CRITICAL CARE:
CARING FOR CRITICALLY ILL AND INJURED PATIENTS IN THE EMERGENCY DEPARTMENT

EMCREG-INTERNATIONAL MONOGRAPH BASED ON THE OCTOBER 27, 2015 SYMPOSIUM BOSTON, MA

COMPLIMENTARY CME MONOGRAPH
FEBRUARY 2016

This educational monograph was supported in part by an unrestricted educational grant from Janssen Pharmaceuticals
Dear Colleagues,

It is our pleasure to provide this February 2016 EMCREG-International Monograph which serves as the proceedings from our October 27, 2015, EMCREG-International satellite Symposium during the 2015 ACEP Scientific Assembly in Boston, MA. This is the first EMCREG-International Symposium and Monograph which focuses on the provision of critical care in the Emergency Department with Jordan B. Bonomo, MD, serving as Symposium Chairman. All of the speakers for the EMCREG-International Symposium on October 27, 2015, in Boston are the authors of this Monograph. These are emergency physician experts with specialty fellowship training in Critical Care. This EMCREG-International Monograph has been accredited by the University of Cincinnati Office of Continuing Medical Education for 4 hours of AMA PRA Category 1 Credits.

Emergency Physicians and Hospitalists care daily for patients who are critically ill and injured. The management of these patients is often complex and requires detailed diagnostic and therapeutic information, as well as a thorough understanding of disease pathophysiology. In this EMCREG-International Monograph, multiple critical care topics including critical respiratory illness/ventilator management and the current therapy for septic shock provide two major areas of interest to the practicing clinician. In addition, the treatment of significant deep venous thrombosis and pulmonary embolism (DVT/PE) and the management of atrial fibrillation are emphasized. For patients with DVT/PE and atrial fibrillation, pharmacologic management now extends beyond rate control and warfarin to treatment with Factor Xa inhibitors and other antagonists to the clotting cascade. For patients presenting to the Emergency Department with significant bleeding who are currently being treated with these agents, the clinician is given practical approaches to reverse the process. In addition, the treatment of patients post-cardiac arrest resuscitation is described, expanding their management beyond hypothermia in the Emergency Department and as an inpatient. Finally, the use of thromboelastography (TEG) to evaluate the critically ill and injured patient’s ability to clot blood is described. As you will note, this information has previously been presented in last month’s January 2016 EMCREG-International Monograph on Acute Coronary Syndrome as this topic is important to both discussions.

Thank you very much for your interest in the EMCREG-International organization as well as our symposiums and enduring material pieces. EMCREG-International is now entering its 27th year as a research and educational organization with membership that includes Steering Committee members from across the world. We appreciate Janssen Pharmaceuticals providing an unrestricted educational grant to help support the October 27, 2015 symposium and this monograph. We hope that you enjoy this February 2016 EMCREG-International Monograph exploring major critical care topics which will help you to continue to provide outstanding care to your patients.

Sincerely,

W. Brian Gibler, MD
President, EMCREG-International
Professor of Emergency Medicine
University of Cincinnati College of Medicine
Cincinnati, Ohio USA
CONTRIBUTING AUTHORS:

W. Brian Gibler, MD
President, EMCREG-International
Professor of Emergency Medicine,
Department of Emergency Medicine,
University of Cincinnati College of Medicine, Cincinnati, OH

Brian M. Fuller, MD, MSCI
Assistant Professor of Anesthesiology and Emergency Medicine; Department of Anesthesiology, Division of Critical Care, Division of Emergency Medicine, Washington University School of Medicine, St. Louis, MO

Nicholas M. Mohr, MD, MS
Departments of Emergency Medicine and Anesthesiology
Division of Critical Care
Roy J. and Lucille A. Carver College of Medicine
University of Iowa, Iowa City, IA

Gregory J. Fermann, MD
Professor & Executive Vice Chairman; Director, Clinical Trials Center, Department of Emergency Medicine, University of Cincinnati College of Medicine, Cincinnati, OH

