|-----------------|-----------------|
| **Class**       | **Drug**        | **Clinical Considerations and Pearls** |
| MSSA            |                 |                               |
| Penicillins     | Oxacillin       | Drugs of choice. Other drugs in this class may not have reliable coverage against MSSA |
|     | Nafcillin       |                               |
| Cephalosporins  | Cefazolin       | Most reliable coverage against MSSA in this class |
| Glycopeptide    | Vancomycin      |                               |
| Lipoglycopeptide| Daptomycin      | Should only be used in patients with severe PCN allergy who cannot receive oxacillin or nafcillin |
| Oxazolidinones  | Linezolid       |                               |
|     | Trimethoprim-sulfamethoxazole | |
| MRSA            |                 |                               |
| Glycopeptides   | Vancomycin      | -Drug of choice -Goal trough 15-20 mg/L: PNA, endocarditis, meningitis, complicated bacteremias with retained hardware, osteomyelitis, abscess/fluid collections -Goal trough 10-15 mg/L: UTI, SSTI -Ototoxicity and nephrotoxicity risk exists especially when administered with drugs with same risks |
| Cephalosporins  | Ceftaroline     | -Will not cover Enterococcus spp. (no cephalosporins cover Enterococcus spp.) -Not recommended for HAP/VAP |
| Lipoglycopeptide| Daptomycin      | -Measure CPK during therapy due to risk for rhabdomyolysis and myalgias (check at baseline and once weekly) -Do not use for treatment of pneumonia |
| Oxazolidinones  | Linezolid       | -Caution when used with drugs with serotonergic properties due to monoamine oxidase A inhibition -Thrombocytopenia associated with Rx > ~ 2 wks |
| Glycylcycline   | Tigecycline     | -Avoid use for management of urinary tract and bloodstream infections due to poor drug concentration -Avoid monotherapy |
| Clindamycin     |                 |                               |
| Trimethoprim-Sulfamethoxazole | Community acquired MRSA | 
a. **Diagnosis:** Clinical signs and symptoms include changes consistent with infection such as new or worsening infiltrate on chest radiograph and positive respiratory cultures. Increased WBC or fever may also be present. Hospital acquired pneumonia (HAP) is defined as a pneumonia occurring ≥48 hours after admission in non-intubated patients and ventilator associated pneumonia (VAP) is defined as occurring ≥48 hours after endotracheal intubation. Noninvasive, semi-quantitative respiratory cultures of endotracheal aspirates should be obtained. For patients who receive invasive sampling with a bronchioalveolar lavage, 10^4 CFU/mL is considered a significant colony count and 10^3 is considered significant when a protected-specimen brush technique is used.

b. **Empiric treatment:** Choose regimens based on local resistance patterns, most likely organism(s), and risk factors for MDR organisms.

1) **Ventilator associated pneumonia**

   a) If risk factors for MDR organisms are present and the patient is in a unit where the MRSA rate is high or unknown, cover for MRSA with either IV vancomycin or linezolid. If risk factors for MDR are not present and the prevalence of MRSA is low, cover for MSSA (not MRSA) with a regimen that includes piperacillin-tazobactam, cefepime,
levofloxacin, imipenem or meropenem. Oxacillin, nafcillin, or cefazolin are preferred for MSSA, but are not needed if the above agents are used. (Table 4)

b) Two agents, from different classes, active against Pseudomonas spp. should be initiated if risk factors for MDR organisms are present, the prevalence of gram-negative resistance is high, or if local antimicrobial susceptibilities are unknown. Patients that do not meet these criteria are suggested to receive only 1 antimicrobial active against Pseudomonas spp.

2) Hospital acquired pneumonia

a) Intravenous vancomycin or linezolid should be used in patients who have risk factors for MRSA.
Patients who have no risk factors for MRSA should be covered for MSSA with a regimen that includes piperacillin-tazobactam, cefepime, levofloxacin, imipenem or meropenem. Oxacillin, nafcillin, or cefazolin are preferred against for MSSA, but are not needed if the above agents are used.

b) Two agents, from different classes, active against Pseudomonas spp. should be used in patients with risk factors for MDR organisms, structural lung disease, and who are at high risk for mortality (i.e., ventilator support due to HAP and septic shock). Patients that do not meet these criteria are suggested to receive only 1 agent active against Pseudomonas spp.

c. **Duration of treatment:** 7-day treatment is preferred for HAP and VAP, although therapy can be extended up to 15 days depending on rate of clinical, radiologic, and laboratory parameter improvement.

2. **Catheter-related bloodstream infection (CRBSI)**

   a. **Diagnosis:** A catheter-related blood stream infection (CRBSI) is defined as a primary bloodstream infection ≥48 hours after placement or within 24 hours after removal of a central line. A CRBSI can be diagnosed in several ways. Paired blood cultures, one from vascular catheter and one that is percutaneously drawn, should be obtained. A catheter blood culture that is greater than 3-fold higher CFU than peripheral blood culture and/or becomes positive with the same organism more than 2 hours before the peripheral blood culture (differential time to positivity) is highly suggestive of a CRBSI. If a peripheral blood culture cannot be obtained, ≥2 cultures from different catheters should be obtained. A CRBSI can also be diagnosed if the same organism grows from the catheter tip and peripheral blood culture.

   b. **Empiric treatment:** Infected catheters should be removed, if possible. Antimicrobial lock therapy should be used in adjunct to systemic therapy when catheters cannot be removed. Common antimicrobial locks include cefazolin, daptomycin, gentamicin, or vancomycin. Antimicrobials with good activity against Staphylococcus (including MRSA) and Streptococcus spp. such as IV vancomycin or daptomycin should be chosen. Empiric linezolid should be avoided. Patients with severe disease and depending on local hospital flora should also receive gram-negative coverage with cefepime, carbapenem, or piperacillin/tazobactam. Patients with neutropenia, sepsis, or septic shock should be treated with 2 agents active against Pseudomonas app. Antifungal therapy with fluconazole or an echinocandin should be started in patients with the following risk factors: total parenteral nutrition, suspected CRBSI involving a...
femoral catheter, neutropenia, hematologic malignancy, bone-marrow or solid-organ transplant, colonization with Candida spp., or prolonged antibiotic use.

c. **Duration of treatment:** Clearance of the bacteremia will determine duration. Repeat blood cultures should be collected every 24-48 hours after starting appropriate therapy. Day 1 of antimicrobial therapy is considered to be the first day of negative blood cultures. The recommendations below are for scenarios when the infected line has been removed. Duration of therapy will be longer in patients with retained infected lines.

1) **Blood stream infections related to short-term (<14 days) central venous lines or arterial catheters that have been removed**

   a) **Complicated bacteremias**

      i. Thrombophlebitis, endocarditis, hardware infection: 4-6 weeks
      
      ii. Osteomyelitis: 6-8 weeks

   b) **Uncomplicated bacteremias** (fever resolved within 72 hours, no intravascular hardware, endocarditis, thrombophlebitis; no active malignancy or immunosuppression in patients with Staphylococcus aureus)

      i. Coagulase-negative staphylococci: 5-7 days
      
      ii. *Staphylococcus aureus:* ≥14 days
      
      iii. *Enterococcus spp.:* 7-14 days
      
      iv. *Gram negative bacteria:* 7-14 days
      
      v. *Candida spp:* 14 days

2) **Recommendations for blood stream infections related to long-term (>14 days) central venous lines or ports** can be found in the Clinical Practice Guidelines for the Diagnosis and Management of Intravascular Catheter-related Infection. (6)

3. **Catheter-associated urinary tract infection** (7)

   a. **Diagnosis:** A catheter-associated urinary tract infection (CAUTI) is defined as the presence of signs and symptoms of a urinary tract infection and >10^3 CFU/mL of ≥1 organism in a single urine culture obtained from a catheter, or in a urine culture from a midstream void after the catheter had been removed within the previous 48 hours. Urine analysis should be obtained in patients with a suspected CAUTI.

   b. **Empiric treatment:** Discontinue indwelling catheters when they are no longer required. Treatment should be based on local resistance, MDR risk factors, previous microbiologic growth, and antimicrobial exposure. Common organisms
that cause CAUTI include Escherichia coli, other Enterobacteriaceae, Pseudomonas spp., coagulase-negative staphylococci, Enterococcus spp., and Candida spp.

c. **Duration of treatment:** Antimicrobials should be continued for 7 days in patients with resolution of signs and symptoms within 72 hours, and for 10-14 days in patients with a delayed response after 72 hours regardless of the presence of a catheter. Women who are ≤65 years and do not have upper urinary tract symptoms after removal of an indwelling catheter may get antimicrobials for 3 days.

4. *Clostridium difficile infection (8)*

   a. **Diagnosis:** Clostridium difficile infection (CDI) is defined as the presence of symptoms (e.g., diarrhea defined as ≥3 unformed stools within 24 hours) and a positive C. difficile toxin or pseudomembranous colitis. Severe CDI is defined as having a WBC ≥15 x 10⁹/L or a serum creatinine ≥1.5 times baseline. Severe, complicated CDI is defined by severe CDI with hypotension, colonic ileus, or toxic megacolon. A 2-step diagnostic process involving enzyme immunoassay tests to detect the C. difficile antigen, glutamate dehydrogenase (GDH), followed by a confirmatory stool culture in patients who are GDH positive can be done. Another method for detection can include PCR testing. Testing should occur only on unformed stools, but can be performed on formed stools in patients with ileus, cecal CDI or right-sided CDI. Pseudomembranous colitis can be seen on lower endoscopy, but is rarely necessary. Abdominal CT scans may also facilitate diagnosis of CDI, but is neither sensitive nor specific.

   b. **Treatment:** All antimicrobials should be discontinued, if clinically allowable. Repeat testing to document cure after CDI therapy is not recommended.

   1) Mild-moderate CDI: metronidazole 500 mg orally or via feeding tube every 8 hours

   2) Severe CDI: vancomycin 125-250 mg orally or via feeding tube every 6 hours

   3) Severe, complicated CDI: vancomycin 500 mg orally or via feeding tube every 6 hours and metronidazole 500 mg IV every 8 hours. Vancomycin enemas 500 mg rectally every 6 hours can be administered in patients with decreased distal delivery of oral vancomycin.

   4) Patients with a first reoccurrence of disease can be treated according to disease severity, but patients with a second reoccurrence of CDI should be treated with oral vancomycin followed by a 28-day taper.

   c. **Duration of treatment:**

   1) Mild-moderate or severe CDI: 10-14 days
5. Complicated intra-abdominal infection (9)

a. **Diagnosis:** Complicated intra-abdominal infections extend into the peritoneal space and are associated with abscess formation or peritonitis. A combination of a detailed medical history with a physical exam, laboratory tests, imaging, and intraoperative findings can be used for diagnosis. Intra-abdominal cultures in patients with mild-moderate community-acquired disease is not recommended, but is recommended in patients with severe community-acquired or healthcare-acquired disease. Patients who have physiologic disturbance (e.g., septic shock), advanced age, a delay or failure of achieving source control, or are immunocompromised should be considered as having a severe complicated intra-abdominal infection.

b. **Empiric treatment:** Source control should be achieved either surgically or with percutaneous drainage, if possible.

1) Community-acquired (mild-moderate):

Aerobic gram-negative bacteria and enteric streptococci should be covered. Patients with distal small bowel, appendiceal, or colonic sources of infection should also be covered for anaerobic bacteria. Coverage is not needed against Enterococcus spp. and Pseudomonas spp. Options include the following: cefazolin, ceftriaxone, cefotaxime or cefuroxime with metronidazole; cefoxitin; ertapenem; moxifloxacin; levofloxacin or ciprofloxacin with metronidazole; or tigecycline

2) Community-acquired (severe)

Antimicrobial therapy should cover MDR organisms, Enterococcus spp, and anaerobes. MRSA coverage is not recommended. Carbapenems (e.g., doripenem, imipenem, meropenem); cefepime, ceftazidime, ciprofloxin, or levofloxacin with metronidazole; or piperacillin-tazobactam can be used. Caution should be exercised when using fluoroquinolones due to resistance seen with E. coli and Pseudomonas. The addition of IV vancomycin could be considered in patients receiving cephalosporin or fluoroquinolone therapy for additional Enterococcus spp. coverage.

3) Healthcare associated

MDR organisms, enterococci, anaerobes and MRSA should be covered. Double gram-negative coverage may be added with an aminoglycoside depending on local susceptibility rates. Possible regimens include carbapenem (e.g., doripenem, imipenem, meropenem) plus IV vancomycin; cefepime or ceftazidime plus metronidazole and IV vancomycin; or piperacillin/tazobactam plus IV vancomycin. Antifungal therapy with an echinocandin can be added if the patient is colonized with yeast or if the gram stain is positive for yeast.
c. **Duration of treatment:** Although recommendations are for 4-7 days, the duration may be longer in patients with uncontrolled sources and delayed clinical response.

**Importance of antimicrobial stewardship**

Antimicrobial resistance is a global epidemic that is only expected to worsen with continued use and lack of new antimicrobials being produced by drug companies. Antimicrobials must be used judiciously. Empiric regimens should be de-escalated within 3-5 days once cultures and susceptibilities are finalized. Stewardship has been associated with decreased resistance without worsening outcomes, and reduced risk for CDI and antimicrobial-associated adverse effects.

*This chapter is a revision of the prior chapter authored by Peter von Homeyer MD.*

**References:**


Review Questions:

1. An ICU patient with femoral central line access becomes febrile and hypotensive 7 days later. After drawing paired blood cultures (peripheral and catheter), which antibiotic regimen would you empirically initiate for a suspected CRBSI?
   a. Vancomycin
   b. Cefepime
   c. Cefepime and vancomycin
   d. Cefepime, vancomycin, and micafungin

2. A 58 year old woman status post liver transplant is suspected of having a VAP after being mechanically ventilated for 7 days. The ICU team would like to start an empiric regimen consisting of piperacillin-tazobactam, IV vancomycin and a second antibiotic that has additional activity against MDR gram-negative bacteria. Which of the following should be added?
   a. Vancomycin
   b. Tobramycin
   c. Cefepime
   d. Caftaroline

3. A 40 year old woman presents to the SICU with an esophageal leak after undergoing an esophagectomy 1 month ago. Her temperature is 38.5 °C and she is requires norepinephrine and vasopressin to maintain a MAP of 65 mmHg. Her current empiric antimicrobial regimen includes piperacillin-tazobactam and tobramycin. You get a call from the microbiologist who reports that she is growing yeast in her blood culture. Which of the following agents should you start next?
   a. Fluconazole IV
   b. Nystatin PO
   c. Micafungin IV
   d. Itraconazole PO
**Introduction**

Historically, viral illnesses played an integral role in the development of intensive care units worldwide. Specifically, the first critical care units were designed to provide ventilatory support to patients with poliomyelitis in the early 1950s. While the relative incidence of viral illnesses in the critically ill has diminished with the development of key vaccinations and anti-viral medications, they continue to play a major role in ICU admissions.

**Key Points**

- The majority of viral illnesses in the ICU involve the respiratory tract and/or the central nervous system
- As much as 3-10% of severe community acquired pneumonia cases in the ICU are associated with an underlying viral infection
- Treatment is primarily supportive care with anti-viral medications where available
- Early recognition, diagnosis and treatment are key to successful outcomes

**Patient Case:**
A 76 year-old woman with a three-day history of malaise and muscle weakness followed by nausea and vomiting is admitted to the intensive care unit for dyspnea and orthopnea. Her family states she has a history of congestive heart failure and hypertension but is usually very active. They do not know if she has received the influenza vaccine. On admission her temperature is 35.6° C, pulse 109 bpm, blood pressure 149/66 mmHg, with a respiratory rate of 30/minute. She has bilateral wheezing and rhonchi on auscultation. Chest radiograph shows bilateral pulmonary infiltrates. It is concluded that she has congestive heart failure with possible underlying pneumonia and is placed on supplemental oxygen, diuretics and a course of intravenous antibiotics.
Viral infections often involve the respiratory system or central nervous system and can cause significant morbidity and mortality. However, other organ systems, particularly the gastrointestinal tract, can also be affected, causing hemorrhagic and hypovolemic shock. International viral outbreaks still pose a threat today. The incidence of viral infections varies across geographical regions, thus intensivists need to be aware of new and continually emerging diseases such as Middle East Respiratory Syndrome coronavirus, avian influenza, and more recently the Ebola virus. Clinical presentation of a viral infection can be nonspecific and often masquerades as a bacterial infection. Hence, early recognition and diagnosis and close monitoring are key to improved outcomes.

**Presentation and Diagnosis**

Severe viral infections can present with a wide variety of symptoms including fever, myalgias, malaise, neurologic symptoms, respiratory insufficiency or failure, gastrointestinal symptoms including nausea, vomiting and diarrhea, cardiogenic or distributive shock, rhabdomyolysis, renal failure, disseminated intravascular coagulopathy (DIC), multiple organ system failure and death. Although the majority of viral illnesses in critically ill patients involve the respiratory tract and/or the central nervous system, one needs to be aware of other organ system involvement (such as the gastrointestinal system).

**Respiratory infections**

The most common cause of community-acquired pneumonia is typically bacterial in nature. However, newer developments in diagnostic technologies, such as polymerase chain reaction (PCR), which can detect even the smallest amounts of viral nucleic acid, have shown that viruses account for approximately 3-10% of cases in the intensive care unit. Presentation is often nonspecific (fever, tachycardia, hypotension, respiratory distress, altered mental status, and elevated leukocytosis) and can be confused with bacterial infections. Hence, most patients are treated with empiric broad spectrum antibiotics. Without resolution of the infection with antibiotics, one must explore the possibility of a viral infection. Early recognition and appropriate antiviral therapy are vital to improve outcome.

Viral illnesses causing hypoxic respiratory failure include influenza virus, type A and B, parainfluenza viruses, respiratory syncytial virus (RSV), and adenoviruses. Influenza virus is the most common cause of viral pneumonia in patients with predisposing conditions (diabetes mellitus, chronic lung disease, or immunocompromised) and the elderly. In patients with asthma or COPD exacerbation, respiratory failure with poor oxygenation and poor ventilation can lead to significant morbidity. Antivirals with neuraminidase inhibitors (zanamivir, peramivir, oseltamivir, laninamivir) should be considered.

Severe viral infections such as influenza and severe acute respiratory syndrome (SARS) may cause respiratory failure and
may rapidly progress to acute respiratory distress syndrome (ARDS) and multi-organ failure. Risk factors for worsened morbidity and mortality include delayed initiation of antiviral therapy, history of inhalational substance abuse and symptoms including productive cough, hemoptysis, chest pain, confusion, and loss of consciousness. On occasion, severe ARDS necessitates salvage therapies such as extracorporeal membrane oxygenation (ECMO) support, prone ventilation, and/or neuromuscular paralysis.

Central nervous system infections

Several viruses may infect the central nervous system (CNS) and cause inflammation of the meninges and brain parenchyma causing meningitis or encephalitis. This may lead to cerebral edema, seizures, and coma, and places these patients at risk for further complications including respiratory failure secondary to aspiration, neuromuscular weakness and atelectasis.

Common viral etiologies include HSV, VZV (in immunocompromised patients), enteroviruses, and arboviruses (depending on geographic location). Other possible viruses include West Nile Virus, CMV, mumps, measles, rubella, and JC virus.

Viral causes of shock

Shock is an uncommon presentation in viral illnesses but can lead to significant morbidity and mortality. Viral myocarditis, most notably caused by coxsackie viruses, can lead to acute cardiogenic shock. Symptoms resemble that of acute heart failure and may lead to respiratory failure.

Viral Hemorrhagic Fever (VHF) is a syndrome caused by some of the most virulent viral pathogens in the world and often presents with distributive shock. Table 1 highlights and summarizes the viruses which cause hemorrhagic fever. These are primarily RNA viruses and include filoviruses (Ebola and Marburg), flaviviruses (dengue, yellow fever), bunyaviruses [Hanta, Congo-Crimean hemorrhagic fever (CCHF), Rift Valley Fever], and arenaviruses (South American hemorrhagic fevers, Lassa fever). Early symptoms can be non-specific but eventually patients show signs of increased vascular permeability and ultimately disseminated intravascular coagulation (DIC). Thrombocytopenia, leukopenia, hepatitis, encephalitis, neuropathy as well as multi-organ failure can occur depending on the specific virus involved.

Management and Treatment

Treatment of all viral illnesses remains largely supportive with an emphasis on early diagnosis and recognition. This includes adequate fluid resuscitation and replacement of gastrointestinal and insensible fluid losses as well as respiratory and cardiovascular support.

For viral illnesses causing hypoxic respiratory failure, management is supportive care, including lung-protective
<table>
<thead>
<tr>
<th>Virus</th>
<th>Outbreaks/Endemic</th>
<th>Presentation</th>
<th>Transmission</th>
<th>Treatment</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bunyaviridae</td>
<td>Crimean-Congo Hemorrhagic Fever (CCHF) Other diseases include Rift Valley Fever, Hantavirus Pulmonary Syndrome (HPS), Hemorrhagic Fever with Renal Syndrome (HFRS)</td>
<td>Africa, the Balkans, the Middle East and Asian countries south of the 50th parallel north</td>
<td>Fever, myalgia, neck pain/stiffness, photophobia, nausea/vomiting, diarrhea, confusion, petechial rash, hepatomegaly/hepatitis, kidney failure</td>
<td>Primarily supportive. Ribavirin has been used with some benefit</td>
<td>40%</td>
</tr>
<tr>
<td></td>
<td>Rift Valley Fever (RVF)</td>
<td>Rift Valley of Kenya (1931). Egypt, Somalia, Tanzania, Saudi Arabia, Yemen</td>
<td>Primarily flu-like symptoms. Severe forms include ocular form (retinal lesions), meningoencephalitis form, and hemorrhagic fever form</td>
<td>Mosquitoes. No human-human transmission documented</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Filoviridae (filovirus)</td>
<td>Ebola Virus Disease (EVB)</td>
<td>Central Africa (first known outbreak, 1976) and West Africa, near tropical rainforests</td>
<td>Fever, fatigue, myalgias, headache, nausea/vomiting, impaired kidney and liver function, coagulopathy</td>
<td>Droplet, fruit bats</td>
<td>50% (25-90% in past outbreaks)</td>
</tr>
<tr>
<td></td>
<td>Marburg Hemorrhagic Fever (MHF)</td>
<td>Initial outbreaks in Marburg (1967) and Frankfurt, Germany, and Belgrade, Serbia</td>
<td>High fever, severe lethargy, rash, nausea/vomiting, diarrhea, coagulopathy, CNS involvement</td>
<td>Droplet, fruit bats</td>
<td>24-88%</td>
</tr>
<tr>
<td>Flaviviridae</td>
<td>Dengue Hemorrhagic Fever Other diseases include: Yellow fever, Omsk Hemorrhagic Fever, Kyasanur Forest Disease (KFD), Alkhurma Hemorrhagic Fever (AHF)</td>
<td>Severe Dengue first recognized 1950s with epidemics in the Philippines and Thailand. Affects most Asian and Latin American countries, in tropical and sub-tropical climates</td>
<td>Primarily flu-like symptoms. Severe forms progress to hemorrhagic fever with multi-organ failure</td>
<td>Supportive. First dengue vaccine, Dengvaxia was registered late 2015 – early 2016. Leading cause of serious illness and death among children in some Asian and Latin American countries. 20% mortality improved to less than 1% with early recognition and treatment</td>
<td>20% mortality improved to less than 1% with early recognition and treatment</td>
</tr>
</tbody>
</table>
mechanical ventilation depending on the severity of the respiratory failure. Influenza is currently the only virus with FDA-approved therapeutic agents. The influenza vaccination is the most effective preventative measure and is recommended for patients who are > age 65 or are immunocompromised. Neuraminidase inhibitors such as oseltamivir or zanamivir are recommended in settings where patients are admitted to the ICU with acute respiratory failure. Newer medications such as laninamivir may be used to treat oseltamivir-resistant viruses.

For patients presenting with altered mental status or seizures, supportive management of neurologic symptoms such as increased intracranial pressure, cerebral edema, seizure, and fever forms the foundation of therapy. Mechanical ventilation may be necessary for those with hypoxemia or for airway protection from aspiration if mental status is significantly depressed. Early aggressive antiviral therapy with acyclovir has been shown to improve outcomes and reduce cognitive impairment sequelae for patients with HSV or VZV infection. For patients with CMV encephalitis, ganciclovir should be considered.

For most other viruses including those that cause viral hemorrhagic fever, there are no known effective therapeutic interventions besides supportive therapy. Other than yellow fever 17D, there are no approved vaccinations. Corticosteroids are not currently recommended. Ribavirin has been shown to be an effective therapy for Lassa fever and possibly CCHF and Rift Valley Fevers and is recommended where available.

In addition to the treatment of the affected patient, immediate isolation is critical for effective infection control and prevention of transmission. Appropriate choice of isolation including differentiating between airborne, droplet and contact precautions should be identified and implemented immediately. In the case of potentially epidemic and pandemic diseases, communication with local and national public health authorities may help prevent a possible outbreak.

References:


2. Centers for Disease Control and Prevention: Updated interim recommendations for the use of antiviral medications in the treatment and prevention of influenza for the 2009-2010 season. 2014


**Review Questions:**

1. In the ICU, viral infections are most frequently involved which system?
   a. Central nervous system
   b. Respiratory system
   c. Gastrointestinal system
   d. Hematologic system

2. Which of the following is the most common cause of viral encephalitis in adult?
   a. West Nile virus
   b. HSV-1
   c. EBV
   d. JC Virus

3. Management of viral infections includes:
   a. Appropriate antibiotics within the first hour of presentation
   b. Empiric antiviral therapy
   c. Supportive care
   d. Administration of corticosteroids
Many patients in the ICU are immunocompromised as the result of disease processes, surgical instrumentation, side effects of medications, or deliberate immunosuppressive therapies after transplantation. Management of such patients by the intensivist centers on:

1. Recognition of the immunocompromised state

2. Acute management of immunosuppressive agents until the appropriate specialists can be engaged

Key Points:

- The management of an immunosuppressed critically ill patient requires a multidisciplinary team.
- Empiric broad-spectrum antibiotics should be administered immediately for all immunocompromised patients with severe sepsis/septic shock.
- An infection in an immunocompromised patient may not present in the usual manner as for an immunocompetent patient.
- Antimicrobial guidelines are available for organ transplant patients on immunosuppressive therapy.

Patient Case:

A 65-year-old woman with a history of renal transplant 4 years prior was admitted to the ICU status post 2-vessel CABG. Intraoperative course was notable for long cardiopulmonary bypass time, hypotension requiring pressors, and large blood loss. Postoperatively she did well and was transferred to the floor on POD3. She then developed a waxing and waning mental status, which was interpreted as delirium by the floor team, along with several episodes of relative hypotension. Upon admission back to the ICU, she was found to be hypothermic (35.1 °C) with a CBC and BMP that were unchanged from prior ones. The patient’s transplant medications and prophylactic antimicrobials were never interrupted and she had finished the standard 24-hour antibiotic prophylaxis for surgical procedures.
3. Recognition of the altered presentation of infection and sepsis, and prompt initiation of appropriate antimicrobial therapy

A multidisciplinary approach is imperative and relevant consults should be obtained early. However, often times the intensivist will need to make decisions quickly and should, therefore, be familiar with immunosuppressive pathophysiology and pharmacology.

**Solid Organ Transplant Patients**

Management of the solid organ transplant (SOT) patient is complex and varies by organ transplanted as well as the time since transplant. These patients are prone to life-threatening infections (secondary to surgical/technical complications combined with immunosuppression) and, thus, prevention and prompt treatment of infections are imperative. Detailed guidelines are available from the American Society of Transplantation and the American Society of Transplant Surgeons (2,4).

Risk factors that predispose to infections after SOT can be present before transplant within the recipient (e.g. a cystic fibrosis patient with pseudomonal and fungal infections, HCV cirrhosis, or chronic malnutrition). Risk factors can also come from the donor: active or latent infections at time of procurement and those secondary to intraoperative events (e.g. anastomotic stenosis, injury to phrenic, vagal, or recurrent laryngeal nerves, ischemic injury to allograft, prolonged operative time, or bleeding near surgical site). Lastly, they may be related to post-transplant events: immunosuppression, indwelling cannulas, and nosocomial or community exposure.

Immunosuppression is induced just before or during transplantation with high-dose steroids and/or antibody therapy. Polyclonal antibody therapy (antithymocyte globulin) carries the risk of serum sickness as well as broad immunosuppressive effects. For the most part, antithymocyte globulin has been replaced with monoclonal antibodies (e.g., basiliximab) that specifically target IL-2 receptors. High-dose steroids are typically tapered down and maintained at low doses for life. Maintenance therapy also usually includes a calcineurin inhibitor (tacrolimus or cyclosporine – inhibits secretion of IL-2), and/or an mTOR (mammalian target of rapamycin) pathway inhibitor (sirolimus or everolimus – inhibits T cell response to IL-2), and an antiproliferative agent (azathioprine, mycophenylate [MMF]).

The health care provider must continually reassess the patient’s net state of immunosuppression, which comprises all factors that contribute to the risk for infection which include: dose, duration and sequence of immunosuppressive therapies (including chemo/radiation and plasmapheresis treatments), neutropenia, underlying immune deficiencies (SLE, hypogammaglobulinemia), viral coinfection, poor HLA match, rejection, graft dysfunction, surgical/technical complications (anastamotic leaks, bleeding near/at graft), breeches in mucocutaneous integrity (tracheal, vascular and urinary cannulas), and the presence of fluid collections (hematoma, ascites, effusion).
While management of immunosuppressive regimens and assessment of organ rejection are performed by appropriate specialists, often the intensivist will have to make medication 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 compromised. Serum levels need to be monitored daily and frequent consultation with the hospital pharmacist, in addition to transplant sub-specialist, 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. The timing of specific infections is generally predictable regardless of which organ is transplanted and is divided into three major intervals: early (0-1 months), intermediate (1-6 months), and late (> 6 months) periods (Table 1). The assessment by this timeline is not absolute and can be altered by the use of prophylactic medications and the net state of immune suppression (see above). It is imperative to continually reassess the risk of infection and the patient’s overall state of immunity so that the appropriate response can be initiated.

Common nosocomial infections can occur at any time and are related to the presence of foreign bodies (catheters, lines) or other procedures performed incidentally.

Table 9.4.1 Timing of Infectious Complications Following Transplantation

<table>
<thead>
<tr>
<th>Early period (0-1 months)</th>
<th>Intermediate period (1-6 months)</th>
<th>Late period (&gt; 6 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacterial infections</strong></td>
<td><strong>Viral infections</strong></td>
<td><strong>Viral infections</strong></td>
</tr>
<tr>
<td>- Gram negative enteric bacilli (small bowel, liver, neonatal heart)</td>
<td>- CMV (all transplant types, CMV- recipient of CMV+ donor)</td>
<td>- EBV (all transplant types, less than in intermediate period)</td>
</tr>
<tr>
<td>- <em>Pseudomonas/Burkholderia</em> spp. (cystic fibrosis: lung tx)</td>
<td>- EBV (all transplant types, EBV- recipient, small bowel highest risk)</td>
<td>- VZV (all transplant types)</td>
</tr>
<tr>
<td>- Gram positive organisms (all transplant types)</td>
<td>- <em>VZV</em> (all transplant types)</td>
<td></td>
</tr>
<tr>
<td><strong>Fungal infections</strong></td>
<td><strong>Opportunistic infections</strong></td>
<td><strong>Bacterial infections</strong></td>
</tr>
<tr>
<td>- All transplant types</td>
<td>- PCP (all transplant types)</td>
<td>- <em>Pseudomonas/Burkholderia</em> spp. (lung recipients with chronic rejection or cystic fibrosis)</td>
</tr>
<tr>
<td></td>
<td>- Toxoplasma gondii (seronegative heart recipient from seropositive donor)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- <em>Listeria</em>, <em>Nocardia</em> spp.</td>
<td></td>
</tr>
<tr>
<td><strong>Viral infections</strong></td>
<td><strong>Bacterial infections</strong></td>
<td></td>
</tr>
<tr>
<td>- HSV (all transplant types)</td>
<td>- <em>Pseudomonas/Burkholderia</em> spp. (pneumonia, cystic fibrosis: lung tx)</td>
<td></td>
</tr>
<tr>
<td>- Nosocomial respiratory viruses (all transplant types)</td>
<td>- Gram negative enteric bacilli (small bowel tx)</td>
<td></td>
</tr>
<tr>
<td><strong>General</strong></td>
<td><strong>General</strong></td>
<td><strong>General</strong></td>
</tr>
<tr>
<td>- Infections are usually donor- or recipient-derived</td>
<td>- Onset of infections from donor organs or reactivation from recipient tends to occur in this time-frame</td>
<td>- Risks vary with immunosuppression and exposures</td>
</tr>
<tr>
<td>- Surgical site infections are most common</td>
<td>- Opportunistic infections present during this period</td>
<td>- Underlying comorbidities (DM, malignancies) increase risk</td>
</tr>
<tr>
<td>- Patients are at risk for line infections and aspiration</td>
<td>- Febrile episodes are often caused by viral pathogens and graft rejection</td>
<td>- PTLD may manifest in this period</td>
</tr>
<tr>
<td>- Technical difficulties and complications (e.g., anastomotic stenosis, leaks, hematomas, peritonitis, reperfusion injury) are important risk factors for invasive infection</td>
<td></td>
<td>- Uncorrected anatomic or functional abnormalities (e.g., vesicoureteral reflux, biliary strictures, hepatic artery thrombosis, mediastinal bleeding) increase risk for chronic/recurrent infections</td>
</tr>
<tr>
<td>- <em>C. difficile</em> colitis is common</td>
<td></td>
<td>- With low levels of immune suppression and normal graft function infections are well tolerated</td>
</tr>
</tbody>
</table>

Listed in decreasing order of relative importance. Adapted from references 2, 4.
Empiric therapy is guided by targeting likely organisms and the hospital’s antibiogram for nosocomial organisms. It is NOT recommended that organ transplant patients be treated presumptively for multi-drug resistant organisms (MDROs) unless evidence exists that one might be present. (8)

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.

**Hematopoietic Cell Transplant Patients**

Hematopoietic cell transplantation (HCT) is used to treat nonmalignant diseases that affect bone marrow function (e.g., aplastic anemia, myelodysplastic syndromes, immunodeficiency syndromes [severe combined immunodeficiency, chronic granulomatous disease], genetic diseases [mucopolysaccharidoses, glycogen storage diseases], hemoglobinopathies) and neoplastic diseases (e.g., acute or chronic leukemia, lymphomas, multiple myeloma, myeloproliferative diseases). Hematopoietic cells can be harvested from the bone marrow, peripheral blood, or umbilical cord blood. (10) Possible sources for these cells include the patient’s own cells (autologous), an identical twin (syngeneic, HLA identical), a sibling, related, or unrelated donor (allogeneic, HLA identical, haploidentical, or mismatched), or umbilical cord blood (HLA identical, haploidentical, or mismatched). Despite advances in transplantation methods and antimicrobial therapies, infection is the primary cause of death in 8% of autologous HCT patients and 20% of allogeneic HCT recipients. (9)

The risk of infection depends on interplay between these three factors:

1. The intensity of exposure to and the relative virulence of the offending microorganisms
2. The patient’s net state of immunosuppression (see the “Solid Organ Transplant Patients” section above)
3. The presence of tissue and/or organ damage (e.g., mucositis, renal failure, lung damage) and/or the use of central venous catheters (CVCs)

This risk decreases with immune reconstitution (faster in autologous HCT compared with allogeneic).

Infectious complications of HCT are divided into 3 time-frames: pre-engraftment (0 to ~30 days), early post-engraftment (engraftment to 100 days), late post-engraftment (> 100 days) (Figure 1).
For the definition and management of neutropenia, please refer to the “Cancer Patients” section below. Otherwise, the overall approach to the management of an infection is similar to organ transplant patients.

**Patients with HIV/AIDS**

CD4 counts > 200 cells/μL generally indicate immunocompetency and the patient may be treated in the normal fashion. Counts less than 200 cells/μL may require prophylactic therapy for opportunistic infections. Opportunistic infections such as PCP, toxoplasmosis, and Cryptosporidium 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 preferred 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.

**Patients with Autoimmune Disorders**

Patients with autoimmune disorders such as SLE, rheumatoid arthritis, ANCA vasculitis, Crohn’s disease, ulcerative colitis, or psoriasis are often on immunosuppressive agents that generally include steroid therapy, 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 for use of 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**

Neutropenia, a decrease in the absolute number of neutrophils in the blood, is common in oncology patients. Certain malignancies, including leukemia, myelodysplastic syndrome, and Hodgkin’s and non-Hodgkin’s lymphoma, can cause bone marrow destruction and decreased neutrophil production. Most commonly, neutropenia in cancer patients is related to chemotherapy and radiation. Both therapies are cytotoxic and can cause bone marrow suppression. (5)

Neutropenia is defined by the absolute neutrophil count (ANC), which can be calculated by multiplying the total white blood cell (WBC) count by the percentage of polymorphonuclear cells and bands. Mild, moderate, and profound neutropenia are defined as ANC < 1500, < 1000, and < 500 cells/mL, respectively. The fever threshold for neutropenic patients is lower than for healthy patients, as they frequently are unable to mount robust immune responses. A single oral temperature greater than 38.3°C (101°F) or a sustained temperature greater than 38.0°C (100.4°F) for more than one hour constitutes a fever. (5) Neutropenic patients can be risk-stratified according to degree and duration of neutropenia. Patients with severe neutropenia, downtrending ANCs, and prolonged immunosuppression (longer than seven days) are at the highest risk for infection and sepsis.

Infection prevention in neutropenic patients is critical in the intensive care unit. Hand hygiene is the most important step in preventing in-hospital transmission of infectious diseases. Measures should be taken to avoid exposure of neutropenic patients to opportunistic pathogens. For example, plants and flowers, which may carry molds, should not be brought into rooms of immunosuppressed patients. “Neutropenic diets” consist of well-cooked meats and well-washed fruits and vegetables. It is recommended that stem cell transplant patients be placed in single-patient rooms. (3)

Management of neutropenic fever requires rapid diagnosis and
treatment. Please refer to “Infection and sepsis” section below. It is important to note, however, that not all fevers in cancer patients are infectious in etiology. Constitutional symptoms, such as fever, may be caused by malignancy. New metastases should be included in the differential diagnosis of symptoms such as altered mental status or end-organ dysfunction.

**Additional Causes of Immunosuppression**

Additional causes of immunosuppression in critically ill patients include:

1. Blood transfusion
2. Drug therapy (especially typical antipsychotics, procainamide, steroids, non-steroidal anti-inflammatory drugs, anti-thyroid medications)
3. Chronic alcohol and drug use
4. Extracorporeal circulation (ECMO, CRRT, VAD)
5. End stage renal disease
6. Liver failure
7. Trauma, burns and major surgery
8. Splenectomy, common in patients with sickle cell disease
9. Congenital disorders of the immune system, unlikely to present de novo in adults

**Presentation of Infection and Sepsis in the Immunocompromised Patient**

Typical signs and symptoms of infection, such as high fever and leukocytosis, may not be seen in an immunocompromised patient. Therefore, intensive care physicians must maintain a high index of suspicion for infection whenever there is a change in a patient’s clinical status. The first observable signs of infection and sepsis may be changes in end-organ function and may present as leukopenia, hypothermia, thrombocytopenia, new arrhythmia, altered mental status, acidosis, supranormal SvO$_2$, or hyperglycemia.

Presentation of the common surgical diseases (e.g cholecystitis, appendicitis, diverticulitis) may be altered in the setting of immunosuppression. Specifically lack of typical degree of abdominal pain or tenderness is possible in the immunosuppressed patient. Also adequate response to standard antibiotic regimens or resolution of intraabdominal abscesses may not be obtained with antibiotic therapy and may require further interventions for adequate source control.

Swift diagnosis and treatment of these patients is crucial. Initial resuscitation with crystalloid is required in the setting of capillary leak and third space losses. Resuscitation typically is titrated to achieve a MAP > 65 mmHg and UOP > 0.5 cc/kg/hr, with additional goals determined by clinical scenario. Diagnosis of sepsis requires prompt cultures of blood and any other suspected
bodily fluid, including respiratory secretions, urine, wound drainage, or cerebrospinal fluid. It is critical to initiate broad-spectrum antibiotics as soon as possible, ideally within 60 minutes of a suspected diagnosis of sepsis. (1)

Mortality in neutropenic patients with severe sepsis or septic shock is decreasing, but remains high. Predictors of hospital mortality include old age, use of vasopressors, neurologic, respiratory, or hepatic dysfunction, acute noninfectious conditions. Conversely, predictors of lower mortality include combination antibiotic therapy including an aminoglycoside and early removal of indwelling catheters. (7)

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 (MDROs). When indicated, rapid administration of broad-spectrum antibiotics remains critical.

Selection of antibiotics should be as narrow as possible while covering all likely sources of infection. It is important to consider the patient’s infection history, previous antibiotic exposures, local microbe prevalence and resistance patterns, and mechanism and timing of immunosuppression. As microbiology results become available, therapy should be narrowed or discontinued. In severely immunosuppressed patients, it is reasonable to include empiric viral and fungal coverage.

Case Resolution:

This patient’s management was extremely difficult due to multiple confounding factors including mixed shock states, immunosuppression, and delayed recognition of signs and symptoms of SIRS/sepsis on the floor in an immunocompromised patient. Her temperature was the only firm sign of incipient septic shock. Central access was quickly established, vasopressors were initiated, she was cultured, and broad-spectrum antibiotics, antivirals and antifungals were promptly administered. However, the patient progressed to fulminant septic shock and multi-organ failure within hours and died.

This chapter is a revision of the prior chapter authored by Mark Caridi-Scheible MD, Christopher Paciullo PharmD, Joel Zivot MD.

References:


Review Questions:

1. A 45 year-old woman with colon cancer currently receiving chemotherapy has an absolute neutrophil count of < 500 cells/mL and an oral temperature of 38.3° C. The next best course of action is:
   a. Continue to monitor vital signs, urine output, and mental status
   b. Pan-culture the patient and wait for positive cultures to start antibiotics
   c. Pan-culture the patient and initiate broad-spectrum antibiotics
   d. Initiate sulfamethoxazole/trimethoprim prophylaxis
2. A 25 year-old man with HIV on HAART with a CD4 count of 379 cells/µL presents with small bowel obstruction and is to be kept NPO. The next best course of action is:

a. Pan-culture the patient and begin broad-spectrum antibiotics

b. Discontinue all HAART medications

c. Administer AZT intravenously

d. Begin sulfamethoxazole/trimethoprim prophylaxis

3. An 72 year-old man with a history of liver transplantation and recent failure to thrive presents with altered mental status, poor urine output, oral temperature of 36.4 °C, and white blood cell count 3.5 x 10^9/L. The next best course of action is:

a. Bolus fluid and continue to monitor

b. Give lactulose and rifaximin, pan-culture the patient and continue to monitor

c. Pan-culture the patient and begin broad-spectrum antibiotics within one hour

d. Obtain an infectious disease consult
Fever/Hyperthermia

Definition and Measurement of Fever:

While numerous definitions of fever have been published, the most widely accepted is a temperature $\geq 38.3^\circ C (101^\circ F)$ or $\geq 38.0^\circ C (100.4^\circ F)$ in immunocompromised patients. The gold standard for measurement of core temperature is via a pulmonary artery (PA) catheter; however, other accurate measurements can be obtained from the esophagus and bladder. Less accurate methods are rectal, oral, and tympanic membrane, in that specific order. It is not...

Key Points:

- Only 50% of fevers in the ICU are infectious in nature.
- It is not necessary to pan-culture, order “rainbow” labs, or treat every fever.
- Reconsider using antipyretics.
- Avoid using cooling blankets.
- Hypothermia can have profound complications in ICU patients and it is important to understand these conditions and how they affect our ICU patients.

Patient Case:

A 50 year-old woman is admitted to the Surgical Intensive Care Unit after undergoing a cytoreductive procedure with hyperthermic intraperitoneal chemotherapy using mitomycin for ovarian carcinoma. Later that night, you receive a phone call from the nurse stating the patient is now febrile with a core temperature of 38.4°C (101.1°F). The rest of her vital signs are: BP 130/70, HR 90, and oxygen saturation 99% on a FiO$_2$ of 0.4 via the mechanical ventilator. Laboratory values upon the patient’s arrival were unremarkable. The nurse asks if you would like to pan-culture the patient, start empiric antibiotics, write an order for acetaminophen and start cooling the patient.
recommended to measure axillary and temporal temperatures, and it is important to note that the same site must be used consistently to ensure accurate trends.

Sources of Fever:

Fever can be due to infection, a noninfectious cause, drugs, or other miscellaneous etiologies.

It is important to note though that only half of all ICU fevers are due to an infectious cause. The most common infectious causes of fever are pneumonia, urinary tract infection, surgical site infection, catheter related infection, bacteremia, and sinusitis.

The list of noninfectious etiologies of fever is more extensive and requires further workup. More common causes include: SIRS (as a result of ischemia, major surgery, inflammatory cytokine translocation), postoperative fever (of note, atelectasis does not cause fever), drugs, pulmonary embolism (PE), or transfusions. Less common are: thyrotoxicosis, adrenal insufficiency/crisis, acalculous cholecystitis, pancreatitis, iatrogenic fevers (e.g.: from warming blankets or water mattress), adult respiratory distress syndrome (ARDS), burns, drug overdose, drug withdrawal, gout, intracranial hemorrhage (ICH), malignancy, myocardial infarction (MI), pheochromocytoma, seizures, and vasculitis. In addition, there are hyperthermic conditions that will be discussed: malignant hyperthermia (MH), neuroleptic malignant syndrome (NMS), and serotonin syndrome (SS).

Many drugs are associated with fevers. These can occur immediately or even weeks after taking the medication, and are typically a diagnosis of exclusion. Drug fever is most common with amphotericin, cephalosporins, penicillins, phenytoin, procainamide, and quinidine. Some less common offenders include: cimetidine, carbamazepine, hydralazine, rifampin, streptokinase, and vancomycin.