Jon C. Rittenberger, MD, MS
Associate Professor, University of Pittsburgh Department of Emergency Medicine
Pittsburgh, PA

Evie G. Marcolini, MD
Assistant Professor, Departments of Emergency Medicine and Neurology, Divisions of Neurocritical Care and Emergency Neurology; Medical Director, SkyHealth Critical Care, Yale University School of Medicine, New Haven, CT

Charles V. Poliac Jr., MA, MD
Associate Provost for Innovation in Education; Director, Jefferson Institute of Emerging Health Professions; Professor and Senior Advisor for Interdisciplinary Research and Clinical Trials; Sidney Kimmel Medical College of Thomas Jefferson University
Philadelphia, PA

Jordan B. Bonomo, MD
Associate Professor, Emergency Medicine; Director, Division of Critical Care; Department of Emergency Medicine; Associate Professor, Neurosurgery; Neurocritical Care; Director, Neurocritical Care Fellowship, University of Cincinnati College of Medicine, Cincinnati, OH

Natalie E. Kreitzer, MD
Assistant Professor of Emergency Medicine Fellow, Neurovascular Emergencies and Neurocritical Care
Department of Emergency Medicine
University of Cincinnati College of Medicine
Cincinnati, OH

Christopher R. Zammit, MD
Assistant Professor of Emergency Medicine and Neurology
Department of Emergency Medicine, Critical Care Division
University of Cincinnati College of Medicine
Cincinnati, OH

Christopher M. Palmer, MD
Assistant Professor of Anesthesiology and Emergency Medicine, Department of Anesthesiology, Division of Critical Care, Division of Emergency Medicine, Washington University School of Medicine, St. Louis, MO

Trenton C. Wray, MD
Critical Care Fellow
Division of Critical Care, Division of Emergency Medicine, Washington University School of Medicine, St. Louis, MO
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<td>Gregory J. Fermann, MD</td>
<td>Advisory Board: Janssen, Pfizer; Consultant: Janssen, Pfizer, Novartis; Speaker’s Bureau: Janssen</td>
</tr>
<tr>
<td>Barb Forney</td>
<td>No relevant relationships</td>
</tr>
<tr>
<td>Brian M. Fuller, MD</td>
<td>No relevant relationships</td>
</tr>
<tr>
<td>W. Brian Gibler, MD</td>
<td>Advisory Board: AstraZeneca, Entegrion, Intelemage; Shareholder: Intelemage, Siloam, MyocardioCare, Entegrion</td>
</tr>
<tr>
<td>Natalie E. Kreitzer, MD</td>
<td>No relevant relationships</td>
</tr>
<tr>
<td>Evie G. Marcolini, MD</td>
<td>Advisory Board: AstraZeneca, Novartis, Janssen</td>
</tr>
<tr>
<td>Nicholas M. Mohr, MD</td>
<td>No relevant relationships</td>
</tr>
<tr>
<td>Charles V. Pollack, Jr., MD</td>
<td>Consultant: Boheringer, Ingelheim, Janssen, BMS/Pfizer, Daiichi-Sankyo</td>
</tr>
<tr>
<td>Jon C. Rittenberger, MD</td>
<td>Grant Recipient: AHA, National Institutions of Health, David Scaife Foundation</td>
</tr>
<tr>
<td>Christopher M. Palmer, MD</td>
<td>No relevant relationships</td>
</tr>
<tr>
<td>Rick Ricer, MD</td>
<td>No relevant relationships</td>
</tr>
<tr>
<td>Susan P. Tyler</td>
<td>No relevant relationships</td>
</tr>
<tr>
<td>Trent C. Wray</td>
<td>No relevant relationships</td>
</tr>
<tr>
<td>Christopher R. Zammit, MD</td>
<td>No relevant relationships</td>
</tr>
</tbody>
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Departments of Emergency Medicine and Anesthesiology; Division of Critical Care  
Washington University School of Medicine, St. Louis, MO  
Nicholas M. Mohr, MD, MS  
Departments of Emergency Medicine and Anesthesiology; Division of Critical Care  
Roy J. and Lucille A. Carver College of Medicine, University of Iowa, Iowa City, IA