Management of Fever (Workup, Treatment)

Do We Need to Treat?

The management of infection-related fevers is covered elsewhere. (see Chapter 9.2) Of note, empiric antibiotics should only be started if there is a high likelihood of an infectious etiology. Some general guidelines to follow for when to start antibiotics empirically after culturing the patient are: clinical deterioration, shock, neutropenia, the need for a ventricular assist device, or generally a temperature >38.9°C (102°F), as the likelihood of infection is high at these temperatures.

Whether to treat with antipyretics or external cooling devices is a commonly discussed topic in the ICU. Previous arguments have been made that fever increases mortality, length of stay, and cost of care – however, there have been numerous studies that have refuted this claim. Fever is a normal adaptive response by the body and enhances immune function. Treatment with antipyretics is associated with higher mortality rates in septic patients and has
been proven to worsen outcomes in sepsis. Cooling blankets exacerbate cutaneous vasoconstriction and increased muscle activity and are thus inappropriate in management of a fever, although their use has some validity in hyperthermic syndromes where the patient’s thermoregulatory system is not properly functioning. There are several ongoing randomized controlled trials further investigating the treatment of fever, but until those results are published, it is widely accepted that there is no role for antipyretics or external cooling devices in patients not exhibiting increased intracranial pressure or hyperthermia.

**Hyperthermia (Conditions, Management, Complications)**

Hyperthermia is a defect in thermoregulation, as opposed to a fever where the thermoregulatory system is intact. With normal body response, blood flow is increased to the skin (convection), and sweating (evaporation) is increased in order to compensate for the increased thermal stress. Heat related illness occurs when this response is overwhelmed. Conditions that predispose patients to this injury include cocaine use (secondary to generalized sympathetic activation), use of beta blockers (due to decreased sweat gland production), treatment with diuretics, hypokalemia, and use of barbiturates.

In **heat exhaustion**, the patient’s temperature will be < 39°C. They will commonly present with flu-like symptoms, and the most important management in these patients is volume repletion and supportive measures.

Comparatively, **heat stroke** occurs in patients whose temperature is > 41°C, or > 40.6°C with altered mental status. Patients with heat stroke present with severe CNS dysfunction, minimal sweating, multiorgan involvement, and hypotension from volume depletion. The condition can progress to rhabdomyolysis, acute kidney injury, and even disseminated intravascular coagulation (DIC). Other complications include: hepatocellular injury (due to direct toxic effect on hepatocytes), ARDS, electrolyte abnormalities (due to renal failure), and dehydration. Susceptible patients are the elderly, alcoholics, and otherwise debilitated patients.

**Management of Hyperthermia:**

The duration of hyperpyrexia is the most reliable predictor of morbidity and mortality. Therefore, it is imperative to begin cooling and resuscitating the patient immediately. Cooling can be performed externally via ice packs, cooling blankets, or via evaporative methods (cool spray followed by fanning). On rare occasions, internal cooling can be facilitated with intravascular cooling, or lavaging of the stomach, bladder, or rectum for a more rapid response. It is important to note, however, that shivering is detrimental and occurs when skin temperature drops below 30°C (86°F).

**Hyperthermic Syndromes:**

1) **Malignant Hyperthermia (MH):**
Occurs in 1 in 15,000 patients after exposure to a halogenated volatile anesthetic or succinylcholine, and is the result of an autosomal dominant inherited mutation in the ryanodine type 1 receptor. This causes an increased release of calcium from the sarcoplasmic reticulum in skeletal muscles, leading to an uncoupling of oxidative phosphorylation. The presenting triad is hyperthermia, muscle rigidity, and a combined respiratory and metabolic acidosis. After the acute event resolves, diagnosis of MH can be confirmed by obtaining a muscle biopsy, which is then exposed to a single dose of 3% halothane followed by increasing doses of caffeine. Muscle fiber contractures are increased in susceptible patients. Genetic testing is also available, however not all genes have been identified, so a negative genetic test does not rule out MH definitively. Thus, the muscle contracture test remains the gold standard for diagnosis.

As in all hyperthermic syndromes, the initial treatment is discontinuation of the offending agent. This is followed by the administration of dantrolene (a muscle relaxant that blocks the release of calcium) with a 1-2 mg/kg bolus, which is repeated every fifteen minutes to a total of 10mg/kg, and then 1mg/kg IV or 2mg/kg PO QID for three days. Late recurrences may occur in cases of inadequate treatment. It is important to avoid diltiazem and verapamil, as these may cause hyperkalemia as a result of the interaction with dantrolene. The most common side effect of dantrolene is muscle weakness, however the most concerning is hepatocellular injury – and it is therefore contraindicated in patients with active hepatitis or cirrhosis.

2) Neuroleptic Malignant Syndrome (NMS):

Occurs due to a reaction to certain medications that results in hyperthermia, muscle rigidity, altered mental status, and autonomic instability. It occurs in 2-3% of patients receiving neuroleptic medications and typically presents within the first few days, and almost always within the first month of initial exposure. The most common offending agents are haloperidol and fluphenazine, but other antipsychotic medications, antiemetics, CNS stimulants, or the discontinuation of dopaminergic drugs can lead to this phenomenon. Its mechanism is postulated to be due to a decrease in dopaminergic transmission in the basal ganglia and hypothalamic-pituitary axis. Treatment involves stopping the offending medication or restarting the dopaminergic drug. Additionally, dantrolene and bromocriptine may be used for severe cases.

3) Serotonin Syndrome (SS):

Occurs as a result of an overstimulation of serotonin receptors, whether due to an increased production or decreased breakdown of serotonin. These patients present with a combination of altered mental status, autonomic hyperactivity, hyperthermia and neuromuscular abnormalities. The most common offending agents are mood enhancers and SSRIs, although numerous
medications have been implicated with this condition. The onset is usually fairly abrupt and is treated by discontinuation of the offending agent, controlling the agitation and hyperthermia, and the use of serotonin antagonists (such as cyproheptadine).

**Hypothermia (Management, Complications)**

Hypothermia is defined as a core temperature < 35°C (95°F). Mild hypothermia ranges from 32-35°C (90-95°F), moderate from 28-32°C (82-90°F), and severe < 28°C (82°F). Most standard thermometers are inaccurate below 34°C (94°F) and bladder, rectal, or esophageal measurements are thus considered more accurate. The majority of heat loss occurs via radiation, followed by evaporation, and subsequently conduction and convection. The body responds to decreased body temperatures by hypothalamic-mediated responses that include peripheral vasoconstriction and reduced heat conduction to the skin. Heat is subsequently produced via shivering, which increases basal metabolic rate by 2-5 times the normal rate, as well as nonshivering thermogenesis, which increases levels of catecholamines and thyroxine. This response only lasts for several hours, at which point muscle fatigue occurs and glycogen becomes depleted. Below 32°C, the responses slow down and eventually stop – and below 24°C, the responses fail altogether.

The process is related to impaired thermoregulation, increased heat loss, decreased heat production, or a combination thereof. Impaired thermoregulation occurs in both the elderly and chronic medical patients (specifically those who have had a stroke, multiple sclerosis, diabetes mellitus, or Parkinson’s disease). Certain medications can also be responsible, such as beta blockers, anxiolytics, or antidepressants. Increased heat loss occurs in patients with burns, psoriasis, those receiving cold intravenous fluids and products, and several other conditions (sepsis, residual anesthesia, and alcohol use). Finally, decreased heat production can be present in the setting of malnutrition and starvation, endocrine disorders (hypopituitary, hypothyroid, hypoglycemia, hypoadrenalism), or an inhibited shivering response (TCAs and alcohol).

There are serious complications associated with hypothermia that occur along a continuum as temperature drops. Complications involve every system. Neurologically, patients can have decreased consciousness, loss of cerebrovascular autoregulation, and loss of reflexes. Cardiovascularly, patients can have bradycardia/tachycardia, hypertension, increased oxygen consumption, acidosis, myocardial irritability, and lethal arrhythmias. The kidneys exhibit an initial increase in renal blood flow, followed by decreased flow and glomerular filtration rate leading to renal failure, and profound intravascular volume depletion. Other side effects include a generalized coagulopathy, ileus, and decreased hepatic function.

**Management of Hypothermia:**

Because patients with hypothermia have a propensity to
experience chest wall rigidity and inadequate ventilation and oxygenation, it is important to monitor their airway and breathing. Continuous cardiac monitoring and core temperature monitoring are imperative.

It is also paramount to immediately begin volume repletion with warmed intravenous fluids. Cardiopulmonary resuscitation in these patients is more complicated as the hypothermic heart may not be as responsive to cardiac medications, electric pacing and defibrillation. Antiarrhythmics are held until 30°C is reached and then the lowest dose is administrated due to decreased metabolism. At 35°C, normal drug protocols may be utilized.

As with cooling, rewarming can be facilitated externally or internally. External warming follows the same principles as with a patient in the operating room. Warm blankets, warming the environment, heating pads, and radiant energy can be utilized. Internal warming is only performed in severe cases and can be achieved by increasing the temperature and humidity of air via a mask or ETT, peritoneal or pleural lavage, extracorporeal blood warming (hemodialysis, CPB, ECMO), or via warmed intravenous fluids. Careful attention during the process is imperative, as rewarming shock may occur in which patients experience hypotension due to hypovolemia, myocardial depression, and vasodilation. Additionally, “afterdrop” may also occur as a result of cold, acidic blood returning from the periphery to the core, which causes a decrease in core temperature. This serves to worsen acidemia and can lead to hypotension and fatal arrhythmias. Ventricular fibrillation is possible from central displacement. Warming the trunk prior to the extremities has been postulated as a method to help avoid some of these responses.

References:


**Review Questions:**

1. Which of the following is the most significant mechanism of heat loss in a patient:
   a. Radiation
   b. Convection
   c. Conduction
   d. Evaporation

2. Which of the following is NOT a complication of hypothermia:
   a. Platelet dysfunction
   b. Altered drug metabolism
   c. Increased MAC requirements
   d. Wound infections

3. Which of the following disease processes is MOST associated with malignant hyperthermia:
   a. Duchenne Muscular Dystrophy
   b. Central Core Disease
   c. Becker’s Muscular Dystrophy
   d. Neuroleptic Malignant Syndrome

4. Which of the following is the most appropriate action in an ICU patient with a new onset fever:
   a. Pan-culture
b. Treat the fever with anti-pyretics

c. Start empiric antibiotics

d. Evaluate the patient and consider the clinical picture
Chapter 10

Miscellaneous Topics
Hyperglycemia: The presence of hyperglycemia in the ICU is not limited to patients with a history of type I or type II diabetes. Serum glucose can be profoundly elevated in most critically ill patients, but especially in patients suffering from strokes, MI or post-cardiac surgery. Hyperglycemia predisposes patients to adverse outcomes in the ICU: 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

Patient Case:
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), febrile (39 °C), 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 his clinical condition, the patient is started on hydrocortisone 100 mg IV every 8 hrs.

Key Points:

- Tight glucose control has an increased rate of hypoglycemic events and mortality. A more liberal strategy with goal glucose levels below 180 mg/dL better balances glucose control while avoiding dangerous hypoglycemia.
- Evaluating the HPA axis in critically ill patients can be diagnostically challenging. Stress dose steroids are more commonly administered in response to refractory shock than a laboratory value such as random cortisol or response to corticotropin.
- The most common thyroid related illness in critically ill patients is non-thyroidal illness syndrome (NTIS) with low T3 and low/normal TSH.

Hyperglycemia: The presence of hyperglycemia in the ICU is not limited to patients with a history of type I or type II diabetes. Serum glucose can be profoundly elevated in most critically ill patients, but especially in patients suffering from strokes, MI or post-cardiac surgery. Hyperglycemia predisposes patients to adverse outcomes in the ICU: 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 has been attributed to the increased frequency of hypoglycemic events leading to an increased sympathetic response. (1,2) A less intensive blood glucose lowering strategy with targeted levels below 180 mg/dL, appears to be a more appropriate approach to controlling hyperglycemia and significantly decreases the episodes of hypoglycemia.

**DKA:**

Diabetic ketoacidosis (DKA) occurs mainly in the setting of type I diabetes mellitus. A combination of hyperglycemia, inadequate insulin supply and lipolysis results in the production of ketones and an anion gap metabolic acidosis (AGMA). DKA is usually precipitated by poor patient compliance (20-40%) or a physiologic stressor: infection (30-50%), surgery, MI (3-6%) or other diseases (<2%). These states increase 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; lipolysis results with an increase in blood ketones. DKA is diagnosed by the presence of hyperglycemia (plasma glucose >250 mg/dL), AGMA (pH <7.3, AG > 12) and presence of ketones.

Patients present with severe dehydration and electrolyte abnormalities secondary to glucosuria and an osmotic diuresis. Goals of treatment are to decrease glucose levels with insulin (bolus + infusion), replace the volume deficit with crystalloid solutions (5-10L), and correct electrolyte abnormalities. Potassium should be corrected if low levels are present before the initiation of an insulin infusion to avoid severe hypokalemia. After the blood glucose is <250 mg/dL, dextrose should be added to the fluid replacement and insulin continued until the anion gap has closed (indicating clearance of ketones). The administration of sodium bicarbonate is usually unnecessary to correct the low pH. Resolution of the AGMA will occur with the administration of insulin as the body metabolizes the ketones and creates bicarbonate. (3) The American Diabetes Associations has published protocols for DKA treatment. Cerebral edema is a rare, but potentially fatal complication of treatment for DKA that results from overaggressive resuscitation leading to fluid shifts in the CNS.

**HHS:**

Hyperosmolar hyperglycemic state (HHS) is characterized by severe hyperglycemia leading to increased plasma osmolality, which results in the shift of intracellular water into the intravascular space. Glucosuria and an osmotic diuresis lead to significant dehydration. As in DKA, a stressor and poor compliance usually precipitate HHS; however mortality is
significantly higher than for DKA. Plasma osmolality is typically >350 mOsm/L and can be as high as 400 mOsm/L from marked hyperglycemia (>600 mg/dL). 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. HHS is often not associated with the presence of a metabolic acidosis but patients with profound hypovolemia may develop a lactic acidosis secondary to tissue hypoperfusion. The presence of an AGMA and weakly positive ketones may confuse the diagnosis with DKA. 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 with subsequent clinical manifestations. Graves’ disease, toxic nodular goiter, paraneoplastic syndromes or excessive exogenous intake of thyroid hormone are among the common causes. Clinical symptoms are the direct result of increased metabolism and include pyrexia, delirium, seizures, arrhythmias (sinus tachycardia and atrial fibrillation), 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 disease. This diagnosis 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 and the index of suspicion is high, empiric therapy should be started before laboratory confirmation. 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 as iodine can cause a release of pre-formed thyroid hormone and worsen the disease. Non-specific beta-blockers also decrease peripheral conversion of T4 to T3 and help mediate the cardiovascular manifestations of hyperthyroidism. 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:**
The most commonly encountered thyroid illness in the ICU is Non-Thyroidal Illness Syndrome (NTIS) - also known as euthyroid sick syndrome or low T3 syndrome. It is characterized in critically ill patients with low T3, low/normal T4, high/normal rT3, and low/normal TSH. While previously thought to represent an euthyroid state, current evidence suggests the presence of hypothyroidism at the cellular level. The mechanism of decreased T3 is unclear, but may be mediated by inflammatory markers, lack of nutrients (adaptive fasting response to reduce energy expenditure during illness) or from medications such as dopamine, glucocorticoids, amiodarone and propranolol. Patients who present with NTIS have a higher mortality than those who do not have thyroid abnormalities. Treatment of NTIS remains controversial as it may increase metabolic demand during critical illness and could worsen outcomes. As patients move towards the chronic phase of critical illness, T4 levels also begin to decline, resembling central hypothyroidism. Patients with a significantly decreased rT3 should be suspected of having clinical hypothyroidism and may warrant treatment with levothyroxine.

Myxedema Coma: A clinical syndrome of severe hypothyroidism characterized by mental status changes and hypothermia, substantiated by laboratory findings of elevated serum TSH and low free/total T4. Hemodynamic and respiratory compromise may also be seen. If suspected, treatment with parenteral thyroid replacement (T3, T4 or combination) should not be delayed for confirmatory testing. Concurrent adrenal insufficiency may be present; a cortisol level should be obtained with initial labs and treatment started with hydrocortisone until adrenal insufficiency is ruled out. Additional supportive care includes cardiac monitoring, electrolyte replacement (hyponatremia), glucose management, empiric antibiotics, passive rewarming, volume expansion, vasopressors, mechanical ventilation and identification of precipitating causes.

Adrenal Insufficiency:

Cortisol is a glucocorticoid that mediates many important functions in the critically ill: immunity (cellular and cytokines), 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 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. This 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 vasoplegic shock, the overall cardiac output in these
patients may be elevated, normal or reduced.

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. In addition to clinical presentation, two tests, a random cortisol level and the corticotropin stimulation test can help establish the diagnosis. A random cortisol level should be greater than 10-15 mcg/dL. Cortisol levels below this threshold are highly suggestive of adrenal insufficiency when clinical signs are present. Levels between 15-25 mcg/dL for patients without septic shock and 15-34 mcg/dL for patients in septic shock may indicate adrenal insufficiency and should be further evaluated by a corticotropin stimulation test. Patients not in septic shock with levels greater than >25 mcg/dL and patients in septic shock with levels >34 mcg/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 begin by drawing a baseline serum cortisol level and then giving a dose of corticotropin. In the high-dose ACTH test, 250 mcg of corticotropin is given and in the low-dose ACTH test, only 1 mcg. Cortisol levels are measured at 30 and 60 minutes after giving the corticotropin and the increase in serum cortisol should be >9 mcg/dL or a final level >18 mcg/dL. Lack of cortisol response suggests the patient may benefit from supplemental steroids. Because of the nuances of performing a test that will yield accurate results and uncertainty when interpreting results, most physicians will choose to treat empirically with steroids and evaluate for clinical improvement rather than using a corticotropin stimulation test to evaluate for adrenal insufficiency.

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 in septic shock that suggested a decreased mortality and faster reversal of shock when treating patients with hydrocortisone and fludrocortisone. (6) However, in 2007, CORTICUS suggested that there was no improvement in mortality despite a faster reversal of shock in the steroid group. (7) Even patients that were thought to be adrenally insufficient based on random cortisol and corticotropin stimulation testing showed no improvement in mortality with steroids.

After the CORTICUS trial, treatment of septic shock with hydrocortisone fell out of favor. The Surviving Sepsis Campaign limits its recommendation for steroid use to those patients that have shock refractory to intravascular volume repletion and vasopressors. (8) Common stress dose steroid dosing regimen is hydrocortisone 50-100 mg IV q6-8hrs or a bolus of 100 mg IV and then an infusion of 10 mg/h for a total dose between 200 mg/day.
When steroids are used they should be tapered as soon as there is clinical improvement. Common side effects of steroid therapy in the ICU include hyperglycemia and hypernatremia. The role of steroids in the development of infections and critical illness myopathy is not entirely clear. (9)

Certain medications can decrease cortisol production, most notably etomidate. Etomidate suppresses the function of 11-\(\beta\)-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. (10)

References:


Review Questions:
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

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. Supportive care
   d. Methimazole

3. A patient in refractory septic shock was started on hydrocortisone 100 mg 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 steroids
   c. Perform a corticotropin stimulation test
   d. Change the hydrocortisone to a continuous infusion
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, overdoses, or withdrawal syndromes. Additionally, toxic reactions to commonly encountered plants and animals can also produce life-threatening reactions. Occasionally, some patients in the ICU, and even the OR,

Patient Case:
A 28 year old man presented to the emergency department at 0200 accompanied by his girlfriend who found him foaming at the mouth, acting belligerent and paranoid, and hallucinating. When you see him, he is speaking incoherently and unable to maintain a conversation. He is alert but not oriented, tremulous, and unable to hold still. Vital signs are HR 142 bpm, temp 39°C, RR 34, SpO₂ 99% on RA. Collateral history includes a past medical history of asthma not using an inhaler, depression on paroxetine, past suicide attempt, and poly-substance abuse including alcohol, tobacco, and “other stuff” per the girlfriend. She found a packet of white powder in their living room before coming to the emergency department. What do you think this patient took? How would you manage him?
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 assuring 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 a summary 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.

**Toxidromes**

Many types of poisonings or ingestions fall into similar categories based on their symptomatology. Classically these categories are designated opioid, sedative hypnotic, antimuscarinic, cholinergic, and sympathomimetic. More recent categories also include neuroleptic malignant syndrome, serotonin syndrome, and sedative withdrawal (which can look very similar to sympathomimetic). The general presentation for each category can be seen in Table 1. In general, poisonings and overdoses should all be managed similarly at first with assessment of the patient’s airway, breathing, circulatory symptoms, and neurologic status. Rapid actions for decreased mental status can initially include glucose testing and naloxone or flumazenil administration if the history or exam suggests opioid or sedative hypnotic overdose, respectively. Close attention should be paid to co-administering thiamine in alcoholics, although the administration of glucose should not be stalled in order to obtain thiamine. Vital signs and further laboratory tests including analysis of acid base status, osmolar gap, and toxicology studies should be conducted. Prevention of further absorption and enhanced elimination are controversial and discussed below.

**Toxicology and Laboratory Studies**

Urine drug screens are commonly collected for poisoning and overdose victims. However, it should be noted that these screening tests only demonstrate whether the patient took these medications in the past and does not give a quantitative value for current exposure or necessarily correlate with current intoxication. Because these tests are constantly being challenged by the plethora of new drugs being ingested, they can produce a lot of false negatives. Serum drug levels are available for certain medications and toxins. Ones that may be especially useful include acetaminophen, digoxin, lithium, phenytoin, salicylates, and toxic alcohols.