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Professor & Executive Vice Chairman; Director, Clinical Trials Center, Department of Emergency Medicine, University of Cincinnati College of Medicine, Cincinnati, OH

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Associate Professor, University of Pittsburgh Department of Emergency Medicine, Pittsburgh, PA

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Assistant Professor, Departments of Emergency Medicine and Neurology, Divisions of Neurocritical Care and Emergency Neurology; Medical Director, SkyHealth Critical Care, Yale University School of Medicine, New Haven, CT

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Associate Provost for Innovation in Education; Director, Jefferson Institute of Emerging Health Professions; Associate Dean for CME and Strategic Partner Alliances; Professor, Department of Emergency Medicine, Thomas Jefferson University, Philadelphia, PA

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Jordan B. Bonomo, MD  
Associate Professor, Emergency Medicine; Director, Division of Critical Care, Department of Emergency Medicine; Associate Professor, Neurosurgery/Neurocritical Care; Director, Neurocritical Care Fellowship, University of Cincinnati College of Medicine, Cincinnati, OH  
Natalie E. Kreitzer, MD  
Assistant Professor of Emergency Medicine; Fellow, Neurovascular Emergencies and Neurocritical Care, Department of Emergency Medicine, University of Cincinnati College of Medicine, Cincinnati, OH  
Christopher R. Zammit, MD  
Assistant Professor of Emergency Medicine and Neurology; Department of Emergency Medicine, Critical Care Division, University of Cincinnati College of Medicine, Cincinnati, OH

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Christopher M. Palmer, MD  
Assistant Professor of Anesthesiology and Emergency Medicine, Department of Anesthesiology, Division of Critical Care, Division of Emergency Medicine, Washington University School of Medicine, St. Louis, MO  
Trenton C. Wray, MD  
Critical Care Fellow, Division of Critical Care, Division of Emergency Medicine, Washington University School of Medicine, St. Louis, MO
TREATMENT OF CRITICAL RESPIRATORY ILLNESS IN THE EMERGENCY DEPARTMENT AND INTENSIVE CARE UNIT

Brian M. Fuller, MD, MSCI
Departments of Emergency Medicine and Anesthesiology
Division of Critical Care
Washington University School of Medicine in St. Louis
St. Louis, MO

Nicholas M. Mohr, MD, MS
Departments of Emergency Medicine and Anesthesiology
Division of Critical Care,
Roy J. and Lucille A. Carver College of Medicine University of Iowa, Iowa City, IA

Objectives
1. Describe the general principles of mechanical ventilation, including ventilator modes, basic mechanics, and various airway pressures.
2. Describe the basic strategy for prescribing and managing mechanical ventilation in the Emergency Department (ED).
3. Describe the three broad patient cohorts that will be encountered in mechanically ventilated ED patients and how the approach to mechanical ventilation differs for each.

Introduction
Endotracheal intubation is a common procedure in the emergency department (ED), and is a defining trait of the specialty of emergency medicine (EM). It has been studied extensively, producing high-quality evidence and practice recommendations.1 Endotracheal intubation is followed by the initiation of mechanical ventilation, but the clinical study of mechanical ventilation has primarily been confined to the intensive care unit (ICU). Comparatively, little attention has been paid to the mechanically ventilated patient in the ED. Consequently, acquiring the basic skills to prescribe a safe and effective mechanical ventilation strategy has not been a historical training focus of EM.2

This knowledge gap may put critically ill patients at risk during the most vulnerable time in critical illness. Close to 300,000 patients receive mechanical ventilation in the ED annually.3 The use of mechanical ventilation in the ED is on the rise, as are lengths of stay for intubated ED patients. These factors converge to create a scenario where ED management of mechanical ventilation impacts vulnerable patients more than at any other time in the specialty’s history. Patients ventilated in the ED carry a high mortality, and ventilator associated lung injury (VALI) is a significant factor that influences morbidity and mortality in the critically ill. VALI is a broad term used to describe the effects of mechanical ventilation on the initiation and propagation of pulmonary and non-pulmonary organ failure.4 This can occur even during the duration of the ED length of stay. Additionally, ventilator management in the prehospital and ED setting influences ventilator management in the ICU, suggesting that early care is impactful beyond the hours actually spent in the ED.5,6

Mechanical Ventilation: General Principles

Mechanical ventilation does not treat disease; it simply provides respiratory support and time for healing to occur. It does, however, have potential for causing harm. Effective mechanical ventilation should prioritize limiting VALI while preventing primary clinical deterioration. Applying basic principles of mechanical ventilation can allow the clinician to use the ventilator to maximum therapeutic potential and to minimize iatrogenic injury, which undermines the healing process.

The Four Phases of a Mechanical Breath

Triggering represents the transition from expiration to inspiration, and occurs either due to elapsed time or patient effort. Inspiration occurs after the initiation of a breath, when pressurized gas flows from the ventilator to the patient. It is controlled (or targeted) based on either volume or pressure. Cycling represents the transition from inspiration to expiration and occurs due to a decrease in flow, elapsed time, or delivered volume (depending on mode). Expiration occurs when flow from the ventilator stops and gas passively flows out from the lungs through the exhalation valve of the ventilator.

Ventilator Modes

A mode describes the set of breath characteristics and patient-ventilator interactions that occur during the respiratory cycle. The mode is simply an instruction set, which guides the ventilator’s interaction with patient effort. Table 1 provides an overview of common modes of mechanical ventilation. A positive pressure breath can be designed to target either tidal volume or drive pressure. Neither strategy is clearly superior, but both rely on a fundamental understanding of the relationship between pressure and volume (respiratory compliance). Either can achieve similar goals with respect to gas exchange and limitation of VALI. For this reason, clinician familiarity should really determine the mode of ventilation employed.

In most EDs, volume control/assist control (VC/AC) is the most commonly used mode.5,7 Assisted breaths can either be volume- or pressure-targeted (i.e., volume control or pressure control). With volume control, a clinician determines a target tidal volume and respiratory rate, and classically that tidal volume is delivered with a constant flow rate. Modern ventilators often allow for other inspiratory wave forms, but in all modes of volume control, the flow pattern is determined by the ventilator. In pressure control ventilation, the venti-
TREATMENT OF CRITICAL RESPIRATORY ILLNESS IN THE EMERGENCY DEPARTMENT AND INTENSIVE CARE UNIT

Table 01

<table>
<thead>
<tr>
<th>Ventilator Mode</th>
<th>Trigger</th>
<th>Target/Limit</th>
<th>Cycling</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>Volume control/assist control (VC/AC)</td>
<td>Patient or time</td>
<td>Volume</td>
<td>Volume</td>
<td>• Decrease work of breathing</td>
<td>• May lead to excessive inspiratory pressures</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Guaranteed minute ventilation</td>
<td>• May be more challenging to achieve patient comfort because of prescribed inspiratory flow pattern</td>
</tr>
<tr>
<td>Pressure control/assist control (PC/AC)</td>
<td>Patient or time</td>
<td>Pressure</td>
<td>Time</td>
<td>• Easy control of inspiration: expiration ratio</td>
<td>Tidal volume and minute ventilation may change with a change in lung compliance</td>
</tr>
<tr>
<td>Synchronized intermittent mandatory ventilation (SIMV)</td>
<td>Patient or time</td>
<td>Pressure for patient breaths (PSV)</td>
<td>Flow for spontaneous breaths</td>
<td>Volume or time for mandatory breaths</td>
<td>• Increased work of breathing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Flow/volume (VC) or pressure (PC) for mandatory breaths</td>
<td></td>
<td></td>
<td>• Difficult patient adjustment to two breath types within same mode</td>
</tr>
<tr>
<td>Pressure-support ventilation (PSV)</td>
<td>Patient</td>
<td>Pressure</td>
<td>Flow</td>
<td>• Patient comfort</td>
<td>Requires spontaneous breathing to be preserved</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Decreased work of breathing</td>
<td>• Variable tidal volumes</td>
</tr>
</tbody>
</table>