Anion gap and osmolar gap can further help differentiate the differential diagnosis in a poisoning or overdose patient. The
<table>
<thead>
<tr>
<th>Toxin</th>
<th>T</th>
<th>BP</th>
<th>HR</th>
<th>RR</th>
<th>Mental Status</th>
<th>Pupils</th>
<th>Mucous Membrane/Skin</th>
<th>Bowel Sounds</th>
<th>Reflexes</th>
<th>Sensitive Signs</th>
<th>Common Drugs</th>
<th>Antidote</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinergic</td>
<td>†</td>
<td>†</td>
<td>†</td>
<td>†</td>
<td>Delirium</td>
<td>†</td>
<td>Dry</td>
<td>†</td>
<td>†</td>
<td>mydriasis, dry flushed skin, delirium, hyperthermia, tachycardia, urinary retention, and hypoactive bowel sounds</td>
<td>tricyclic antidepressants, antihistamines, antipsychotics, and cyclobenzaprine</td>
<td>atropine, pralidoxime</td>
</tr>
<tr>
<td>Cholinergic</td>
<td>†</td>
<td>†</td>
<td>†</td>
<td>†</td>
<td>Variable</td>
<td>† ⊥</td>
<td>Wet</td>
<td>† †</td>
<td>† ⊥</td>
<td>lacrimation, salivation, bronchorrhea, and urinary and fecal incontinence</td>
<td>organophosphate, edrophonium or physostigmine</td>
<td>dantrolene</td>
</tr>
<tr>
<td>NMS</td>
<td>†</td>
<td>†</td>
<td>†</td>
<td>†</td>
<td>Variable</td>
<td>† ⊥</td>
<td>Moist/diaphoretic</td>
<td>† ⊥</td>
<td>† ⊥</td>
<td>&quot;lead-pipe&quot; rigidity</td>
<td></td>
<td>flumazenil (can precipitate seizure in long term users of sedative hypnotics)</td>
</tr>
<tr>
<td>Opioid</td>
<td>⊥</td>
<td>⊥</td>
<td>⊥</td>
<td>⊥</td>
<td>Depression</td>
<td>⊥ ⊥</td>
<td>...</td>
<td>⊥</td>
<td>⊥ ⊥</td>
<td>hypoventilation miosis</td>
<td>morphine, codeine, hydromorphone, fentanyl, heroin</td>
<td>naloxone</td>
</tr>
<tr>
<td>Sedative-hypnotic</td>
<td>⊥</td>
<td>⊥</td>
<td>⊥</td>
<td>⊥</td>
<td>Depression</td>
<td>⊥ ⊥</td>
<td>...</td>
<td>⊥</td>
<td>⊥ ⊥</td>
<td></td>
<td>benzodiazepines, barbiturates, carisoprodol, chloral hydrate, ethanol, and baclofen</td>
<td>flumazenil (can precipitate seizure in long term users of sedative hypnotics)</td>
</tr>
<tr>
<td>Sedative withdrawal</td>
<td>†</td>
<td>†</td>
<td>†</td>
<td>†</td>
<td>Moist/diaphoretic</td>
<td>†</td>
<td>†</td>
<td>†</td>
<td>†</td>
<td>agitation, delirium tremens, abnormal neuromuscular activity and autonomic hyperactivity</td>
<td>benzodiazepines, dexmedetomidine</td>
<td></td>
</tr>
<tr>
<td>Serotonin syndrome</td>
<td>⊥</td>
<td>⊥</td>
<td>⊥</td>
<td>⊥</td>
<td>Variable</td>
<td>† ⊥</td>
<td>Moist/diaphoretic</td>
<td>† ⊥</td>
<td>†</td>
<td>hyperthermia, myoclonus, muscle rigidity, opsoclonus, agitation</td>
<td>proserotonergic medications</td>
<td></td>
</tr>
<tr>
<td>Sympathomimetic</td>
<td>⊥</td>
<td>⊥</td>
<td>⊥</td>
<td>⊥</td>
<td>Moist/diaphoretic</td>
<td>†</td>
<td>†</td>
<td>†</td>
<td>†</td>
<td>agitation, hyperthermia, hypertension, increased CNS activity</td>
<td>cocaine, methamphetamine, pseudoephedrine, caffeine, methylphenidate, MDMA</td>
<td>may respond to benzodiazepines, dexmedetomidine depending on mechanism of offending agent</td>
</tr>
</tbody>
</table>
normal anion gap (the difference between measured anions and cations in the blood) is 4-12 mEq/L. An elevated gap is usually due to an unmeasured anion such as demonstrated in the acronym MUDPILES:

- **M**: methanol/metformin
- **U**: uremia
- **D**: diabetic ketoacidosis
- **P**: paraldehyde/propylene glycol/propofol
- **I**: iron/isoniazid/ibuprofen
- **L**: lactate
- **E**: ethanol/ethylene glycol
- **S**: salicylates/starvation ketoacidosis

The osmolar gap is the difference between the measured osmolarity and the calculated osmolality as demonstrated in Figure 1. The normal osmolar gap is 4-10 mosmol/L. Larger gaps may be attributable to acetone, ethanol, ethylene glycol, isopropyl alcohol, methanol, and propylene glycol. A small elevated serum osmolar gap can be seen in ketoacidosis and in lactic acidosis.

**GI Decontamination and Enhanced Elimination**

Activated charcoal is the only routinely used method for lowering absorption. Gastric lavage, induced emesis, and scheduled repeated doses of activated charcoal have not been shown to be helpful and are sometimes harmful, given the aspiration risk in patients with an altered sensorium. Whole bowel irrigation may be useful in ingestions that involve extended release tablets and endoscopy is indicated for removal of button batteries. Surgery or endoscopy should be undertaken in the case of illicit drug packet ingestion especially in the case of sympathomimetic drugs ingestions.

Enhanced elimination may be accomplished in a number of ways including hemodialysis and alkalinization of urine. Drugs that are
removed by hemodialysis include salicylates, methanol, ethylene glycol, and lithium, among others. Urine alkalinization improves removal of TCAs, methotrexate, and salicylates.

**Specific Drug Overdose Examples**

To follow will be a concise review of specific drug overdoses and their management. It is by no means a complete list of drugs or complete management plans, but should be representative of common drug overdoses managed in the ICU. Please also refer to Table 1 for general categories of drugs, their overdose presentation, and specific management.

**Acetaminophen**

A common drug used in attempted suicides, acetaminophen toxicity occurs when N-acetyl-p-benzoquinoneimine depletes glutathione stores in the liver; this leads to hepatotoxicity. N-acetylcysteine (NAC) helps regenerate glutathione stores and can reverse this process. The Rumack-Matthew nomogram (Figure 2) describes when to use NAC in the setting of a single large ingestion of acetaminophen. When NAC is given in the first 8 hours after ingestion, fulminant hepatic failure rates drop to almost zero. Because of its favorable safety profile and low risk of administration, some clinicians favor empiric use of NAC in all suspected acetaminophen overdoses as well as other presentations of acute liver failure.

![Figure 10.2.2 Rumack Matthew Nomogram](https://en.wikipedia.org/wiki/Rumack-Matthew_nomogram)
**Cardiovascular Medications**

Calcium channel blockers and beta blockers are common medications prescribed in the US making them not uncommon drugs implicated in intentional or unintentional overdoses. Calcium channel blocker overdose can produce bradycardia, AV blocks, junctional rhythms, hypotension, and hyperglycemia. Management includes BP management with direct acting medications and or calcium infusions, external pacing, CPB, ECMO, or IABP, and glucose management. Beta blocker overdose similarly causes bradycardia, conduction abnormalities and arrhythmia, hypotension and hypoglycemia. Glucagon is the main treatment and blood pressure support may also be necessary.

**Ingestions Affecting Oxygen Carrying and Delivery**

Carbon monoxide, cyanide toxicity, and exposure causing induced hemoglobinopathies demonstrate classic but mechanistically different causes of hypoxia. Carbon monoxide decreases oxygen delivery by binding to Hgb and forming carboxyhemoglobin (COHb) that cannot subsequently bind oxygen. Although the PaO₂ and SpO₂ will not change dramatically, COHb levels will climb. Arterial blood gas analysis with co-oximetry is key for diagnosis and measurement of COHb levels. Management is with 100% FiO₂.

Cyanide (CN) toxicity acts at the level of the mitochondria and inhibits mitochondrial ability to use O₂ and to form ATP. Laboratory findings may not be diagnostic (ie: normal SpO₂, PaO₂, and Hgb saturation, however, SvO₂ may be elevated). A severe anion gap metabolic acidosis with an elevated lactate and high venous oxygen concentration is the hallmark of cyanide poisoning. Management is with sodium nitrite (induces methemoglobinemia which has a higher affinity for CN), sodium thiosulfate (sulfur donor to produce sodium thiocyanate), or hydroxocobalamin (forms cyanocobalamin). All act to create a metabolite that removes CN and increase renal elimination.

Lastly, methemoglobinemia is acquired by exposure to oxidizers which create a ferric ion in Hgb. SpO₂ is often in the high 80% range, while PaO₂ is normal, and measured MetHgb is high. Methylene blue activates reduction of MetHgb.

**References:**


Review Questions:

1. Which of the following is NOT consistent with cyanide toxicity?
   
   a. Metabolic acidosis
   
   b. Tachycardia
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

3. Methanol ingestion leads to a non-anion gap metabolic acidosis.

a. True  
b. False

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. Heroin  
b. Diazepam  
c. Acetaminophen  
d. Nortriptyline

5. Prior to administering glucose to a patient with alcohol intoxication, what drug should be administered?

a. Folate  
b. Magnesium  
c. Thiamine  
d. Clonidine
Introduction

Resuscitation of the injured patient is a topic of ongoing evolution and change. The surgical management of the traumatized patient is governed by the principle of damage control, where normal anatomy is sacrificed to preserve vital physiology. Severely injured patients cannot tolerate prolonged interventions, so the initial surgery is aimed at the minimal necessary stabilization and control of hemorrhage. Effective trauma care mandates a dynamic, systematic focus on evaluation, resuscitation and re-assessment. The Advanced Trauma Life Support

Patient Case:
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°C   HR 119 bpm   BP 100/80 mmHg, SaO₂ 99%   He is placed on volume control ventilation at 16 breaths/minute with FiO₂ 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 (HCO₃ 15). What are your concerns? How would you evaluate and manage the patient? What immediate and delayed complications is he at risk for?
(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 non-operative 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 1 illustrates a typical emergency airway algorithm for trauma patients.

Figure 10.3.1 Emergency Airway Algorithm

- In-line Cervical Stabilization
- Preoxygenation
- Cricoid Pressure

**Induction:** Propofol/ Etomidate/ Ketamine
- **Paralysis:** Succinylcholine/ Rocuronium

- Layngoscopy #1
- **Failure**
- Bougie-Assisted Layngoscopy #2
- **Failure**
- LMA Insertion
- **Failure**
- Cricothyroidotomy
- **To OR for Definitive Airway**

- Capnography Ascultation
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, 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 is 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 altered mental status or agitation. 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). See Table 1.

Table 10.3.1 Standard Glasgow Coma Scale

<table>
<thead>
<tr>
<th>Eye Opening</th>
<th>Best Verbal Response</th>
<th>Best Motor Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Obey Commands</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>Oriented</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>Confused</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>Inappropriate Words</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>Incomprehensible Sounds</td>
<td>2</td>
</tr>
<tr>
<td>1</td>
<td>None</td>
<td>1</td>
</tr>
</tbody>
</table>

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.

Secondary and Tertiary Surveys

The secondary survey involves a head-to-toe examination while continuously reevaluating the progress of resuscitation. A more
through 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) (see Chapter 2.3) 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 laboratory tests is initially drawn from all severely injured trauma patients. In the ICU, any abnormal values should be repeated. A few parameters deserve special attention:

**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. While significantly elevated PT and PTT upon admission herald poor outcome from injury, they do not provide reliable end-points of resuscitation and correction to “normal” values may require large amounts of fluid and FFP and introduce transfusion and volume-related complications. (5)
Although most laboratories utilize a standard coagulation panel, reliable point-of-care hemostatic monitoring are becoming more prevalent in leading trauma centers and the data supporting their use becomes more robust. The two most commonly used viscoelastic technologies, TEG® (thromboelastography) and ROTEM® (thromboelastometry), both provide a rapid assessment of the coagulation status of severely injured patients with the potential for massive bleeding and diffuse coagulopathy. (6,7)

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 (CKD). A serum creatinine level that begins to rise within 48 hours of contrast administration may indicate contrast-induced nephropathy (CIN). The most important risk factor for contrast-induced nephropathy is CKD followed by age and diabetes. It is more common following intra-arterial administration of contrast than after intravenous contrast. The creatinine level typically peaks at approximately 96 hours and then normalizes with supportive care over several weeks.

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 creatinine 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. An anion 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.

Lactic Acid:

Serial lactate levels are recommended for all severely injured trauma patients. Lactate is a marker of anaerobic metabolism and is suggestive of occult hypoperfusion. 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 euvoilema, an aggressive search for a missed injury, liver dysfunction and/or cardiac decompensation must immediately commence. (8) Studies have suggested that using serial lactate levels to guide treatment of critically ill patients may reduce mortality. (9,10)

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

412
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. (11) 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. (12)

To this day, the optimal blood product transfusion ratios in bleeding major trauma patients are not known. Ratios of FFP to RBC of 1:3 have historically been used, but more recent data from military studies supports a ratio more like whole blood (i.e. 1:1:1). The 2015 PROPPR trial randomized 680 severely injured patients to receive plasma:platelets:RBC in a 1:1:1 or 1:1:2 fashion. There was no significant difference in morbidity or mortality between the groups. (13) However, the 1:1:1 group had greater proportion of patients where hemostasis was achieved and a lower mortality due to exsanguination at 24 hours. This significant difference might have been achieved by the early administration of platelets in the 1:1:1 group. Other interesting findings regarding trauma patients and massive transfusion highlighted by the PROPPR trial were a very low rate of transfusion related complications and overall mortality rate. Of those who died, exsanguination and traumatic brain injury were the most common causes.

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. (14) Accordingly, a high index of suspicion coupled with a sensitive diagnostic approach must be used to identify occult injuries.

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.

**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.

**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.

**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.

**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 1<sup>st</sup> and 2<sup>nd</sup> 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.

**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.

**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%).(15)(Table 2)

<table>
<thead>
<tr>
<th>NEXUS Criteria</th>
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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. (16)

**Traumatic Brain Injury**

Once the severely head-injured patient has been transferred to the ICU, the management consists of the provision of high quality general care and various strategies aimed at maintaining hemodynamic stability and hemostasis. These include stabilization of the patient, prevention of intracranial hypertension, maintenance of an adequate and stable cerebral perfusion pressure, avoidance of systemic, secondary brain insults, and optimization of cerebral hemodynamics and perfusion.

Intracranial hypertension after TBI reduces cerebral perfusion pressure and carries an increased risk of death. Intracranial pressure is routinely monitored in TBI patients and tiered interventions are implemented to reduce elevated pressures including: 1) sedation, analgesia, and head elevation; 2) ventriculostomy, pharmacologic blood-pressure augmentation, osmotherapy, and moderate hypocapnia. If the intracranial pressure remains >25 mmHg for 1–12 hours despite these all of
these measures, then a decompressive craniectomy appears to improve chances of survival. However, patients who undergo decompressive craniectomy for persistently elevated ICP are more likely to remain in a persistent vegetative state. (17) The results of this trial leave intensivists with a very difficult decision in young patients with refractory intracranial hypertension secondary to TBI.

**Compartment Syndromes**

Trauma patients are at risk for both extremity and abdominal compartment syndromes. Rhabdomyolysis occurs due to destruction of striated muscle. Crush injuries, long bone fractures and ischemia-reperfusion scenarios place the injured patient at a heightened risk for developing a fascial compartment syndrome. Although creatinine kinase (CK) and myoglobin levels may aid in diagnosis, a high index of suspicion coupled with a low threshold to quantitatively monitor compartment pressures remain mandatory. CK levels greater than 5000 IU/L are associated with acute kidney injury. The mainstays of treatment for rhabdomyolysis remain aggressive hydration and forced diuresis with diuretics (mannitol and furosemide) with a goal urine output of 100-200cc/hour.

Abdominal compartment syndrome (defined as an intraabdominal pressure >20mmHg with associated end-organ dysfunction) 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. (18)

**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. Not all patients respond to aggressive resuscitative measures. This can be due to occult injury or poor physiologic response.

It has been estimated that 5-10% of all trauma-related deaths are attributable to clinically undiagnosed injury. (14) 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 (pressure ulcers) and even the
resuscitative efforts themselves (TRALI, TACO, 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.

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. Once stabilized, full-calorie enteral nutrition should be targeted, however even trophic feeding provides benefit. (19) 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. (20)

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.

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, neuraxial 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. (21)

This chapter is a revision of the original chapter authored by Mark J Baskerville MD and T Miko Enomoto MD.

References:

1. American College of Surgeons Committee on Trauma: Advanced Trauma Life Support: Course for Physicians, 8th Ed. Chicago, American College of Surgeons, 2008


16. AANS & CNS: Guidelines for the management of acute


**Review Questions:**

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

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

3. The most common arrhythmia after blunt cardiac injury is:
   
   a. Ventricular fibrillation  
   b. Sinus tachycardia  
   c. Atrial fibrillation  
   d. Normal sinus rhythm

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:

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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
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-

Patient Case:
A 56-year-old man is in the ICU after orthotopic heart transplant for non-ischemic cardiomyopathy. Operative course was notable for transfusion of 8 PRBC, 8 units FFP, and 2 units of platelets. 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, the patient again became hypotensive with a decrease in MAP from 65 to 50. CVP increased from 10 to 20 and cardiac index decreased from 3.5 to 2.5. No changes had been made to pressor and inotrope infusion rates. Patient was being paced synchronously at 115 bpm. Echocardiogram revealed a dilated RV with poor right ventricular global function and no evidence of pericardial effusion.
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 addressed 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, rejection, immunosuppression therapy and antimicrobial prophylaxis.

HEART TRANSPLANTATION

1. Demographics and Outcome

More than 2000 heart transplantations are performed annually in the United States. The most common indications for heart transplantation are cardiomyopathy (56%) and coronary artery disease (37%), with a much smaller proportion of transplantation being performed for congenital heart disease and valvular disease. Forty-eight per cent of patients had a ventricular assist device (VAD) in place at time of transplant. Outcomes following heart transplantation are generally quite favorable, with 77% of patients alive five years after transplantation and 58% alive after ten years. The most common causes of death in the first year after transplant are infection, cardiovascular disease, cerebrovascular disease, and graft failure. (2)

2. Postoperative ICU Management

A. Incision

Orthotopic heart transplants are performed through a median sternotomy incision. In the event of RV dysfunction or hemodynamic instability in the operating room, the sternum may be left open and closed at a later time. Patients with preexisting cardiovascular implantable electronic devices (CIEDs) will have an incision where the device has been removed; patients with VADs will have an incision at the site of driveline removal.

B. Monitors and Access

Patients arrive from the operating room (OR) with a variety of monitors and lines in place. In addition to standard monitors and a Foley catheter, patients will have an arterial line, a large-bore central venous catheter, a pulmonary artery (PA) catheter, 1-2 sets of epicardial pacing wires, and multiple pleural and mediastinal chest tubes.

C. Medications and Mechanical Support
Patients may arrive on a multitude of vasoactive infusions, including inotropes (e.g. epinephrine, milrinone, dobutamine) and vasopressors (e.g. norepinephrine, vasopressin). In addition, patients may be on continuous inhaled nitric oxide or inhaled prostacyclins. 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). If there was difficulty weaning from bypass or significant ventricular dysfunction intraoperatively, the patient may also have an intraaortic balloon pump (IABP) in place or be on extracorporeal membrane oxygenation (ECMO).

D. Ventilator Management

Careful consideration should be given when choosing ventilator settings, as hypoxia and hypercarbia can lead to elevated pulmonary arterial pressures (PAP) and poor right ventricular (RV) function, and high levels of PEEP may interfere with venous return. If hemodynamically stable, patients can often be weaned from the ventilator and extubated within the first one to two post-operative days. Patients with an open chest or on ECMO usually remain intubated until sternum is closed and/or ECMO cannulas are removed.

E. Fluid Management

Patients who present for transplant in decompensated heart failure are often grossly volume overloaded prior to surgery. Despite this, patients may arrive to the ICU in a relative hypovolemic state, due to bleeding and fluid removal via ultrafiltration on cardiopulmonary bypass. All resuscitative volume, whether it is blood products, colloid or crystalloid, should be administered with care to avoid RV distention. Forced diuresis should begin once the fluid shifts have stabilized, usually within the first two days following surgery.

F. Hemodynamic instability

The differential diagnosis for hemodynamic instability in the post-operative heart transplant recipient includes tamponade, hypovolemic shock due to hemorrhage, and right or left ventricular dysfunction, which can be caused by primary graft dysfunction, post-cardiopulmonary bypass inflammatory response, and hyperacute rejection. (3)

Values obtained from the PA catheter, including pulmonary vascular resistance (PVR), systolic and diastolic pulmonary arterial pressures (PAPs and PAPd), pulmonary capillary wedge pressure (PCWP), SVR, cardiac output (CO), central venous pressure (CVP), and mixed venous oxygen saturation (SvO₂), can be useful in determining the etiology of the instability.

A low CVP, low PAPd, low PCWP and low CO is consistent
with hypovolemia. A combination of high CVP, low CO, and hypotension can reflect either tamponade or RV failure; emergent echocardiogram may be helpful in differentiating between these two conditions. (4) Tamponade should prompt an immediate return to the OR for re-exploration. The management of RV failure is discussed below.

Diagnosis of left ventricular (LV) failure can be made by echocardiogram and is supported by hypotension, low CO, and possibly a high PCWP. LV failure can be precipitated by primary graft dysfunction and hyperacute rejection. VA ECMO, IABP or LVAD should be considered as bridge-to-recovery or bridge-to-re-transplantation if LV dysfunction does not improve with inotropic therapy. (4)

G. Laboratory Assessment

Labs should be checked frequently in the early postoperative period. ABGs should be monitored; results can be used to guide fluid resuscitation or adjust ventilator settings. Electrolytes should be optimized to maintain normal values of serum potassium, magnesium and calcium. Trending hemoglobin and coagulation factors should guide transfusion of blood products. Creatinine values should be frequently monitored to assess for the development of acute kidney injury.

H. Postoperative Complications

1) Right Ventricular Failure

Right ventricular failure is one of the most common and serious complications following heart transplantation, occurring in >50% patients and accounting for more than 20% of early deaths. (4)

a) Etiology

The etiology of RV failure in the early post-operative period is multifactorial. The donor heart is exposed to multiple stressors, including ischemia, cardioplegia, and surgical manipulation, all of which contribute to myocardial stunning and decreased contractility. The donor RV, previously naïve to high afterload, is exposed to the elevated PVR present in the recipient. The thin walled RV is unable to generate enough pressure to overcome this resistance and subsequently dilates. 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)

Severe RV volume and pressure overload can cause shifting of the interventricular septum into the LV, which interferes with LV filling and leads to LV failure and decreased cardiac output. Multisystem organ
failure can result, including liver failure from hepatic congestion and acute kidney injury. (4) Due to the critical nature of this complication, a multimodal approach is used to prevent and treat elevated PVR and RV failure.

b) Optimization of Preload

Many patients arrive to the ICU in a hypovolemic state and require volume resuscitation for hemodynamic instability in the early post-operative period. Once volume status has stabilized, aggressive diuresis is needed to avoid volume overload, often as early as the first post-operative day. Loop diuretics are first-line therapy; high bolus doses and/or infusions may be necessary. Boluses of thiazide diuretics may be added if loop diuretics are insufficient. Renal replacement therapy (RRT) may be necessary to remove volume if pharmacologic therapy is inadequate. Volume status can be assessed by measurements from PA catheter (CVP, PAPd) and by echocardiography.

Epicardial pacing wires should be used to pace the transplanted heart at rates between 90-115 beats per minute (bpm) to minimize diastolic time, (i.e. time for RV filling) and subsequently reduce the risk of RV distention. Pacing modes of AAI or DDD should be utilized to maintain atrial-ventricular synchrony. Heart rate can be gradually decreased over time to the intrinsic rate.

c) Optimization of Contractility

Infusions of inotropic medications, including epinephrine, milrinone and dobutamine, are used to maintain adequate RV contractility. Milrinone and dobutamine are inodilators, and will result in decreased systemic vascular resistance. Vasopressors, such as norepinephrine or vasopressin, may be needed to treat resulting hypotension. Inotropes should be weaned slowly over the course of several days, even if cardiac index is normal or supranormal, as a quick wean can precipitate acute RV failure.

d) Minimizing Afterload

Inhaled pulmonary vasodilators are frequently started prophylactically in the operating room, to reduce elevated PAPs that may contribute to RV dysfunction. Inhaled prostacyclins and inhaled nitric oxide can be administered to both intubated and non-intubated patients to selectively dilate the pulmonary vasculature in well-ventilated areas of lung and subsequently reduce PVR. These agents
should be weaned slowly to avoid acute rebound pulmonary hypertension. 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)

Dynamic causes of elevated PVR should also be avoided; appropriate ventilator management, use of supplemental oxygen, adequate pain control and aggressive pulmonary toilet should all be employed to reduce risk of hypercarbia, hypoxia and acidosis.

e) Rescue Therapies

If conservative measures fail and RV dysfunction persists, a right ventricular assist device (RVAD) or VA ECMO may be required until RV function recovers.

2) 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) The etiology of PGF is thought to be ischemia-reperfusion injury. 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. Treatment is supportive, and includes increase in inotropic support, ECMO, and VAD placement. Despite therapy, PGF remains a leading cause of early death in heart transplant recipients.

3) Special Electrophysiology Concerns in the Heart Transplant Recipient

a) Denervation of the Transplanted Heart

The donor heart has been denervated from its autonomic nerve supply, which alters both its intrinsic activity as well its response to physiologic and pharmacologic triggers. Lack of parasympathetic tone results in a resting heart rate of 90-110 bpm. 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)

The denervated heart will have a decreased or no response to indirect acting medications such as atropine. Phenylephrine fails to cause reflex bradycardia. The allograft responds appropriately to direct beta-agonists such as isoproterenol, epinephrine, and dobutamine. Adenosine may cause an exaggerated response of prolonged asystole. (4)
4) Arrhythmias

Sinus node dysfunction occurs often in the postoperative period, due to surgical manipulation or ischemia. First degree atrioventricular (AV) block and right bundle branch block are common. (6) Epicardial pacing or isoproterenol infusion may be necessary to maintain adequate heart rate. (7) Sinus node dysfunction is usually temporary, but 2-5% of cases will require a permanent implanted pacemaker. (6)

Atrial fibrillation and flutter occur much less frequently after heart transplantation compared with other cardiac surgeries. (4) Both atrial and ventricular tachycardias may be signs of acute cardiac allograft rejection. These arrhythmias should trigger investigation of rejection with an endomyocardial biopsy (EMB). Class III anti-arrhythmics sotalol and amiodarone can be safely used in heart transplant patients. (7)

Of note, the EKG tracing may demonstrate two p waves, one from the residual native right atrium and the second from the donor heart.

5) Rejection

a) 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, plasmapheresis, and potentially re-transplantation. (3,4)

b) Acute Rejection

Acute rejection occurs quite frequently in heart transplantation recipients. Approximately 24% of patients will experience an episode by the end of the first year; by five years, 50% of patients will experience acute rejection. (2) 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) ACR may present with fatigue, shortness of breath, RV dysfunction, or LV dysfunction. (10) Diagnosis is made with EMB and is treated with either steroids or anti-lymphocyte agents such as thymoglobulin. Acute vascular or humoral rejection is caused by recipient antibodies against mismatched human leukocyte antigens (HLAs) present within the allograft. (3) Acute vascular rejection can present with severe ventricular dysfunction and diffuse
ischemia. Like with ACR, diagnosis is made with EMB. However, acute vascular rejection can be treated by intensifying the immunosuppressive regimen with cyclophosphamide to modulate antibody production, or by plasmapheresis. Patients admitted in acute decompensated heart failure due to rejection may need to be supported with inotropic medication or temporary mechanical support until ventricular function recovers.

c) 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) CAV is diagnosed on routine coronary angiography. 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) While CAV can progress to myocardial infarction, and ultimately, graft failure, patients rarely experience classical anginal pain due to cardiac denervation.

LUNG TRANSPLANTATION

1. Demographics and Outcomes

The number of lung transplantations performed yearly in the United States has steadily risen over the last decade, with 1930 performed in 2014. Bilateral lung transplantation is much more common (69%) than single lung. The majority of patients received a transplant for either restrictive lung disease (62%) or obstructive lung disease (24%), with a smaller proportion for cystic fibrosis (11%). Outcomes after lung transplantation are among the worst for solid organ transplantation; only 58% of patients are alive five-year post-transplant. (2) Leading causes of death include graft failure and infection.

2. Postoperative ICU Management

A. Incision

The incision will depend on the type of surgery performed; a single lung transplantation is usually performed through a thoracotomy incision, whereas a bilateral lung transplantation is performed through a large clamshell incision.

B. Monitors and Access

Patients will arrive from the OR with standard monitors, arterial line, a large bore CVC, and a PA catheter. Ideally, the
CVC will have been placed in the left neck, leaving the right neck free for VV ECMO cannulation if needed. Other lines will include a Foley catheter, multiple chest tubes, and possibly an epidural. If a double-lumen endotracheal tube (ETT) is used intraoperatively, it should be changed out for a single-lumen ETT prior to arrival on unit.

C. Medications and Mechanical Support

Medications often include infusions of vasopressors and inotropes. Inhaled pulmonary vasodilators (iNO or prostaglandins) are started in the operating room to encourage dilation of donor pulmonary vasculature and improve oxygenation. VV or VA ECMO may have been deployed intraoperatively due to persistent hypoxemia, or cardiac dysfunction, respectively. Vasoactive agents and ECMO should be weaned as quickly as tolerated; inhaled pulmonary vasodilators should be weaned slowly over time.

D. Ventilator Management

Ventilator management will depend on the underlying disease process. Patients with emphysema who underwent single lung transplantation may require zero to low PEEP and prolonged expiratory time to prevent air trapping in the native lung. Ventilator management following bilateral lung transplantation varies by institution: a strategy of minimizing PEEP, minimizing FiO$_2$ or a combination thereof may be employed.

Patients can usually be weaned from mechanical ventilation and extubated within the first 1-2 post-operative days. (11) Inability to wean from mechanical ventilation will likely result in placement of a tracheostomy. Persistent or worsening hypoxemia may warrant urgent VV ECMO deployment. Bronchoscopy should be performed prior to extubation to evaluate the bronchial anastomosis and clear any secretions. Aggressive pulmonary toilet is imperative after extubation to reduce the risk of mucous plugging. (4)

E. Fluid Management

The allograft is at risk for pulmonary edema due to increased vascular permeability and disruption of lymphatic drainage. Judicious fluid administration is essential and filling pressures (CVP and PCWP) should be maintained as low as is tolerated without significantly compromising renal perfusion. Vasopressors may be necessary to treat hypotension. Diuretics and inotropes may be used to minimize the risk of cardiogenic pulmonary edema.

F. Hemodynamic instability

Patients who are hemodynamically unstable post-operatively should be evaluated for hypovolemia, hemorrhage, tension pneumothorax, tension pneumocardium, and tamponade physiology.
G. Laboratory Assessment

Frequent ABGs are used to assess pulmonary function, to wean ventilator settings, assess readiness for extubation, and adjust ECMO settings. Electrolytes should be checked often and appropriately supplemented, to reduce risk of postoperative atrial fibrillation.

H. Pain management

Poor pain control in lung transplant recipients may lead to splinting and inability/unwillingness to cough, which can result in poor ventilation, mucous plugging and, in severe cases, reintubation. Aggressive opioid use can also be detrimental if respiratory drive is reduced and hypercarbia results. Neuraxial analgesia with epidural catheters is often used as the primary method of pain control; non-opioid analgesic adjuncts may be added as needed. Of note, non-steroidal anti-inflammatory drugs should be avoided due to interaction with immunosuppressive medications. The epidural may be placed preoperatively or postoperatively (prior to extubation); timing depends on institutional culture, likelihood of cardiopulmonary bypass use in the OR, and coagulopathy in the postoperative period.

I. Postoperative Complications

1) 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) Ischemia of the bronchial wall is a major contributor to many airway complications. 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) Ischemia can be exacerbated by hypotension, hypovolemia and low cardiac output in the intra- and post-operative periods.

The resulting airway complications are often compounded by airway infections, ischemia-reperfusion injury, and prolonged mechanical ventilation. Ischemia-reperfusion injury contributes to airway complications by increasing interstitial edema and compromising pulmonary blood flow. (13) Prolonged mechanical ventilation and PEEP put continuous stress on the bronchial wall and anastomosis and may interfere with graft perfusion and collateralization. (13)

Surprisingly, while airway complications result in
significant morbidity, overall survival is unaffected. (13) Airway complications include bronchial stenosis, bronchial dehiscence, exophytic granulation tissue, tracheo-bronchomalacia, and bronchial fistulae. Many of these complications will not require ICU-level care; however bronchial dehiscence and bronchial fistulae often lead to significant morbidity.

2) Bronchial Dehiscence

Bronchial dehiscence is a serious complication that occurs in 1-10% of patients, typically within the first 1-5 weeks after transplantation. Patients present with dyspnea, prolonged mechanical ventilatory requirements, lung collapse, persistent air leak, pneumothorax, pneumomediastinum or subcutaneous emphysema. (13) Dehiscence increases the risk of developing an airway infection or abscess, which can progress to sepsis. (13) Diagnosis is suggested with chest CT and confirmed with flexible bronchoscopy. Mild or moderate dehiscence can often be treated with antibiotics and surveillance, whereas more severe dehiscence requires stent placement or surgical repair. Severe dehiscence can be life-threatening and prognosis is generally poor.

3) Bronchial Fistulae

Fistulae can form in various places along the bronchial tree; lung transplant recipients have suffered from bronchopleural, bronchomediastinal, and bronchovascular fistulae. (13) While these complications are rare, they result in significant morbidity and mortality. Bronchopleural fistulae may present with dyspnea, subcutaneous emphysema, tension pneumothorax, or persistent air leak. Management ranges from chest tube placement to surgical intervention.

Bronchomediastinal fistulae can occur at any location in the airway and present as bacteremia, mediastinal abscess, or cavitation. Treatment includes appropriate antimicrobial therapy, percutaneous drainage of any abscesses, and potentially surgical debridement.

Bronchovascular fistulae can also form between the bronchus and the aorta, pulmonary artery or left atrium. Presenting symptoms include hemoptysis, air embolus, and sepsis. Patients have been treated with bi-lobectomy or pneumonectomy.

4) Airway Infections

Infections are a frequent source of morbidity in the post-transplantation period. The allograft is exposed to not only the flora of both the donor and the recipient
airways, but also that of the external environment. Pseudomonas and staphylococcus aureus are the most prevalent bacterial infections, whereas Aspergillus is the most common fungus encountered. (13) Immunotherapy increases risk of opportunistic infection. Ischemia of the allograft and prolonged mechanical ventilation impair cough and swallow strength, and reduce mucociliary clearance, which subsequently encourage microorganism growth. (12)

Infection can arise anywhere along the respiratory track, resulting in tracheitis, bronchitis, pneumonia or anastomotic infection. Airway infections increase the risk of other airway complications, including dehiscence, stenosis, malacia and fistulae. (13) Antimicrobial prophylaxis, source control, and appropriate antimicrobial treatment are all indicated in the management of airway infections.

5) Primary Graft Dysfunction

Primary graft dysfunction (PGD) is seen in up to 25% of lung transplant recipients, (4) and is usually diagnosed within the first three post-operative days. (14) 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. Increased vascular permeability and subsequent noncardiogenic pulmonary edema result. (12) PGD significantly increases mortality, duration of mechanical ventilation, hospital length of stay, as well as the risk of developing subsequent bronchiolitis obliterans (BOS). (14) Patients with moderate to severe PGD suffer from an all-cause 30-day mortality of 63% compared to 9% of patients without PGD. Patients experience progressive hypoxemia; chest radiograph demonstrates new bilateral infiltrates. (12) Unfortunately, the only treatment for PGD is supportive and includes lung protective ventilation, judicious fluid management, and temporary ECMO. (14)

6) Rejection

a) Hyperacute Rejection

Hyperacute rejection after lung transplantation manifests as pulmonary edema and allograft dysfunction. (15) Described treatments include plasmapheresis, rituximab, and IVIG, but this condition is often fatal. (4)

b) 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) Acute cellular rejection is diagnosed by transbronchial lung biopsy.

Treatment usually consists of optimization of the immunotherapy regimen and a pulse of high dose steroids. (15) ACR puts the patient at significantly increased risk of developing BOS. (15) Humoral rejection is diagnosed by detecting circulating donor-specific anti-HLA antibodies. Treatment options include IVIG, plasmapharesis, or anti-CD20 monoclonal antibodies (ex. rituximab). (12)

c) 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. 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) Diagnosis and staging is based on the degree of FEV₁ decrease from baseline. CT imaging often shows air trapping and bronchiectasis. (12) Most treatments are focused on optimizing immunosuppressive therapy (15) and palliative measures. (12)

LIVER TRANSPLANTATION

1. Demographics and Outcomes

Liver transplant recipients are the most common solid organ transplantation patients encountered in the ICU, with 6729 liver transplantations being performed in 2014 alone in the United States. Hepatitis C virus is the leading indication for liver transplantation, with approximately one-quarter of the transplants performed for this reason. Other indications are malignancy, particularly hepatocellular carcinoma, alcoholic cirrhosis, and non-alcoholic steatohepatitis. Outcomes after liver transplantation are quite favorable, 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)

2. General Postoperative Management

A. Incision

The standard approach to orthotopic liver transplantation is through a mercedes or chevron shaped incision (bilateral
subcostal incisions with or without small upper midline laparotomy), although some advocate for a J-shaped subcostal incision, which has been associated with fewer post-operative complications in some studies. (18)

B. Monitors and Access

In addition to standard monitors, patients will arrive to the ICU with a large bore CVC, possibly a PA catheter, arterial line, Foley catheter, nasogastric tube, and multiple abdominal drains in place. In anticipation of massive intraoperative blood loss, patients will frequently also arrive with either very large bore peripheral IVs such as rapid infusion catheters (RICs) or a “double stick,” in which two central lines are placed in the same vessel. Depending on the surgical technique used, a T-tube may be present in the bile duct, allowing for monitoring of bilious drainage. If a PA catheter is in place, it can often be removed immediately after arrival to the ICU, as its main utility in the management of these patients is during the intraoperative period.

C. Medications

Following liver transplantation, patients will often arrive to the ICU on vasopressor support with infusions of one or more agents (phenylephrine, norepinephrine, and/or vasopressin). This support should be weaned off within the first several post-operative hours with volume resuscitation.

Given the high-cardiac output physiology of their pre-existing liver failure, it is uncommon for these patients to require inotropic support.

D. Ventilator management

Ventilator settings can be weaned and patients can be extubated relatively quickly, sometimes even immediately post-operatively in the operating room. (19) Patients with significant deconditioning prior to transplantation may require more prolonged mechanical ventilation. (20)

E. Fluid management

Patients often receive massive transfusions and large volume fluid resuscitation in the OR that can lead to post-operative pulmonary edema and allograft congestion. Patients often require ongoing transfusion of blood products including packed red blood cells, fresh frozen plasma, platelets and cryoprecipitate after arrival to the ICU; however, if the hepatic allograft is functioning, transfusion requirements should decrease over the first several post-operative hours if there is no ongoing surgical bleeding. 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 related to volume overload. (21)
F. Hemodynamic instability

Patients may require infusions of one or more vasopressors, as the pre-operative hemodynamic profile of liver failure, including vasoplegia and hyperdynamic cardiac output, often persists into the early post-operative period. Furthermore, hypotension may be exacerbated post-operatively by metabolic acidosis and allograft ischemia. However, an increasing vasopressor requirement or the inability to wean from vasopressors is concerning for a more serious complication. 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 citrate intoxication following massive blood transfusions. Workup may include assessment of laboratory values and drain output, duplex Doppler ultrasound to evaluate the vasculature of the new graft, and echocardiogram.

G. Laboratory assessment

Laboratory values, including markers of acid-base status, liver function, coagulopathy, and renal function, should be checked frequently and serially in the post-operative period. (22) The quantity and quality of abdominal drain and t-tube output should be also monitored closely. Electrolyte abnormalities, including hyponatremia, may persist from the pre-operative period. It is important to correct hyponatremia slowly, as a rapid increase in serum sodium could result in osmotic demyelination syndrome. (20) Liver function tests (LFTs) will be grossly elevated post-operatively, but should begin to trend towards normal in the first several days in the presence of a functioning hepatic graft. Persistently elevated or rising LFTs should raise concern for graft dysfunction or hepatic arterial thrombosis. (20) Hypoglycemia is another marker for poor liver function and should prompt additional investigation into the state of the hepatic allograft. (21) The INR, which is a reflection of the activity of clotting factors that are synthesized in the liver, can act as an indirect measure of graft function. (22) Thrombocytopenia is common in the post-operative period and can also contribute to clinical bleeding. (21)

H. Postoperative Complications

1) Surgical Complications

Liver transplantation is a complex surgical procedure involving multiple anastomoses. Surgical complications can be divided into three categories: vascular (arterial and venous), biliary, and other complications.

2) Arterial complications
Arterial complications, which can be very serious, occur in 2-25% patients, and include anastomotic bleeding, anastomotic stenosis secondary to thrombosis, steal syndrome or aneurysm. Approximately half of these patients will require re-transplantation. (23) Hepatic artery thrombosis (HAT) occurs in approximately 3% of patients and can manifest as fulminant liver failure. Several imaging modalities can assist in the diagnosis of HAT, including duplex Doppler ultrasound, celiac angiography, computerized tomography (CT) angiography and magnetic resonance angiography (MRA); however, surgical exploration is the gold standard. While treatment options exist, including catheter-directed thrombolysis and surgical arterial reconstruction, re-transplantation is frequently necessary. (24)

3) Venous complications

Venous problems are rare and can include occlusion of the portal vein or inferior vena cava. Portal vein thrombosis (PVT) occurs in 0.5-1.5% of patients and can be diagnosed by duplex Doppler ultrasound. Symptoms include transaminitis, ascites, intestinal congestion, and GI bleeding. In the case of portal vein thrombosis, immediate operative thrombectomy is indicated, although emergent re-transplantation may be required. Without treatment, PVT is almost universally fatal. (24)

4) Biliary complications

Biliary complications occur in 10-20% of patients and include biliary leak and biliary stricture, among others. (23) The majority of biliary complications occur early, within the first six months after transplant. (23) Patients present with pain, fever, ascites and persistent drain output. Diagnosis is made by a variety of modalities, including abdominal ultrasound, CT, CT cholangiography, magnetic resonance cholangiopancreatography (MRCP), and endoscopic ultrasound (EUS). Treatment options include endoscopic retrograde cholangiopancreatography (ERCP) and stenting, percutaneous transhepatic cholangiography (PTC) with percutaneous transhepatic biliary drainage (PTBD), or surgical exploration. (25)

5) Other surgical complications

Other surgical complications include early internal bleeding (from non-anastomotic sites), evisceration, wound infection, and incisional hernia.

a) Infection

Infectious complications develop frequently in liver transplantation recipients, occurring in more than one-half of patients in the first post-operative year. (24) They are the leading cause of early death in these patients. Most early causes of infection are similar to
those seen in non-transplantation surgeries, and include surgical wound infections, bloodstream infections, pneumonia, and Clostridium difficile-associated diarrhea. (24) Opportunistic infections (OI) tend to arise during the first several months after transplant at the height of immunosuppression. (24) The most prevalent OIs are cytomegalovirus (CMV) in previously CMV-seronegative recipients and fungal infections caused by aspergillosis and endemic fungi. Late infections (more than six months after transplant) include community-acquired pneumonia, hepatic abscesses, and recurrent chronic infection with hepatitis B or C virus. (23) As with any infection, management should include source control and appropriate antimicrobial therapy.

6) 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. (26) Graft dysfunction is accompanied by elevated transaminases, elevated INR, decreased bile production, and elevated lactate. Multi-organ system failure may develop and is characterized by coma, oliguria, clinically significant bleeding, and hypoglycemia. (21) Primary non-function (PNF) is defined as graft failure within 10-14 days of transplantation. This serious complication is seen in 4-6% of patients (23) and is universally fatal without re-transplantation. Initial poor function (IPF) does not have a standard definition. Some have defined IPF as graft dysfunction 15-30 days after transplantation. (23) Some patients with IPF recover liver function while others go on to require re-transplantation. (24)

7) Rejection

a) Hyperacute Rejection

Hyperacute rejection after liver transplantation presents as thrombosis and hemorrhagic graft necrosis. (24) Treatment options include plasma exchange, IVIG, B-cell depleting therapy, or splenectomy. Without therapy, acute liver failure ensues.

b) 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% at five years post-transplantation. (2) Acute cellular rejection (ACR) occurs in 25-60% of patients within the first six months after liver transplantation. Suspicion is raised
by rising aminotransferase and bilirubin levels, and diagnosis is confirmed by liver biopsy. Treatment is based on the severity of rejection; options include optimizing immunosuppression, steroids pulses, T-cell depleting therapy, and re-transplantation. (24)

c) Chronic Rejection

Chronic rejection after liver transplant is much less prevalent than acute rejection, occurring in only 4% of patients. (27) Chronic rejection is characterized as immunologic injury to the bile ducts, arteries and veins of the allograft resulting in ductopenia and perivascular fibrosis. (28) Chronic rejection is usually seen in patients who have experienced prior episodes of acute rejection that were resistant to standard steroid treatment. (27) Diagnosis is made by liver biopsy.

**IMMUNOSUPPRESSIVE and ANTIMICROBIAL THERAPY**

Solid organ transplant patients require often complex medication regimens in order to (1) induce immunosuppression to prevent or treat graft rejection and to (2) provide prophylaxis against common opportunistic infectious organisms to which patients become susceptible as a result of immunosuppression. A summary of these medications, including class, indication, mechanism, side effects, and interactions, can be found in tables 1 and 2.