A pressure-volume (PV) curve (Figure 1) demonstrates some key features of respiratory system mechanics. The lower (LIP) and upper inflection points (UIP) demonstrate areas of reduced compliance due to low and high volumes respectively. As alveoli are opened from a collapsed, atelectatic state, the lower inflection point transitions into the steeper, more linear and compliant portion of the compliance curve. At higher volumes, the upper inflection point represents a transition to over-distention, risk for barotrauma, and reduced compliance. The linear portion of the curve between the LIP and the UIP represents the portion of the compliance curve at which it is safest for ventilating patients.

Basic Mechanics

Breathing occurs when a pressure gradient is generated. For spontaneous breathing, this requires negative intrathoracic pressure that draws air into the lungs, whereas for mechanical ventilation, the ventilator generates positive pressure that pushes air into the lungs. While mechanical ventilators can seem complex, the primary variables are only pressure, flow, and volume; a ventilator generates pressure or flow, which increases lung volume. Compliance refers to the fundamental relationship between pressure and volume, and compliance is defined as the tidal volume generated by a given change in airway pressure. As such, improved compliance suggests that the greater tidal volumes will be achieved at a given airway pressure. Resistance describes the impedance to airflow through the respiratory system, and can be increased by bronchospasm, or any occlusion in the airways that obstructs air flow. Resistance is defined as the ratio of changes in pressure to flow, suggesting that increased resistance requires a greater change in pressure to achieve a given rate of airflow.
to ventilate patients, because it is the least likely to cause repetitive atelectrauma or over distention and barotrauma. Unfortunately, generating this curve for an individual patient can be difficult, and the curve can change in a dynamic fashion.

**Airway Pressures**

In most modes of ventilation, airway pressures are used to alert the clinician to changes in lung compliance or safety of mechanical ventilation. The three most common airways pressures displayed for monitoring on a mechanical ventilator are: peak airway pressure, inspiratory plateau pressure, and mean airway pressure (Figure 2). Peak pressure is the greatest pressure generated during the respiratory cycle, and represents the summation of the pressure required to generate a tidal volume (based on respiratory compliance), and the resistance to inspiratory flow. Often, clinicians want to isolate the proportion of the peak pressure generated by respiratory compliance (the pressure theoretically observed at the level of the alveolus). This pressure is estimated only under no-flow conditions, which can be approximated by performing an inspiratory hold maneuver, where a valve is closed at end-inspiration. Flow is arrested, and the equilibrium pressure reflects alveolar pressure, also known as the *inspiratory plateau pressure*. Plateau pressure, though imperfect, is the most readily available and simplest reflection of transalveolar pressure, the distending pressure of an alveolus, and is an important marker for VALI potential. *Mean airway pressure* is the average airway pressure observed through the respiratory cycle, and should be viewed as the best indicator of how airway pressure can contribute to lung recruitment (maintaining open alveoli to participate in gas exchange).

**Intrinsic PEEP**

The last concept that is important to understanding how to safely provide mechanical ventilation is the concept of intrinsic positive end-expiratory pressure (PEEP). Exhalation is typically a passive process, where air flows from the alveolus to the airway and out of the respiratory system. In patients who have airway disease, however, this process can be impaired. Dynamic airway collapse causes a heterogeneous retention of air in alveolar subunits, because increased intrathoracic pressure collapses airways and prevents exhalation from occurring. Intrinsic PEEP can pose significant risks to mechanically ventilated patients. While any patient can exhibit intrinsic PEEP with a respiratory rate that is high enough, those with chronic obstructive pulmonary disease (COPD) or asthma are at greatest risk.

These basic principles of mechanical ventilation can be applied to three general categories of mechanically ventilated patients in the ED. These include patients who: 1) are prone to have intrinsic PEEP; 2) have ARDS; or 3) are at risk for ARDS.

**Patients at Higher Risk for Intrinsic (or Auto-) PEEP**

Setting PEEP on a ventilator (i.e., extrinsic PEEP) is used to maintain end-expiratory lung volume, prevent derecruitment, and maintain oxygenation. This is not to be confused with intrinsic PEEP. Under normal conditions, expiratory flow declines to zero before the onset of a subsequent breath; this is true for spontaneous breathing and for positive pressure breathing. A decrease in elastic forces, or an increase in resistive forces, will increase the time needed to fully expire a delivered tidal volume. If inspiration occurs prior to the end of exhalation, lung volume and alveolar pressure increases. This process is called dynamic hyperinflation, and the resultant increase in alveolar pressure is called auto-PEEP (Figure 3). Since exhalation is determined by elastic forces and resistance, the most common scenario in which the emergency physician will encounter intrinsic PEEP is the intubated patient with COPD or status asthmaticus.

**Physiology**

Intrinsic PEEP has predictable physiologic effects. By preventing flow termination at end-exhalation, end-expiratory lung volume increases, leading to an increase in airway pressure. Juxta-cardiac pressure, and therefore right atrial pressure, increases and venous return decreases. As a result of dynamic hyperinflation, lung volume continues to rise, which is eventually accompanied by an increase in pulmonary vascular resistance (PVR) and right ventricular afterload. If this process goes unchecked, two scenarios can occur:

1. cardiovascular collapse due to a combination of decreased preload and right ventricular failure secondary to high right ventricular afterload (high pulmonary vascular pressures)
2. barotrauma, such as pneumothorax.
Identifying Intrinsic PEEP

The first step in recognizing intrinsic PEEP is having a high suspicion for patients prone to developing it (i.e., those with obstructive lung disease). The flow waveform on the ventilator will show that expiration does not completely terminate prior to the onset of the subsequent breath (Figure 3). In volume targeted ventilation, airway pressures will increase, and in pressure targeted ventilation, tidal volumes will decrease. An expiratory hold maneuver can be performed, which can quantify the level of intrinsic PEEP present. This maneuver allows the clinician to close the expiratory valve at the time the next breath would be delivered. Although this requires a passive patient with no additional respiratory effort, measured airway pressure should equilibrate to the level of set PEEP. If intrinsic PEEP is present, airway pressure will be measured higher than set PEEP, and this difference equals the level of intrinsic PEEP present under the set respiratory conditions.

Setting the ventilator

Life-threatening intrinsic PEEP can lead to cardiovascular collapse, so the set minute ventilation should be high enough only to avoid life-threatening hypoventilation and subsequent respiratory acidosis. In the sickest cohort, a balance has to be struck so that some amount of hypercapnia and acidosis, as well as some amount of intrinsic PEEP, are tolerated. If the clinician over-prioritizes the normalization of pH, dynamic hyperinflation and intrinsic PEEP can lead to cardiovascular collapse; if the clinician over-prioritizes complete resolution of intrinsic PEEP, minute ventilation will be so low that hypercapnia and acidosis can become severe. Table 2 shows the general recommendations on initial ventilator settings.

As a general approach, during the most acute phase of critical illness in the ED, these patients should be deeply sedated to facilitate respiratory muscle rest and to prevent ventilator dysynchrony. For spontaneously breathing patients, the presence of intrinsic PEEP promotes dysynchrony and increased work of breathing. If deep sedation is achieved, PEEP can be set at 0 – 5 cm H2O. Patients with life-threatening intrinsic PEEP usually do not suffer from severe hypoxemia, and the fraction of inspired oxygen (FiO2) can usually be set at 30-40%.

Patients with Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) is an inflammatory form of lung failure that typically occurs secondary to another life-threatening insult, often as part of multisystem organ dysfunction. It is defined according to the presence of bilateral opacities on chest imaging, primarily non-hydrostatic pulmonary edema, and impaired oxygen exchange.9 It is characterized by pulmonary capillary endothelial injury and alveolar epithelial injury, and widespread pulmonary and non-pulmonary inflammation.