**Table 10.4.1 Immunosuppressive Therapy Agents, Their Mechanisms of Action, and Side Effects**

<table>
<thead>
<tr>
<th>Category of Drug</th>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyclonal anti-lymphocyte antibodies</td>
<td>ATGAM, Thymoglobulin</td>
<td>Antibodies bind B- and T-cell antigens, leading to death of B- and T-lymphocytes</td>
<td>Acute hypersensitivity allergic reaction, serum sickness, leukopenia, thrombocytopenia</td>
</tr>
<tr>
<td>IL-2 receptor antagonists</td>
<td>Basiliximab, Daclizumab</td>
<td>Monoclonal antibody preparation binds to the IL-2 receptor on activated T-cells, inhibiting proliferation.</td>
<td>Minimal</td>
</tr>
<tr>
<td>Antimetabolites</td>
<td>Mycophenolate Azathioprine</td>
<td>Interferes with purine synthesis and DNA synthesis, inhibiting lymphocyte proliferation</td>
<td>Anemia, leukopenia, thrombocytopenia, GI distress</td>
</tr>
<tr>
<td>Calcineurin inhibitors</td>
<td>Tacrolimus, Cyclosporine</td>
<td>Drug complexes bind to calcineurin which leads to inhibition of T-cell activation</td>
<td>Nephrotoxicity, neurotoxicity, diabetes mellitus, hypertension, hyperlipidemia</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Methylprednisolone Prednisone</td>
<td>Alteration of transcriptional activity of genes involves in immune function and inflammation</td>
<td>Chronic adrenal suppression, hypertension, diabetes, obesity</td>
</tr>
<tr>
<td>Inhibitors of mammalian target of rapamycin (mTOR)</td>
<td>Sirolimus, Everolimus</td>
<td>Drug complexes bind mTOR, interrupting the cell cycle and inhibiting B- and T-cell proliferation</td>
<td>Anemia, neutropenia, thrombocytopenia, hyperlipidemia</td>
</tr>
</tbody>
</table>

1. **Types of Immunosuppression**

   There are three main types or phases of immunosuppression: induction therapy, maintenance therapy, and treatment of rejection. Immunosuppression regimens are not standardized among transplant type or across transplantation centers.

2. **Induction Immunosuppression**
Induction immunosuppression is given peri-operatively, with the intent to induce immunologic tolerance to the graft. (9) Many heart, lung and liver transplant recipients do not receive any induction therapy. (2) When induction therapy is administered, interleukin-2 receptor (IL-2R) antagonists and T-cell depleting therapies are the most frequently used agents. (2)

3. Maintenance Immunotherapy

Maintenance immunotherapy begins in the early post-operative period, and continues for the life of the transplant. Initial maintenance therapy includes a combination of an antimetabolite, a calcineurin inhibitor and steroids. The most common regimen in heart, lung, and liver transplant recipients contains a steroid, mycophenolate mofetil, and tacrolimus. (2) Steroids are frequently reduced over time and often eliminated altogether.

4. Treatment of Rejection

Treatment of rejection involves drugs specific to the type of rejection, either cellular or humoral. As described above, approaches may include optimization of current medications, addition of pulse-dose steroids or anti-lymphocyte agents, or methods such as plasmapharesis.

5. Immunosuppressive Drugs

There are several different categories of immunosuppressive agents in use today (see Table 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 number and severity of side effects.
A. Polyclonal anti-lymphocyte antibodies (ATGAM, Thymoglobulin)

Thymoglobulin is a polyclonal rabbit antibody preparation containing antibodies against human surface B- and T-cell antigens. Binding of antibody to antigen leads to complement-dependent opsonization and ultimately, cell lysis or apoptosis of B- and T-cells. An acute hypersensitivity allergic reaction can occur in response to thymoglobulin, with symptoms of urticaria, fever, chills, and rash. Other side effects include cytokine release syndrome, serum sickness, leukopenia, and thrombocytopenia. In heart transplant recipients, thymoglobulin is used for induction therapy and for treatment of steroid-resistant rejection.

B. IL-2R antagonists (daclizumab, basiliximab)

These drugs are monoclonal antibody preparations that bind to the IL-2 receptor on activated T-cells, resulting in the inhibition of T-cell proliferation. While hypersensitivity reactions can occur, these drugs are generally well tolerated. IL-2R antagonists are used for induction therapy after heart, lung, and liver transplantation.

C. Antiproliferative agents (azathioprine, mycophenolate mofetil)

Azathioprine (AZA) is a prodrug, which is converted into a purine analog, which is then incorporated into DNA. DNA synthesis is inhibited, subsequently impairing proliferation of B- and T-lymphocytes. AZA can cause a dose-dependent, reversible myelosuppression resulting in anemia, leukopenia, and thrombocytopenia.

Mycophenolate mofetil (MMF) is a non-competitive inhibitor of an important enzyme in the de novo synthesis pathway for guanine nucleotides. Unlike other cells, lymphocytes are unable to utilize the salvage pathway; due to this reliance on the de novo pathway for purine synthesis, lymphocyte proliferation is inhibited by MMF. MMF can cause anemia and thrombocytopenia, as well as GI distress. Antiproliferative agents are used for prophylaxis against acute rejection after heart, lung, and liver transplantation.

D. Calcineurin inhibitors (cyclosporine, tacrolimus)

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. Nephrotoxicity is the most prevalent side effect of both
drugs, which can result in end stage renal failure. 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. Other side effects include diabetes mellitus, hypertension, hyperlipidemia, and neurotoxicity, which can present as seizures or altered mental status. Both cyclosporine and tacrolimus are used to prevent rejection in heart, lung, and liver transplant recipients.

E. Inhibitors of mammalian rapamycin (sirolimus, everolimus)

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) The cell cycle is arrested and proliferation of B- and T-lymphocytes is inhibited. Side effects of these medications include hyperlipidemia, thrombocytopenia, anemia, and neutropenia. 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. Sirolimus has been used in place of calcineurin inhibitors to treat rejection in heart transplant patients. 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.

F. Steroids (prednisone, methylprednisolone)

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. Steroids have a wide range of adverse effects, including chronic adrenal suppression, hypertension, diabetes, and obesity. These drugs are used in all aspects of immunotherapy, from induction and maintenance to treatment of rejection.

G. Antimicrobial Prophylaxis

As a result of immunosuppression, solid organ transplant patients are at an increased risk for serious infections. Not only is their risk of usual post-operative infectious complications (pneumonia, surgical site infection) increased above the general surgical population, but they are also at increased risk for opportunistic infections. Infectious exposure can be related to transmission from the donor, exposure in the hospital or in the community, or even reactivation of dormant infections. (29) Both transplant donors and recipients are screened in order to reduce the risks of these infections. Nevertheless, antimicrobial prophylaxis is an important component of the post-operative care of transplant patients. A summary of commonly used antimicrobial prophylactic medications can be found in Table 2.
H. Vaccination

Ideally, solid organ transplant recipients should be evaluated for the need for standard vaccinations during their transplant workup (including pneumococcal and influenza vaccinations), and any necessary vaccination series should be completed. Given their reliance upon the host immune response to establish immunity, vaccinations are less effective once a patient is immunosuppressed, and live vaccines are relatively contraindicated in immunosuppressed patients. (29)

I. Prevention of bacterial and fungal infections

Patients should be counseled to avoid potential exposure to community-acquired infectious organisms. This may include lifestyle changes (avoidance of unpasteurized dairy or raw meat products), avoidance of certain environments (moldy or dusty, construction sites), and avoidance of sick contacts.

Routine surgical antibiotic prophylaxis is dependent upon local microbial resistance profiles and both universal (skin flora) and organ-specific infectious risks. Routine antifungal microbial prophylaxis is less common, but may be indicated in recipients who are deemed to be particularly at risk for fungal infections.

Pneumocystis jirovecii pneumonia, as well as several opportunistic infections (Toxoplasma gondii, Isospora belli, Cyclospora cayetanensis, nocardia spp, listeria spp) may be prevented by routine prophylaxis, either short-term or lifelong, with trimethoprim-sulfamethoxazole. If trimethoprim-sulfamethoxazole is not tolerated or contraindicated, less effective alternative agents such as dapsone or pentamidine may be used for Pneumocystis prophylaxis; however, these agents do not provide the broad coverage of trimethoprim-sulfamethoxazole. (30)

J. Universal prophylaxis vs preemptive therapy for viral infections

For prevention of cytomegalovirus (CMV) and other herpesviruses infections, two strategies exist. Universal prophylaxis provides all patients with prophylactic antiviral therapy over a defined period. While this broadly prevents more infections, it may expose the patient to an increased risk of toxic therapy. Preemptive therapy aims to detect serological evidence of exposure prior to development of clinical infection through serial laboratory testing. This method is more labor intensive but may reduce the downsides of treatment with unnecessary antiviral medications. Specific medications are outlined in Table 2.

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.

References:


13. Santacruz JF, Mehta AC: Airway complications and


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**Review Questions:**

1. Referring to the presented case, which of the following would be an inappropriate action to treat the patient’s failing right ventricle?
   
   a. Increase the rate of the epinephrine infusion
   
   b. Diuresis with infusion of a loop diuretic
   
   c. Decrease the epicardial pacing rate
   
   d. Add inhaled iloprost

2. Which of the following would NOT increase heart rate in the heart transplant recipient?

   a. Isoproterenol

   b. Epinephrine

   c. Atropine

   d. Epicardial pacing

3. Which of the following laboratory abnormalities are common after liver transplantation?

   a. Elevated INR

   b. Hyponatremia

   c. Elevated transaminases

   d. All of the above

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 antilymphocyte antibodies

   b. Steroid, calcineurin inhibitor, and IL-2R antagonist

   c. IL-2R antagonist, antimetabolite, and calcineurin inhibitor

   d. Steroid, antimetabolite, and calcineurin inhibitor
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

Patient Case:
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 Ringer’s 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 SaO₂ is 91%.
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/or 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 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 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 limitations. 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

<table>
<thead>
<tr>
<th><strong>Table 10.5.1 Criteria for Referral to a Burn Center</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial-thickness burns &gt; 10% TBSA</td>
</tr>
<tr>
<td>Burns involving the face, hands, feet, genitalia, perineum, or major joints</td>
</tr>
<tr>
<td>Full thickness burns in any age group</td>
</tr>
<tr>
<td>Electrical burns including lightening injury</td>
</tr>
<tr>
<td>Chemical burns</td>
</tr>
<tr>
<td>Inhalation injury</td>
</tr>
<tr>
<td>Patient co-morbidities that could complicate management, prolong recovery, or affect mortality</td>
</tr>
<tr>
<td>Patients with burns and concomitant trauma where the burn injury poses the greatest risk of morbidity or mortality</td>
</tr>
<tr>
<td>Pediatric burns</td>
</tr>
<tr>
<td>Patients who will require special social, emotional or rehabilitative intervention</td>
</tr>
</tbody>
</table>
skin involvement. Complications can include rhabdomyolysis, compartment syndrome and pigment nephropathy. Tissue loss may lead to extremity amputation. 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

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**Table 10.5.2 Assessment of Burn Depth**

<table>
<thead>
<tr>
<th>Terminology</th>
<th>Structures Affected</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Superficial</strong></td>
<td>Epidermis</td>
<td>Erythema, minimal edema, mild discomfort. Heal without scarring. Example: sunburn</td>
</tr>
<tr>
<td><strong>Partial Thickness</strong></td>
<td>Epidermis + Dermis (&lt;50%)</td>
<td>Wet, pink, blistered, painful. Blanch with pressure. Heal with minimal scarring within 2 weeks. Example: scald</td>
</tr>
<tr>
<td><strong>Deep</strong></td>
<td>Epidermis + Dermis (&gt;50%)</td>
<td>White, mottled, varied appearance. May not blister. Heals by hypertrophic scarring and contracture. Best treated with excision and grafting</td>
</tr>
<tr>
<td><strong>Full Thickness</strong></td>
<td>Epidermis + Dermis + Subcutaneous</td>
<td>Dry, leathery, insensate. Does not blanch with pressure. Requires excision and grafting</td>
</tr>
</tbody>
</table>
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. The pharynx is efficient in dissipating heat and frank thermal injury to the lower respiratory tract is rare except in the case of inhalation of superheated gas such as steam. 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 includes supportive measures but specific therapy is available with hydroxocobalamin and is often initiated in the field. Classic therapies for cyanide toxicity including amyl nitrite and sodium nitrite rely on the generation of methemoglobin to bind cyanide and are contraindicated in patients with elevated carboxyhemoglobin. Sodium thiosulfate is safer but has a delayed onset.

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 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. In the calculation of fluid administration, timing 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. Interest in goal directed methods to guide resuscitation has increased with the availability of new monitors. In general, resuscitation based on hemodynamic variables derived for invasive or minimally invasive technologies appear to result in increased fluid administration. 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. For patients with a difficult resuscitation course, use of colloid in the later phase of resuscitation may decrease total fluid administration and the risk of abdominal compartment syndrome. Serial bladder pressure measurement should be considered for patients at risk of developing abdominal compartment syndrome.

Table 10.5.3 Examples of Burn Resuscitation Formulas

<table>
<thead>
<tr>
<th>Formula</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brooke</td>
<td>LR at 1.5ml/kg/%TBSA + colloid at 0.5ml/kg/%TBSA during first 24 hrs. LR at 0.5ml/kg/%TBSA + colloid at 0.25ml/kg/%TBSA + D5W 2000ml during the second 24 hrs</td>
</tr>
<tr>
<td>Parkland</td>
<td>LR 4ml/kg/%TBSA with ½ given over first 8 hrs and ½ over next 16 hrs. D5W 2000ml + colloid at 0.5 ml/kg/%TBSA over second 24 hrs.</td>
</tr>
<tr>
<td>Modified Brooke</td>
<td>LR 2ml/kg/%TBSA with ½ given over first 8 hrs and ½ over next 16 hrs. Colloid at 0.3 - 0.5 ml/kg/%TBSA + D5W to maintain urine output over second 24 hrs.</td>
</tr>
<tr>
<td>US Army Institute of Surgical Research “Rule of Ten”</td>
<td>%TBSA multiplied by 10 + (100ml for every 10kg over 80 kg body weight) = initial fluid rate (ml/hr). Adjustments made based on clinical response.</td>
</tr>
</tbody>
</table>
**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, 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$_2$. Some centers utilize unconventional ventilator modes including high frequency percussive ventilation for patients with IHI. 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. (see Chapter 4.5)

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 is common and peak serum glucose concentrations and duration of hyperglycemia have been associated with increased mortality. Some studies have associated even modest levels of hyperglycemic with an increased risk of infection in burn patients. Therefore, 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 and multidisciplinary. In spite of an increased understanding of the pathophysiology and wide range of clinical factors that affect the care of burn patients, many questions regarding the best strategies for intensive care management of the thermally injured remain unanswered.

References:


Review Questions:

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.

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

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. 450 cc/hr

b. 575 cc/hr

c. 650 cc/hr

d. 875 cc/hr
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. (1) 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. (2,3)

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 obstetric critical care unit. (4,5)

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 pregnancy, 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 sequelae.

Patient Case:

A 29-year-old woman G1P0 at 35 weeks is being induced for severe pre-eclampsia. A magnesium sulfate infusion is begun at 2 gm/h and intermittent doses of hydralazine and labetalol are required to treat hypertension. Twelve hours later, her urine output falls and despite fluid administration, it remains below 0.5 mL/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. The patient seizes following your assessment.
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, and 5) septic shock.

**Physiologic Changes in Pregnancy**

Obstetrical critical care requires a foundation in the cardiopulmonary physiologic changes of 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 net result is a mild dilutional anemia.

Pulmonary changes also occur with diaphragm elevation by the enlarging uterus and ribcage circumference expansion secondary to increased levels of relaxin. (6) These changes can result in a decrease in functional residual capacity of 25%, and up to 70% in the supine position. (6) 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. (6)

Hypertensive diseases occur in 12% to 22% of pregnancies and account for approximately 17% of maternal mortalities in the United States. (7,8) 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. (9) 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. (9) 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 for 4 to 6 weeks postpartum.

The patient presented in the case has severe pre-eclampsia with multiorgan dysfunction, including acute kidney injury. Therapeutic levels of magnesium for severe pre eclampsia range from 4 to 6 g/dL. A magnesium level above 8 g/dL can manifest in 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 with 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 seizure, securing the airway in the pregnant patient should be a priority if initial therapeutic measures fail.

**Vignette 2**

As an intensivist at a small community hospital, you are called to the labor and delivery room to help resuscitate a 33-year-old woman hemorrhaging after vaginal delivery.

Postpartum hemorrhage occurs in about 4% to 6% of pregnancies, with 80% caused by uterine atony. 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.

**Vignette 3**

Upon arrival, the patient is intubated and sedated. Following infant delivery, the mother complained of dyspnea, had 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.

Amniotic fluid embolism (AFE), although occurring only in 1:26,000 pregnancies, has a high mortality, with reported rates from 26% to 86%. Although mortality has drastically decreased over the years, 85% of survivors suffer some permanent neurological deficit. First described in 1926, the pathogenesis of the disease process is theorized to be caused by amniotic debris entering the maternal circulation.

The cardinal findings for AFE are hypoxia, hypotensive shock, altered mental status, and disseminated intravascular coagulation, all of which are typically present during or shortly after labor. 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, (14) with hypoxic encephalopathy believed to be a major contributor to neurologic deficits in this patient population. (15) Hypoxemia is proposed to be secondary to cardiogenic edema of the alveoli, non-cardiogenic edema of the alveoli, exudative edema, and bronchospasm. (15) 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, (16) although there may be distributive and obstructive components as well. Amniotic debris may cause pulmonary vasospasm and pulmonary hypertension. (17) Cardiac arrhythmias including bradycardia, pulseless electrical activity, and ventricular fibrillation may also occur. (15)

Regardless of the reason for hypotension, these patients should have continuous telemetry. Although it is the practitioner’s decision whether to use arterial access and/or central venous access, these monitoring devices can be of 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). 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 may 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.

Vignette 4

The maternal fetal medicine specialist consults you for a 22-year-old woman at 26 weeks gestation on labor and delivery with pyelonephritis. She works as a dialysis nurse and moonlights in the intermediate care units on the weekend at your hospital. She was initially doing well on ceftriaxone therapy in the morning, but over the course of the day she has become more tachypneic, hypotensive, and tachycardic despite having received 3 liters of crystalloid resuscitation. She now has an oxygen saturation of 88% on 100% non-rebreather.

This patient is in septic shock. The mainstay of therapy for sepsis in pregnancy is similar to that in non-pregnant patients where early antibiotic therapy, volume administration, and source control
are crucial therapies. Sepsis accounts for 5% of maternal ICU admissions and is becoming more prevalent in the US. (18,19) Usually septic obstetric patients have favorable prognosis secondary to youth, fewer co-morbidities, and widely sensitive microbial infections.

When treating sepsis specific to pregnancy, practitioners should broaden microbial coverage, perform endotracheal intubation and provide mechanical ventilation if indicated, and utilize vasoactive medications as needed to support hemodynamics. Currently, norepinephrine is not contra-indicated in pregnancy, and should be used when the clinical circumstances are appropriate. (20) When the pregnant patient is intubated, medications similar to those used in the nonpregnant patient may be indicated depending on the stage of pregnancy. These medications may include propofol, fentanyl, and midazolam, which can safely be used during and after the second trimester, or after organogenesis. One key with maternal sepsis is that the associated cytokine release and inflammatory response places these women at a 2.8 fold increased risk of preterm delivery, and 5.7 fold increase of perinatal mortality. (21) In this case, the intensivist and obstetrician should consider betamethasone therapy for fetal lung maturity with a viable pregnancy while treating septic shock. Timing of delivery should be considered by the multi-disciplinary team but in the setting of septic shock in the pregnant patient, neonatology and obstetric anesthesia should be aware of the patient’s critical status. Fetal monitoring should be considered as well, and there should be a logistical plan for emergent delivery for both maternal and fetal indications.

**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, or chronic hypertension. Management of postpartum hemorrhage, including coagulopathy and disseminated intravascular coagulation and recognition and therapy for a rare but serious pregnancy complication AFE, are discussed.

**References:**


Review Questions:

1. Physiologic changes of pregnancy include:
   
   a. Decreased circulating blood volume
   b. Metabolic acidosis
   c. Decreased functional residual capacity
   d. Elevated liver enzymes

2. Therapeutic levels of magnesium for severe preeclampsia range from:
   
   a. 2 - 2.5 g/dL
   b. 2 - 2.5 g/dL
   c. 4 - 6 g/dL
   d. 8 - 10 g/dL

3. Which of the following about AFE is true?
   
   a. Mortality from AFE usually occurs 24 - 48 h post presentation
   b. Cardiogenic heart failure is common
   c. If patients survive, long term sequelae is rare
   d. Occurs in 1 in 2000 birth
Objectives:

1. Discuss physiologic changes associated with aging.
2. Discuss common problems faced by this age group in the ICU.
3. Discuss considerations of managing geriatric patients.

Admission of geriatric patients 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. Nationally and internationally, the geriatric age group utilizes more ICU resources than other age groups.

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.

Patient Case:

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 warfarin, metoprolol, tiotropium, albuterol, tramadol, simvastatin, and hydrochlorothiazide. She is admitted to the ICU for reversal of her supratherapeutic INR, serial neurologic examinations, and operative planning for the hip fracture.
Demographics of the Aging Population

1. The geriatric population is growing faster than the overall population (1.9% vs. 1.2% per year). (1)

2. Between the years 2000 and 2030, it is estimated that the number of older adults will increase from 550 million to 973 million.

3. By 2050, 9% of North Americans will be greater than 80 years old.

4. In the United States, approximately 50% of all ICU admissions are geriatric patients and 60% of all ICU days are attributed to geriatric patients.

5. Approximately 40% of all Medicare patients who die are admitted to the ICU during their terminal illness.

6. Data suggests higher ICU admission rates for patients greater than 75 years old. (2)

Physiologic Changes Associated with Aging

1. Functional and structural changes naturally occur as patients age.

2. Basal function of organ systems may remain the same or slightly decrease, but the physiologic reserve of each organ system decreases with age. (3)

3. Frailty is increasingly being recognized as the best indicator of overall physical status and may provide insight into prognosis, especially in geriatric trauma patients. (4,5)

4. Central Nervous System Changes (6)
   a. Loss of neural tissue: 26% reduction of white matter
   b. 10-20% reduction in cerebral blood flow
   c. Decreased number of serotonin, acetylcholine, and dopamine receptors
   d. Decline in memory, reasoning, and perception
   e. Disturbed sleep/wake cycle
   f. Prone to delirium and cognitive dysfunction

5. Cardiovascular Changes (6)
   a. Frequently associated comorbidity
   b. Diastolic dysfunction is common
   c. Vascular bed (arteries-arterioles) becomes noncompliant
   d. Less compliant heart and vascular bed results in increased sensitivity to volume changes
   e. Less responsiveness to catecholamines
   f. Common cardiovascular medications blunt sympathetic response
g. Autonomic tissue is replaced by fat and connective tissue
h. Prone to arrhythmias: most commonly atrial fibrillation and AV Block

6. Pulmonary Changes (6)
   a. Loss of pharyngeal reflexes
   b. Decrease in chest wall compliance
   c. Decline in lung elasticity
   d. Alteration in central control of ventilation
   e. Diaphragm strength is 25% reduced in healthy elderly individuals
   f. A-a (alveolar to arterial) gradient increases with age
   g. Closing capacity increases with age

7. Renal Changes (6)
   a. Loss of renal tubular mass
   b. Decreased renal blood flow by 50%
   c. Decreased glomerular filtration rate (GFR is decreased by 45% by age 80)
   d. Reduced ability to dilute and concentrate urine and conserve sodium
   e. Decreased drug clearance

**Management in the ICU**

1. Central Nervous System Management
   a. Delirium is common in the geriatric population
      1) Acute onset or fluctuation in mental status. Inattention is the most prominent feature
      2) May be accompanied with emotional disturbances such as agitation
      3) May be hyperactive or hypoactive; hypoactive is significantly more common and under recognized
      4) Increases morbidity, mortality and length of stay
   b. Contributing factors to delirium
      1) Metabolic derangements
      2) Pain
      3) Hypoxemia
      4) Hypercarbia
      5) Hypotension
      6) Sepsis
      7) Substance abuse
8) Preexisting disease (depression/dementia)
9) Delirium causing drugs (i.e. benzodiazepines, anticholinergics)
10) Sleep deprivation
11) Visual/hearing impairments

c. Delirium Management & Treatment
   1) Delirium is a medical emergency
   2) Have a high index of suspicion and frequently reevaluate (7)
   3) Correct triggers
   4) Avoid deliriogenic drugs
   5) Encourage proper sleep-wake cycle
   6) Minimize noise, interruptions
   7) Frequently reorient patient to time and place
   8) Consider antipsychotic medications for hyperactive delirium
   d. Beware of polypharmacy and possible drug-drug interactions
   e. Be respectful of loss of autonomy, wishes for dignity and end-of-life

2. Cardiovascular Management
   a. Need for tight volume control due to diastolic dysfunction
   b. Consider dynamic monitoring (pulse pressure variation, stroke volume variation) to optimize cardiovascular status
   c. Early diuresis may be needed to avoid pulmonary edema

3. Pulmonary Management
   a. Maintain aspiration precautions
   b. Consider noninvasive ventilation in selected populations, especially COPD exacerbation and congestive heart failure

4. Renal Management
   a. Avoid nephrotoxic agents
   b. Use alternative imaging studies to avoid IV contrast
   c. Remove bladder catheters ASAP to decrease risk of infection
   d. Carefully dose drugs cleared by the kidney

Outcomes
1. Planned surgical admissions have better survival and quality of life post-ICU discharge than unplanned surgical and medical admissions (8,9)

2. Both morbidity and mortality after major surgery increase with age (10)

3. Long-term mortality as a metric may be flawed in the elderly population, and rather quality of life and other indicators should be considered.