Physiology

ARDS results from a combination of predisposing conditions (e.g., trauma, sepsis) and patient-level risk modifiers (e.g., body mass index, acidosis). After the inciting event, activated immune cells recruit neutrophils to the lungs, which serve to propagate the injury. The end

| TABLE 02 | General Recommendations for Emergency Department Ventilator Settings |

<table>
<thead>
<tr>
<th>Patient Cohort</th>
<th>Mode</th>
<th>Tidal Volume</th>
<th>PEEP</th>
<th>RR</th>
<th>FiO2</th>
<th>Monitoring</th>
</tr>
</thead>
</table>
| At risk for iPEEP | VC/AC | 8-10 mL/kg PBW | 5 | 8-12 High enough for adequate ventilation, low enough to not promote iPEEP | .30 - .40 | • iPEEP  
• Airway pressure |
| ARDS | VC/AC | 6 mL/kg PBW | Set with PEEP-Fio2 table | To maintain adequate pH (≥7.15) | Titrated for S_pO2 ≥88% | Plateau pressure<30 |
| At risk for ARDS | VC/AC | 6-8 mL/kg PBW | ≥5 | 20-30 | .30 - .40 | Plateau pressure 25-30 |

iPEEP: intrinsic positive end-expiratory pressure; ARDS: acute respiratory distress syndrome; VC: volume control; AC: assist control; RR: respiratory rate; PBW: predicted body weight; Fio2: fraction of inspired oxygen; S_pO2: peripheral oxygen saturation
result is protein-rich pulmonary edema, surfactant loss, and hypoxia. Trials supporting ARDS therapy have been largely disappointing with no therapy that targets the underlying pathophysiology of ARDS. Mortality-reducing interventions can be summarized as:

1) “lung protective ventilation,” incorporating both limited tidal volume and limited distending pressures.10
2) higher PEEP in severe ARDS.11
3) prone positioning in early, severe ARDS.12
4) cistatricurium infusion in early, severe ARDS.13
5) referral to an extracorporeal membrane oxygenation (ECMO)-capable center for severe ARDS.14

ARDS has historically been viewed as an ICU syndrome, even though the majority of ICU patients with ARDS are admitted from the ED. Recent observational data from academic centers show that 8% of ventilated ED patients have ARDS.5 Adherence to lung-protective ventilation in the ED is poor, and early ED-based ventilator settings influence subsequent lung protective ventilation in the ICU.5,7 As time spent in the ED represents a vulnerable period for many critically ill patients, improving care to incorporate routine delivery of lung protective ventilation has the potential to improve morbidity-free survival for these patients.

**Ventilator Settings**

The goal of lung protective ventilation is to deliver low tidal volumes [6 mL/kg predicted body weight (PBW)], low distending pressures (inspiratory plateau pressure < 30 cm H2O), and PEEP titrated to facilitate lung recruitment. To calculate PBW, the patient’s height should be measured and PBW should be calculated. The tidal volume should be set at 6 mL/kg based on this PBW. Next, PEEP should be set with the aid of a PEEP-FIO2 table.15 This is a table that shows the relationship between the FIO2 required to maintain minimal oxygenation and PEEP designed to recruit the lung. After these settings are programmed into the ventilator, inspiratory plateau pressure should be measured. With a passive patient, inspiratory plateau pressure should be limited to <30cmH2O, and tidal volume should be decreased even further if this pressure goal is not attained.15 This simple approach provides the emergency physician with a manageable framework around which to combat the hypoxemia associated with ARDS.

From this starting point, a variety of other ventilator maneuvers (e.g., recruitment maneuvers, “advanced” ventilator modes) and non-ventilator maneuvers (e.g., prone positioning, inhaled pulmonary vasodilators) can be used to recruit alveoli and improve oxygenation, but these adjunctive therapies are typically not required in the ED.