4. Establishing and adhering to goals of care in end-of-life decision making is an important priority in caring for geriatric patients in the ICU.

5. Family experience during ICU admission and hospitalization, including after the patient’s death, may be an important outcome.

Discussion

The above case is representative of a geriatric patient with multiple comorbidities and an unplanned admission to the ICU. How quickly should her supratherapeutic INR be reversed in the setting of a subdural hematoma? Should reversal be accomplished with multiple units of fresh frozen plasma, vitamin K, or prothrombin complex concentrate? Administration of large volumes of plasma in a patient with no atrial kick and baseline diastolic dysfunction from years of hypertension could quickly result in pulmonary edema and respiratory failure, thus extreme care must be taken in reversing her supratherapeutic INR. 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 her family at the onset of care so that her goals of care coincide with the treatment plan.

References:


**Review Questions:**

1. An 82 year old woman is brought to the hospital by her family who noticed that she was confused, lethargic, and has had a cough for 1 week. CXR reveals right lower and middle lobe infiltrates. In the ED, she develops respiratory distress and cyanosis requiring endotracheal intubation. She is started on broad-spectrum antibiotics for community-acquired pneumonia. Which of the following sedation infusions is best for this patient?
   a. Lorazepam
   b. Hydromorphone
   c. Dexmedetomidine
   d. Ketamine

2. An 86 year old man presents to the emergency department with a COPD exacerbation. He has previously filled out an advanced directive that states “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 him to be intubated
   b. Ask the patient, “Do you want me to place a breathing tube to make your breathing easier?”
   c. Place the patient on bi-level non-invasive ventilation
   d. Intubate the patient and treat him for a COPD exacerbation

3. An 87 year old man is admitted to the ICU after an exploratory laparotomy for a SBO. A 20-cm portion of proximal jejunum was removed with creation of an end-to-end anastomosis. He
received 3 liters of crystalloid in the ED and 3 liters of crystalloid intraoperatively. On physical exam, crackles and wheezes are heard bilaterally. His BP is 158/84, HR 90, RR 25 and SaO₂ 91%. CXR shows hilar congestion and cephalization of pulmonary vessels. What is the next best step?

a. Intubate the patient for respiratory distress

b. Place the patient on noninvasive ventilation

c. Administer 40 mg furosemide IV

d. Place a pulmonary artery catheter to determine LV loading conditions and function of the heart
I. Life-threatening Dermatoses: Only a few dermatologic disorders are life-threatening.

A. Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). The extent of body surface area (BSA) involved in epidermal detachment is the only difference between SJS and TEN. SJS involves <10%, TEN involves >30%, and 10-30% represents a transitional state. The pathophysiology is poorly understood, however both disorders are thought to be caused by a reaction to a medication or an infection. Common offending agents include antibiotics, anticonvulsants, NSAIDS, and allopurinol. Initial symptoms often present within three weeks of administration of the causative medication. (3) Systemic symptoms precede skin lesions by several days and include malaise, fever, cough, sore throat, ocular pain and mucosal erosions. Patients then develop...

Patient Case:
A 47-year-old woman with no significant past medical history is admitted to the ICU two-weeks after a lumpectomy. She completed her prophylactic course of sulfamethoxazole-trimethoprim. Upon admission, she is febrile to 39.2°C, has a symmetric, truncal maculopapular rash, diffuse lymphadenopathy, transaminitis, and leukocytosis with eosinophilia. What diagnoses would you consider? How would you manage this patient?
painful, burn-like, erythematous macules with irregular borders on the trunk, extremities, and oropharynx. Lesions coalesce, necrotize within the center, and blister. Full-thickness epidermal sloughing ensues, exposing the dermis. The Nikolsky sign, the detachment of epidermis with lateral traction, is characteristic of this disease. Laboratory findings include anemia, lymphopenia, thrombocytopenia, hypoalbuminemia and hypocalcemia. Histologic findings of epidermal necrosis with sparing of the dermis confirms the diagnosis. (3)

Since the outer layer of the epidermis, the stratum corneum, is lost, patients are at high risk for infection. Substantial fluid losses, which can exceed 4 L/day with 50% BSA involvement, can also be encountered. (4) Moreover, cutaneous vasodilation increases cardiac output. Maintaining intravascular volume is crucial for preventing end-organ ischemia. (4) Hospital mortality, which ranges from 20-70%, may be estimated using the SCORTEN scale. (2) Mortality rates are increased by concomitant respiratory failure and culprit drugs with a long half-life. (3) Treatment includes immediate discontinuation of the offending medication, referral to an ICU specializing in burn treatment, fluid resuscitation, nutritional optimization, and aggressive wound care (routine skin debridement and continuously moist, silver-releasing dressings). (5) Outcomes may be improved following the treatment algorithm proposed by McCullough et al. (5) Interestingly, withholding nonessential medications decreases mortality rate in TEN by 30%/day. (3) Antibiotics should only be administered for proven infections and ophthalmology must be consulted promptly since ocular lesions can lead to permanent blindness. The use of systemic corticosteroids and intravenous immunoglobulin (IVIG) is controversial. Studies show equivocal benefit weighed against the increased the risk of sepsis, protein catabolism and decreased rate of epithelialization. IVIG risks include renal, hematologic, and thrombotic complications.

B. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is a syndrome of severe immunologic aberrancy that typically presents 2-6 weeks after administration of the culprit drug. Mortality rates approach 10%. The diagnosis is clinical and is frequently missed, though may be aided by the RegiSCAR Scoring System. (6) Common findings include a truncal maculopapular exanthema, fever, lymphadenopathy, eosinophilia, transaminitis, and reactivation of dormant herpesvirus infections. Common culprits include sulfonamide antibiotics, anticonvulsants (especially carbamazepine), and allopurinol. Immediate discontinuation of all non-essential medications is the first step in management, followed by high-dose systemic corticosteroids and supportive care.

C. Toxic Shock Syndrome (TSS) presents with fever, shock, multiple organ failure and a diffuse, blanching erythematous exfoliative exanthema. TSS is often a result of toxins mediated
by group A streptococcus or S. aureus. Supportive care and
empiric antibiotics (clindamycin, with or without a penicillin
derivative) are imperative. (3)

II. Infectious Skin Disorders

A. Cellulitis is a bacterial skin infection. Surgical incisions are
particularly vulnerable. The most common causative bacteria
are Streptococcus pyogenes and Staphylococcus aureus.
Lesions are tender, warm, edematous, erythematous, and have
ill-defined borders. Symptoms include fever, chills, and
malaise. (7) Anaerobe involvement is less frequent, though
when present, lesions often demonstrate subcutaneous gas
and soft tissue necrosis. Suppuration or abscess formation
typically requires aspiration and drainage. Gram stain and
culture of the lesions should be obtained before initiation of
antibiotics if this is possible without causing a significant delay
in administration of antibiotics. For gram-positive infections, a
penicillinase-resistant penicillin, first generation cephalosporin,
vancocycin, or clindamycin may be used.

B. Necrotizing Fasciitis (NF) is a bacterial skin infection which
involves the deep fascia and is characterized by its rapid
spread (via the fascial cleft and subcutaneous fat). It is the
most common dermatologic reason for ICU admission and if
not treated, NF quickly progresses to sepsis and death. (3) In
fact, in-hospital mortality rates of 74% have been reported. (2)
Since superficial skin is not involved until later in the disease
process, the visual appearance may not reflect severity and a
high index of suspicion is paramount for timely diagnosis.
Bacterial invasion occurs at sites of minor trauma, surgical
incisions, or decubitus ulcers. NF is characterized by rapid
spread, tenderness out of proportion to physical exam
findings. Necrosis and bullae become evident within 24 hours.
(3) The most common culprit is group A streptococcus, though
polymicrobial infections also occur. NF involving the genitalia,
referred to as Fournier syndrome, is especially dangerous since
a paucity of subcutaneous fat between the superficial and
deep fascia allows for accelerated bacterial invasion. Diagnosis
of NF is clinical and treatment includes aggressive surgical
debridement, empiric antibiotics guided by initial gram stain,
and monitoring for development of compartment syndrome.
Repeat surgical exploration is usually necessary, as any
residual necrotic tissue may cause disease progression. (7)

C. Varicella Zoster Virus: Herpes zoster (shingles) is commonly
seen in ICU patients because physiologic stress and immune
suppression allows for reactivation of dormant virus within the
dorsal root ganglia. Spread then occurs along the nerve root.
Intense pain precedes onset of the rash, which is typically
unilateral, dermatomal, and does not cross midline. Lesions
appear as vesicles on an erythematous base. Patients are
contagious (aerosolized/respiratory and vesicular fluid contact)
from two days prior to lesion onset until all lesions have
crusted over. Intravenous acyclovir is the mainstay of therapy.
D. Candidal intertrigo is the most common localized dermatologic lesion in ICU patients. (1,8) Risk factors include warmth, humidity, broad-spectrum antibiotics, elevated blood glucose, and total parenteral nutrition. Lesions commonly arise in moist areas (intertriginous folds, axillae, and groin) as erythematous, polycyclic plaques with well-defined, raised borders, central clearing, scaling and peripheral satellite lesions. Diagnosis is clinical, though may be confirmed by visualizing pseudohyphae on potassium hydroxide mount or culture. Treatment includes twice-daily application of allyamines (naftifine, terbinafine) or imidazoles (ketoconazole, clotrimazole).

III. Non-Infectious Conditions

A. Drug Reactions: Adverse cutaneous drug reactions (ACDRs) are the most common generalized skin lesions to develop after ICU admission, with an incidence of 15%. (1,8) The immunologic mechanisms differ from allergic reactions, which are discussed next. Common culprits include antibiotics, NSAIDS, and antiepileptics. (3) The diagnosis is largely clinical and based on a temporal relationship between a medication and rash appearance. Lesions are typically maculopapular, with a symmetric, truncal distribution. Note that eruptions due to corticosteroids are associated with acneiform lesions. Most ACDRs lack major clinical significance, however, signs that the reaction may become serious are outlined in Table 1. (3)

B. Allergic Drug Reactions

Table 10.8.1 Indicators that an Adverse Drug Reaction May Become Serious

<table>
<thead>
<tr>
<th>Cutaneous Findings</th>
<th>Systemic Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confluent erythema</td>
<td>High fever (&gt; 40° C)</td>
</tr>
<tr>
<td>Rash or edema involving the face</td>
<td>Lymphadenopathy</td>
</tr>
<tr>
<td>Tender skin lesions</td>
<td>Joint pain</td>
</tr>
<tr>
<td>Palpable purpura</td>
<td>Dyspnea, wheezing</td>
</tr>
<tr>
<td>Necrotizing skin lesions</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Vesicles/ Bullae</td>
<td></td>
</tr>
<tr>
<td>Positive Nikolsky sign</td>
<td>Laboratory Findings</td>
</tr>
<tr>
<td>Mucous membrane erosions</td>
<td>Abnormal liver function tests</td>
</tr>
<tr>
<td>Urticaria</td>
<td>Lymphocytosis with atypia</td>
</tr>
<tr>
<td>Tongue edema</td>
<td>Eosinophilia (&gt;1000/mm$^3$)</td>
</tr>
</tbody>
</table>

Adapted from Lacouture et al (3) with permission

1. Anaphylactic Reactions are type I (IgE-mediated) drug reactions that usually manifest immediately, however, onset may be delayed up to 72 hours. (3) Anaphylaxis is suspected when patients present with signs and symptoms of massive histamine release (angioedema, bronchospasm, vasoplegia, and urticaria). Serum tryptase levels remain elevated for 1-2 hours after initial mast cell degranulation and support the diagnosis. Common
causative agents include antibiotics, neuromuscular blockers, iodinated contrast dye, and NSAIDs. Management includes immediate discontinuation of the offending agent, administration of epinephrine (to halt further mast cell degranulation, reverse bronchoconstriction and angioedema, and support hemodynamics), airway management, cardiovascular resuscitation (IV fluids and vasopressors, if indicated), corticosteroids, and histamine receptor antagonists.

2. Allergic Contact Dermatitis (ACD) is a delayed-type hypersensitivity reaction caused by T-cells directed at the offending agent. The incidence in ICU patients is 5-10%. The rash presents 4-7 days after allergen contact, though sooner if the patient had a previous exposure. Lesions occur at the site of allergen contact and are pruritic, scaly, erythematous, and vesicular. Chlorhexidine is the most common culprit in ICU patients. (1)

C. Anticoagulant-Induced Dermatoses

1. Heparin is associated with a delayed type-IV skin reaction that appears at injection sites between 2-5 days after administration. Lesions are erythematous, vesicular, and often pruritic. They may progress to skin necrosis 5-10 days after therapy initiation. Heparin should be promptly discontinued as patients are at increased risk of developing heparin-induced thrombocytopenia type II. (3)

2. Warfarin initiation is associated with a brief hypercoagulable state due to depletion of anticoagulant proteins C and S prior to that of pro-coagulant factors II, VII, IX and X, which can produce occlusive thrombi to dermal and epidural veins and subsequent skin necrosis. Erythematous plaques arise 3-10 days after warfarin initiation and progress to necrotic eschars. When skin necrosis is present, the mortality rate is 15%. Therapy includes immediate discontinuation of warfarin, anticoagulation with IV Heparin, and possible surgical debridement. (3)

D. Miliaria (“heat rash”) is common in ICU patients with an incidence of 2.2-10%. (1) Clear vesicles or erythematous papules develop due to the obstruction of eccrine glands, often underneath surgical dressings. Treatment includes reducing warmth and moisture at affected sites.

E. Pressure Ulcers are skin lesions found commonly in critically ill elderly patients with prolonged immobilization (although lesions may develop after just two hours). (1) The pathogenesis involves pressure-induced obstruction of circulation and subsequent tissue ischemia. There are four stages of pressure ulcers: I-persistent erythema on intact skin, II-partial-thickness skin breakdown of the epidermis and/or dermis, III-skin breakdown reaching subcutaneous tissues, though not extending through fascia, IV-skin damage extending through
fascia. Prevention includes frequent patient repositioning, optimization of nutrition status, and skin hygiene. (3)

IV. Other Medical Conditions with Dermatologic Clues to Diagnosis

A. Infective endocarditis can present with petechiae (30% of patients), called splinter hemorrhages in nail beds, Roth spots when involving retina, and Janeway lesions when on palms and soles. (3)

B. Purpura are due to meningococcus-induced thrombi and endotoxin-induced DIC. (3) Neisseria meningitides must be suspected when patients present with shock and concurrent petechiae, ecchymoses, or purpura. This can progress to purpura fulminans, with hemorrhagic bullae within purpuric patches. Serum gram stain and smear or serum PCR may confirm the diagnosis. The mortality rate exceeds 70%. Appropriate antibiotics (high-dose penicillin, Cefotaxime, or Ceftriaxone) must be initiated immediately. (3)

References:


Review Questions:

1. The appearance of scattered erythematous plaques shortly after initiation of warfarin:
   
a. May be prevented by high initial doses of warfarin
   
b. Typically occurs 3-10 days after initiation of therapy
   
c. Is clinically insignificant
   
d. Is due to excessive levels of proteins C and S

2. Regarding TEN:
   
a. The Nikolsky’s sign is diagnostic
   
b. <10% BSA is involved
   
c. Fluid losses may exceed 4L/day
   
d. Fluid losses may exceed 4L/day

3. In necrotizing fasciitis:
   
a. Superficial skin discoloration is the first sign
   
b. Group A *Streptococcus* is the most common culprit
   
c. IV antibiotics alone are usually sufficient
   
d. An indolent form is termed Fournier syndrome
I. Epidemiology

According to the WHO, more than 500,000 deaths each year are due to unintentional drowning. In the United States, drowning is the second leading cause of injury-related death among children 1 to 4 years of age, with a death rate of 3 per 100,000. For every person who dies from drowning, another four people receive care in the emergency department for nonfatal drowning. (1,4)

Patient Case 1:
An 8 year old boy was rescued by emergency services after falling through the ice on a frozen lake while ice fishing with his family. No one in attendance including the victim were strong swimmers or trained in rescue techniques. His total submersion time was 22 minutes. What are your major concerns in this case?

Patient Case 2:
A 56 year old man was found face down in a puddle of water near his home after an unknown downtime. Initial evaluation by EMS revealed an elderly male exhibiting respiratory distress with a GCS of 10 (E+V+M=2+3+5). A past medical history of hypertension, diabetes, stroke and CAD was obtained. What complications do you anticipate in this case? What do you anticipate as the cause of drowning in this particular case?
II. Definition

“Drowning is the process of experiencing respiratory impairment from submersion/immersion in liquid”. The presence of respiratory impairment is a key point. Any submersion or immersion incident without evidence of respiratory impairment should be considered a water rescue and not a drowning. Although the terms “near drowning,” “dry or wet drowning,” “secondary drowning,” “active and passive drowning,” and “delayed onset of respiratory distress” appear in older literature, they historically did not include information related to respiratory impairment and as such they should be avoided. (5)

III. Pathophysiology

Early drowning literature stressed different hemodynamic and electrolyte effects on victims based upon the osmolality of the water aspirated. More recent literature has downplayed the effect of osmolarity of the solution aspirated and describes a common pathway leading to similar degrees of injury for all submersions. The initial injury is from hypoxemia secondary to apnea. Later, progressive hypoxemia is related to the development of acute lung injury from surfactant disruption, abnormal alveolar function, alveolar collapse, atelectasis and intrapulmonary shunting. Acute apnea induced hypoxia precedes the sequence of cardiac rhythm deterioration which is marked by tachycardia followed by bradycardia, pulseless electrical activity, and, finally, asystole. Generally the sequence of drowning is a process which occurs in seconds to a few minutes, but in unusual situations, when associated with rapid hypothermia, the process can last for an hour. It has been postulated that hypothermia associated with drowning provides a protective mechanism that allows affected individuals to survive prolonged submersion episodes (Diving Reflex). (4,6)

IV. Cardiopulmonary resuscitation

Cardiac arrest from drowning is primarily due to lack of oxygen. For this reason, it is important that CPR follows the traditional airway–breathing–circulation (ABC) sequence, rather than the circulation–airway–breathing (CAB) sequence. This sequence starts with five initial rescue breaths, followed by 30 chest compressions, and continues with two rescue breaths and 30 compressions until: 1) return of spontaneous circulation, or 2) advanced life support becomes available. Successful outcomes after an extended period of advanced life support or until the patient has been rewarmed (if the patient has presented in asystole and hypothermic) have been reported. The practice of rapid rewarming of hypothermic victims should be avoided. (4,7)

Recent emphasis on ventilation has discouraged the previous use of active efforts to expel water from the airway (by means of abdominal thrusts or placing the person head down). Any such maneuvers serve only to delay the initiation of ventilation and greatly increase the risk of emesis with an associated significant increase in mortality. (4) In contrast to the historical trauma adage
that all injured persons should be assumed to have a cervical spine injury until proven otherwise, injuries to the cervical spine occur in less than 0.5% of persons who have drowned. Immobilization of the spine in the water is indicated only in cases in which head or neck injury is strongly suspected (e.g., accidents involving diving, water-skiing, surfing, or watercraft). (8)

V. Care in the Emergency Department

Ventilation is paramount. Efforts to secure the airway, stabilize the circulation, insert a naso-gastric tube and rewarm the patient are key principles in initial resuscitation. Rapid rewarming should be avoided. (4,7) Following a thorough physical examination, chest radiography, measurement of arterial blood gases, and an initial toxicology screen should be sent if supported by rescuer observations. (9) Metabolic acidosis occurs in the majority of patients, and generally improves with resuscitation and ventilation. The routine use of sodium bicarbonate is not recommended. Drowning may be precipitated by an injury or medical condition (e.g., trauma, seizure, or cardiac arrhythmia), and such conditions affect treatment decisions. In patients with a known seizure disorder, status epilepticus should be ruled out and anti-epileptic medications appropriately dosed. If the person remains unresponsive without an obvious cause, a toxicologic screen and computed tomography of the head and neck should be reviewed as soon as possible. (7)

VI. Care in the ICU

A. Respiratory System: In the ICU, the current treatment resembles that of patients with acute respiratory distress syndrome (ARDS). However, since the pulmonary lesion is caused by a temporary local injury, patients with lung injury due to a drowning incident tend to recover much faster than patients with more traditional causes of ARDS. Late pulmonary sequelae are uncommon. It is usually best not to initiate weaning from mechanical ventilation for at least 24 hours, even when gas exchange appears to be adequate, as pulmonary edema may reoccur, necessitating reintubation and further morbidity. There is little evidence for the use of glucocorticoid therapy for reducing pulmonary injury and this practice should be avoided. (2)

Pneumonia is often misdiagnosed initially. In a series of hospitalized cases, only 12% of patients rescued from drowning had pneumonia and needed treatment with antibiotic agents. Early use of prophylactic antibiotics can lead to increased antibiotic resistance and aggressive multi-drug resistant organisms. (10) Patients should be monitored daily for definite fever, sustained leukocytosis, and persistent or new pulmonary infiltrates. Bronchoscopy is reserved for therapeutic clearing of mucus plugs or solid material, or deep cultures in the event of suspicion of pneumonia. If present, an early-onset pneumonia can be due to the aspiration of polluted water,
endogenous flora, or gastric contents. Once a diagnosis is made, empirical therapy with broad-spectrum antibiotics, covering the most predictable gram-negative and gram-positive pathogens, should be started and definitive therapy should be substituted once the results of culture and sensitivity testing are available. (4,10) Submersion in polluted water should raise the suspicion of uncommon pathogens such as *Aeromonas* sp. or fungi. In general the pulmonary insults clear rapidly, however in some patients, pulmonary function deteriorates in such a dramatic fashion that adequate oxygenation can only be maintained with the use of extracorporeal membrane oxygenation (ECMO). (see Chapter 5.7) (2,10)

B. **Circulatory System:** In the majority of patients who have been rescued from drowning, the circulation rapidly stabilizes and becomes adequate after attention to oxygenation, fluid resuscitation, and restoration of normal body temperature occurs. Infrequently, early cardiac dysfunction can occur in severe cases, and this cardiogenic component adds to the noncardiogenic pulmonary edema. No evidence supports the use of a specific fluid therapy, diuretics, or water restriction in persons who have been rescued from drowning in salt water or fresh water. (7) Echocardiography may help guide fluid and vasopressor therapies.

C. **Neurological System:** Permanent neurologic damage is the most dreaded outcome in resuscitated persons after a drowning incident. Brain oriented resuscitation strategies have been recommended to improve neurological outcomes. The injured brain is extremely vulnerable to secondary insults and goals to achieve normal values for glucose, partial pressure of arterial oxygen, partial pressure of carbon dioxide, and cerebral metabolic oxygen consumption have been outlined. (see Chapter 3.1) Arterial hypotension should be anticipated, recognized and treated vigorously. (7)

The main goal is to prevent hyperthermia and the resultant increase in metabolism by aggressively reducing fever. If the patient is neurologically impaired and normothermic, cooling should be started as soon as possible. In cases of neurologic impairment and hypothermia, a goal to maintain a target temperature at 32-34 °C for 12-72 hours is suggested. Provision should be made for appropriate sedation and the prevention of shivering if cooling is used. Clinical seizures or non-convulsive status epilepticus should be investigated and treated. Consideration should be given to CT, MRI, EEG, SSEPs, and serum biomarkers-such as neuron-specific enolase as aides to assist in prognostication. (7)

D. **Unusual Complications:** Sepsis and disseminated intravascular coagulation are possible complications during the first 72 hours after resuscitation. Renal insufficiency or failure is rare, but can occur as a result of anoxia, shock, myoglobinuria,
or hemoglobinuria. (3,4,6)

VII. Prognosis

Reported survival rates for drowning victims vary from approximately 5-28%, although many of the survivors will have varying degrees of neurological impairment. The following features have been associated with death or poor neurological outcomes:

1. Submersion greater than 5-10 minutes.
2. Resuscitation not attempted for more than 10 minutes after rescue.
3. More than 25 minutes of resuscitation to achieve ROSC.
4. Glasgow coma score (GCS) less than 5 or unreactive pupils on arrival to hospital.
5. Pulselessness and apneic on arrival to hospital.
6. pH <7.10 on initial arterial blood gas.

VII. Prevention

Every drowning signals the failure of the most effective intervention - namely, prevention. It is estimated that more than 85% of cases of drowning can be prevented by supervision, swimming instruction, technology, regulation, and public education. (11)

References:

Review Questions:

1. Which of the following is true about drowning?
   a. It is the most common cause of unintentional death worldwide.
   b. It is more common in developed countries than developing countries.
   c. Drowning is associated with laryngospasm when there is prior loss of consciousness.
   d. Cardiac arrest frequently occurs early due to hypoxia and acidosis.

2. Which of the following is true regarding resuscitation of the pulseless patient with drowning?
   a. Start with chest compressions as per BLS protocol and analyze for a shockable rhythm as soon as feasible.
   b. It is associated with good outcome when duration of cardiopulmonary resuscitation (CPR) exceeds 25 min.
   c. Rewarm the patient to at least 32°C, at 0.5°C per hour.
   d. Focus on immediate ventilation followed by chest compressions as per BLS protocol.

3. Pulmonary injury associated with drowning is:
   a. Less severe after saltwater immersion than freshwater immersion.
   b. Treated with prophylactic antibiotic therapy.
   c. Treated with glucocorticoids.
   d. Treated the same as ARDS.

4. Which of the following factors are most likely to be associated with poor outcome after drowning:
   a. Submersion greater than 5-10 minutes.
   b. Resuscitation > 25 minutes.
   c. GCS < 5 on presentation.
   d. All of the above.
Introduction:

The probability of a large scale bioterrorist attack is low. However, if one occurred, the number of victims would likely overwhelm public health facilities and challenge a hospital’s ability to follow conventional critical care practices.

For regional and individual hospitals, preparedness and planning are of vital importance during the time of an emergency mass critical care crisis. Emergency mass critical care (EMCC) requires modification to standards of critical care interventions, staffing and equipment. Preparedness is focused on proper triage, protection of health care workers, disease containment and efficient use of resources (staff, medications, equipment, etc.).

**Table 10.10.1** Inclusion Criteria for Admission to ICU during MCE

<table>
<thead>
<tr>
<th>Category</th>
<th>Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Requirement for invasive ventilator support</td>
</tr>
<tr>
<td></td>
<td>- Refractory hypoxemia (SpO₂ &lt;90% on FiO₂ &gt;0.85)</td>
</tr>
<tr>
<td></td>
<td>- Respiratory acidosis with pH &lt;7.2</td>
</tr>
<tr>
<td></td>
<td>- Clinical evidence of impending respiratory failure</td>
</tr>
<tr>
<td></td>
<td>- Inability to protect or maintain airway</td>
</tr>
<tr>
<td>B</td>
<td>Hypotension</td>
</tr>
<tr>
<td></td>
<td>- SBP &lt;90mmHg or relative hypotension with clinical evidence of shock refractory to volume resuscitation requiring vasopressor/inotrope support</td>
</tr>
</tbody>
</table>

**Key Points:**

- Although the probability of occurring is low, hospital preparedness and planning is critical for response in the event of a bioterrorist attack.
- Triage with the goal of helping the greatest number of people is the first step in providing critical care in the event of a bioterrorist attack.
- Protection of health care workers by providing training and appropriate personal protective equipment is imperative during a massive critical care event.
- Aerosolization of viruses, bacteria, or toxins is the most common threat in bioterrorism.
Triage:

Unlike conventional ICU triage, in which patients likely to benefit from critical care are admitted to and remain in the ICU on a first come first serve basis, during emergency mass critical care, triage is guided by the principle of ensuring the greatest number of people survive the crisis. Each hospital or region may develop their own triage algorithm based on severity of illness score systems (APACHE, SOFA, etc.). Table 1 and table 2 show a proposed ESICM inclusion and exclusion criteria for critical care during a massive casualty event. Table 3 is an example of a triage prioritization tool.

Protecting health care workers:

Contagious pathogens present singular operational challenges that must be anticipated in planning for mass critical care. All critical care staff should be explicitly and routinely trained in infection control procedures, including how to don and doff personal protective equipment (PPE) without contaminating themselves or the nearby environment; what protection is afforded by different levels of PPE; and what environmental controls must be employed for a given situation.

Critical care support:

The working group on EMCC recommends that care should include, when applicable, the following:

---

**Table 10.10.2** Exclusion Criteria from Admission to ICU during a MCE

<table>
<thead>
<tr>
<th>Patient excluded from admission to ICU if any of following is present</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
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<td>B</td>
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</tbody>
</table>

1. Mechanical ventilation
2. IV fluid resuscitation
3. Vasopressor administration
4. Antidote or antimicrobial administration for specific diseases

5. Sedation and analgesia

6. Select practices to reduce adverse consequences of critical illness and critical care delivery

7. Optimal therapeutic and interventions (RRT, nutrition, chest tube placement etc.)

**Table 10.10.3** Triage Prioritization Tool

<table>
<thead>
<tr>
<th>Color code</th>
<th>Initial Assessment</th>
<th>48 Hr Assessment</th>
<th>120 Hr Assessment</th>
<th>Priority/Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blue</td>
<td>Exclusion criteria or SOFA &gt;11</td>
<td>Exclusion criteria or SOFA &gt; 11 or SOFA 8-11 no Δ</td>
<td>Exclusion criteria or SOFA &gt; 11 or SOFA &lt;8 no Δ</td>
<td>Medical management +/- Palliative &amp; d/c from ICU</td>
</tr>
<tr>
<td>Red</td>
<td>SOFA &lt;7 or Single organ failure</td>
<td>SOFA &lt; 11 and decreasing</td>
<td>SOFA &lt;11 and decreasing progressively</td>
<td>Highest</td>
</tr>
<tr>
<td>Yellow</td>
<td>SOFA 8-11</td>
<td>SOFA &lt;8 no Δ</td>
<td>SOFA &lt;8 with &lt; 3 point decrease in past 72 hr</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Green</td>
<td>No significant organ failure</td>
<td>No longer ventilator dependent</td>
<td>No longer ventilator dependent</td>
<td>Defer or d/c, reassess as needed</td>
</tr>
</tbody>
</table>

**Guidelines:**

Clinical guidelines for the management of bioterrorist attack focus on the disease-specific antimicrobial agents for the specific weaponized pathogen. Table 4 summarizes the most widely recognized biological agents used during bioterrorist attacks.

**Anthrax**

1. **Agent:**
   
   Bacillus anthracis (gram positive, spore forming bacteria)

2. **Presentation and manifestation:**

   Aerosolized anthrax spores giving rise to inhalational anthrax. Alveolar macrophages phagocytose inhaled spores and are transported to mediastinal lymph node. Antiphagocytic capsule and 3 toxins (lethal factor, edema factor and protective antigen) lead to edema, hemorrhage, and necrosis causing thoracic lymphadenitis and hemorrhagic mediastinitis.

   Clinically, toxemia manifests with fever, chills, weakness, headache, vomiting, abdominal pain, dyspnea, cough, chest pain, and shock. Laboratory studies can show hypocalcemia, hypoglycemia, hyperkalemia, and acidosis. Chest x-ray may reveal mediastinal widening, pleural effusions and CT chest may show mediastinal lymphadenopathy. Diagnosis can be done by polymerase chain reaction (PCR) using nasal swabbing, blood culture, pleural fluid culture, and/or CSF fluid culture. Confirmatory test is with ELISA.

3. **Treatment:**

   Ciprofloxacin 400mg IV BID, Doxycycline 200mg IV then 100mg IV BID x 60 days. Supportive care includes: mechanical
ventilation for respiratory failure, vasopressors and fluid administration for shock, chest tube placement for pleural effusion, steroids (brain edema) and antiepileptics (seizure) in case of meningeal involvement. Complications include hemorrhagic meningitis (50% cases) and necrotizing enteritis (33% cases).

**Smallpox**

1. **Agent:**

Variola virus (orthopoxvirus family) which is highly infectious via inhalation of respiratory droplet nuclei or via direct contact of mucous membrane or fomites.

2. **Presentation and manifestation:**

Upon deposition in the upper airway mucosa, the virus migrates to regional lymph nodes followed by asymptomatic viremia with dissemination to spleen, bone marrow, and other lymph nodes (3-4 days). Secondary viremia occurs between days 8 and 12 with onset of fever and toxemia. By day 14, the virus localizes in small blood vessels of the dermis and oropharyngeal mucosa (onset of exanthema and enanthem).

The classic or ordinary type (90% of cases) starts with prodromal symptoms (fever, malaise, headache, backache) 2-4 days before a rash appears. Typical progression of rash starts with enanthema of tongue, mouth, and oropharynx, followed by a centrifugal rash (2-3mm reddish macules that begin on face, palms, soles and forearms) that progress to papules, and then vesicles that spread centrally to cover the whole body. Vesicles become pustules that then umbilicate centrally. By day 13, these start to crust and scab. The rash is typically more peripherally distributed and homogenous in stage compared to chickenpox. The hemorrhagic form has a shorter more severe prodromal phase and clinically appears with diffuse hemorrhagic lesions on the mucous membranes and skin, pulmonary edema and hemoptysis. Diagnosis is mainly clinical. Definitive diagnosis is by isolation of virus on chorioallantoic membrane culture and PCR.

3. **Management:**

   a. Contact and airborne isolation to prevent spread of infection

   b. Supportive care and treatment of complications:

   There is a high degree of fluid sequestration complicated by renal failure, electrolyte imbalance, protein loss and metabolic derangement (similar to burn victims). Mechanical ventilation may be required (hemorrhagic type). In addition, treatment of shock and superimposed infections, maintenance of fluid and nutritional balance, and skin care are essential parts of management.

**Plague**
1. Agent:

Yersinia pestis (nonmotile, Gram negative bipolar coccobacillus)

2. Transmission:

Bite by infected flea (Xenopsylla cheopsi), inhaling respiratory secretions of animals or humans with pneumonic forms of plague, or direct handling of infected animal tissues.

3. Manifestation:

Bubonic plague manifests with sudden onset of fever, chills, weakness, headache, and acutely swollen lymph nodes (buboes). It progresses to high fever, tachycardia, vomiting, alteration in mental status, and septic shock in 2 days if not treated, leading to multi-organ failure and ARDS. Symptoms without buboes is called primary septicemic plague. Spread to the lung causes secondary pneumonic plague.

Inhalation of aerosolized bacteria from patients with secondary pneumonic plague or from weaponized Y. Pestis lead to primary pneumonic plague, characterized by sudden fever, chills, headache, body pain, weakness, and chest discomfort eventually progressing to cough, sputum production and hemoptysis. This constellation of symptoms results in hypoxemia and rapidly progressing respiratory failure. Buboes are absent and complications include localized necrosis, cavitation, pleural effusion, ARDS, DIC, septic shock and multiorgan failure. Primary pneumonic plague is highly infectious and mortality approaches 100% if antibiotic therapy is not started within 24 hours of onset.

4. Treatment:

First line therapy is streptomycin or gentamycin which should be given to any exposed person with a temperature >38.5 °C or a new cough. Post-exposure prophylaxis can be done with doxycycline or ciprofloxacin for 7 days. Patients with pneumonic plague should be placed under respiratory droplet isolation plus eye protection in addition to standard precautions until they have received at least 48 hours of appropriate antibiotic therapy or show clinical improvement.

Tularemia

1. Agent:

Francisella tularensis (gram negative, facultative intracellular bacillus).

2. Manifestation:

In case of bioterrorist attack, the more likely mode of transmission is the use of aerosolized F. tularensis. Tularemia has several manifestations including ulceroglandular (glandular, oculoglandular, and pharyngeal) and pneumonic (typhoidal).
forms. Typhoidal form is due to inhalation of microorganism and has an abrupt onset. Patients appear toxic (fever, headache, myalgia, nausea), and have pronounced abdominal pain, prostration and watery diarrhea. Respiratory symptoms and pneumonia occur in 80% of cases. Pharyngitis, pleuritic chest pain, cough with minimal sputum production, and bronchiolitis are common; however, hemoptysis is rare. It can progress to severe pneumonia, ARDS, septic shock with need for mechanical ventilation and vasopressor support but is rapidly responsive to appropriate antibiotics. Mortality is 35% for the pneumonic form without treatment and <5% with antibiotic treatment.

3. Treatment:

First line therapy is streptomycin or gentamycin for 10 days. Alternatives are doxycycline, chloramphenicol or ciprofloxacin. Recovery usually occurs by day 5-7. Isolation is not required since human-human transmission does not occur.

Botulinum toxin

1. Agent:

Clostridium botulinum (Gram positive, anaerobic, spore-forming bacillus).

2. Manifestation:

Most likely bioterrorism scenarios include contamination of food and aerosolization of toxin. Botulism infection results from absorption of the neurotoxin through a mucosal surface. Once absorbed, the toxin is carried to peripheral neuromuscular junctions where the toxin’s light chain irreversibly binds to various components of the synaptic fusion complex, preventing release of acetylcholine into the synaptic cleft (presynaptic inhibition). The toxin affects cholinergic, muscarinic and nicotinic receptors. Patients present with acutely developing fever, gastrointestinal complaints and rapidly progress to cranial nerve paralysis and bulbar symptoms (diplopia, dysphagia, dysarthria, ptosis, mydriasis). A progressive, bilateral, descending flaccid paralysis ensues followed by respiratory failure and death (if not supported). Mortality is <5% if treated and supported, and >60% if untreated.

3. Treatment:

Supportive critical care includes mechanical ventilation, prevention of secondary infection, and administration of an antitoxin (available from CDC). Diagnosis is clinical and treatment should not be delayed while awaiting confirmatory tests. Differential diagnosis includes other neuromuscular disorders (Guillain-Barre, Eaton-lambert, myasthenia gravis) and organophosphate or nerve gas poisoning.
<table>
<thead>
<tr>
<th>Disease (pathogen)</th>
<th>Incubation Period</th>
<th>Mode Transmission</th>
<th>Mortality Rate</th>
<th>Method of Diagnosis</th>
<th>Treatment (adults)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthrax (Bacillus anthracis)</td>
<td>4-6 days Spores can remain dormant for up to 60 days</td>
<td>Cutaneous Inhalation Gastrointestinal (rare)</td>
<td>Cutaneous: 20% Inhaled: 45%</td>
<td>- Gram stain, blood or wound culture - Rapid ELISA test</td>
<td>Ciprofloxacin 400 mg IV BID or Ciprofloxacin 500 mg po BID or Doxycycline 200 mg IV then 100 mg IV BID for 60 days</td>
</tr>
<tr>
<td>Smallpox</td>
<td>12-14 days</td>
<td>Aerosolization Direct contact Fomite</td>
<td>30%</td>
<td>- Clinical - Electron microscopy of vesicular fluid - Virus cell culture</td>
<td>Supportive treatment</td>
</tr>
<tr>
<td>Plague (Yersinia pestis)</td>
<td>2-8 days</td>
<td>Aerosolization Flea vector</td>
<td>Pneumonic: 100% (untreated)</td>
<td>- Clinical - Gram stain, sputum, blood or CSF - Wright's stain for bipolar staining</td>
<td>Streptomycin 30 mg/kg/day IM in 2 divided doses x 14 days or Gentamicin 5 mg/kg IM or IV qd x 14 days or Ciprofloxacin 400 mg IV BID until clinical improvement then 750 mg po BID for total of 14 days or Doxycycline 200 mg IV then 100 mg IV BID until clinically improved then 100 mg po BID to complete 14 days</td>
</tr>
<tr>
<td>Tularemia (Francisella tularensis)</td>
<td>1-14 days</td>
<td>Aerosolization Rodent vector</td>
<td>&lt;2%</td>
<td>- Sputum or blood culture - Sputum and blood for direct fluorescent antibody or immunohistochemical stain</td>
<td>Streptomycin 7.5-10 mg/kg IM BID for 14 days or Gentamycin 3-5 mg/kg/day IV x 14 days or Ciprofloxacin 400 mg IV BID until clinically improved then 500 mg po BID to complete 14 days or Ciprofloxacin 750 mg po BID x 14 days</td>
</tr>
<tr>
<td>Botulism (Clostridium botulinum)</td>
<td>2 hr-8 days</td>
<td>Aerosolization Food</td>
<td>Treated: &lt;5% Untreated: up to 60%</td>
<td>- Clinical - Serum bioassays</td>
<td>Supportive - Botulinum antitoxins (available from CDC)</td>
</tr>
<tr>
<td>Viral Hemorrhagic fevers</td>
<td>2-21 days</td>
<td>Aerosolization Rodent Mosquito Tick</td>
<td>10-90%</td>
<td>- ELISA or IgM Ab detection - RT-PCR - Viral isolation</td>
<td>Supportive treatment - Rivarivir (Crimean-congo, Lassa, Arenaviridae and Bunyaviridae) 30 mg/kg IV (max 2 gm) then 16 mg/kg (max 1 gm/dose) IV q6hr x 4 days then 8 mg/kg (max 500 mg/dose) IV q8h x 6 days</td>
</tr>
</tbody>
</table>

IV= intravenously  IM= Intramuscular  ELISA= enzyme-linked immunoabsorbent assay  CSF= cerebrospinal fluid  RT-PCR= reverse transcriptase polymerase chain reaction  Ab= antibody  BID= twice a day  qd= every day.
Viral Hemorrhagic Fever (VHF)

1. Agent:

RNA viruses: mainly arenaviruses (Lassa), filoviruses (Ebola and Marburg), bunyaviruses (Hantavirus) and flaviviruses (Dengue).

2. Manifestation:

Aerosolization is the most likely mode of terrorist dissemination. VHF viruses target vascular endothelium, causing microvascular damage and vascular permeability. Symptoms include fever, myalgias, malaise, headache, vomiting and abdominal pain. Examination is remarkable for conjunctival injection, hypotension, flushing, and petechial hemorrhages. It progresses to shock, generalized bleeding from mucous membranes, hepatic failure, renal failure, hemorrhagic diathesis, pulmonary involvement, and multiorgan failure. Each virus has unique features that set it apart clinically. Routine laboratory testing is nonspecific but presence of early thrombocytopenia and abnormal coagulation profiles should arouse suspicion. Definitive diagnosis is with isolation in cell culture or immunohistochemical staining (performed at CDC or USAMRIID).

3. Treatment:

Management is mostly supportive. Avoid antiplatelet agents (aspirin), and immunosuppressive medication (steroids). Transfusion of PRBCs, platelet, and clotting factors as needed. Hemodialysis and mechanical ventilation may be necessary. Treatment of hypotension and shock is often difficult and may require invasive hemodynamic monitoring to guide therapy. The only antiviral therapy available for VHF is ribavirin (nonimmunosuppressive nucleoside). It has been shown to reduce mortality in Lassa fever and has promise in treatment of arena- and bunya- viruses. Research in vaccination is ongoing, especially after the recent outbreak of Ebola virus. The only vaccine currently available is for yellow fever.

Adherence to strict isolation guidelines is very important in VHF since it is highly contagious to close contacts and medical personnel. Patients should be isolated in a single room with an adjoining anteroom serving as an entrance. Negative pressure rooms and strict respiratory precautions are appropriate in advanced cases. Stringent full barrier precautions with use of mask, glove, gown and needle precautions along with hazard labeling of all laboratory specimens is imperative. Access to quarantined patients should be restricted and all contaminated material should be incinerated or autoclaved.

References:


**Review Questions:**

1. Which of the following isolation precautions are necessary when caring for patients with viral hemorrhagic fever?
   a. Full barrier contact isolation precautions
   b. Airborne isolation precautions with negative pressure room
   c. Incineration and/or autoclaving of all material to come in contact with patient
   d. All of the above

2. A 50 year old farm worker presents to the emergency department with fever, abdominal pain and dysarthria. Over the course of hours, the patient develops progressive paralysis and respiratory failure requiring mechanical ventilation. Which of the following conditions is LEAST likely to be considered in the differential diagnosis?
   a. Acute myasthenic crisis
   b. Organophosphate poisoning
   c. Anthrax
   d. Botulism

3. All of the following are appropriate treatments for Anthrax EXCEPT
   a. Doxycycline IV x 60 days
   b. Gentamycin IV x 14 days
   c. Ciprofloxacin PO x 60 days
   d. Ciprofloxacin IV 60 days