**Patients at Risk for ARDS**

Most intubated ED patients have neither of the conditions described above, but continue to be at risk for developing pulmonary complications, such as ARDS, during their hospital stay. For patients in the emergency setting, VALI does not need much time to initiate and propagate lung injury. This has been shown in animal studies, as well as human data showing that most patients who develop ARDS do so within 48 hours of hospital admission.16,18 This information provides temporal urgency to get the ventilator set correctly from the beginning. Additionally, lung protection in the ED is rare, and the current practice of ED mechanical ventilation can certainly promote VALI. This has been demonstrated in two observational studies examining mechanical ventilation in the ED.5,7 Another study of 243 patients with severe sepsis and septic shock showed that use of ED mechanical ventilation predicted progression to ARDS, and higher ED tidal volumes were associated with an increased incidence of ARDS.19 The ED ventilator care also influences care in the ICU. Both prehospital and ED ventilator management have been shown to predict inpatient ventilator management, so guideline-adherent care influences patient care even beyond the ED stay.5,6 Finally, lung-protective ventilation is a safe, low risk intervention. “Low” tidal volume is actually normal physiologic tidal volume.20 High tidal volume ventilation was delivered frequently in early anesthesia practice, as knowledge of VALI did not yet exist and the priority at the time was normalization of gas exchange. This led to high tidal volumes being the norm in the operating room, with carryover into the ICU. With improved understanding of VALI and better ventilator technology such as the provision of PEEP when tidal volume is decreased, high tidal volume ventilation no longer carries the allure that it did decades ago. For these reasons, almost all ED patients should receive a lung-protective approach to mechanical ventilation in an effort to mitigate VALI.

**Setting the Ventilator**

The ventilator can be set similarly to that for patients with ARDS. The patient’s height should be measured and tidal volume set at 6-8mL/kg PBW. Plateau pressure should be limited to <25-30 cm H2O, and hyperoxia avoided by initiating mechanical ventilation with a FIO2 of 30-40%, and titrating for an oxygen saturation of 92-96%. The PEEP should be set ≥5 for all patients; consideration should be given for higher PEEP in conditions that promote end-expiratory alveolar collapse secondary to reduced respiratory system compliance such as obesity or ascites. The respiratory rate can be set at 20-30 breaths per minute, depending on the metabolic demands and ventilation requirements of the patient.

**Conclusion**

Mechanical ventilation in the ED is a common therapy for critically ill patients. Applying the basic principles of mechanical ventilation
will allow the emergency physician to safely ventilate patients while limiting the risk that the ventilator imposes on the patient’s outcome. Emergency physicians should be familiar with how to detect intrinsic PEEP and strategies to mitigate it. Patients with ARDS or at risk for ARDS should be managed with a lung-protective approach. An algorithmic approach should be used to optimize safe mechanical ventilation, and these practices and clinical outcomes should be monitored regularly.

References
DEEP VENOUS THROMBOSIS AND PULMONARY EMBOLISM: OPTIMAL THERAPY AND PREVENTION FOR THE CRITICALLY-ILL PATIENT

Gregory J. Fermann, MD
Professor & Executive Vice Chairman; Director, Clinical Trials Center; Department of Emergency Medicine, University of Cincinnati College of Medicine, Cincinnati, OH

Objectives

1. Define massive, submassive, and low risk pulmonary embolism (PE).
2. Describe current guidelines for the treatment of massive and submassive PE.
3. Explain risk stratification strategies in acute PE.
4. Consider disposition decisions as applied to patients with PE.

Introduction

Venous thromboembolism (VTE) is identified as the cause for the hospitalization for over 250,000 patients in the United States (US) annually. VTE collectively refers to both deep venous thrombosis (DVT) and pulmonary embolism (PE) and is often among the differential considerations of patients presenting to the Emergency Department (ED) with leg pain or swelling, chest pain and dyspnea. After the diagnosis of VTE is made, Emergency Physicians typically initiate therapy with anticoagulation after assessment of bleeding risk. Risk stratification based on disease severity and outcomes has been sporadically adopted in the clinical practice of Emergency Medicine. While several risk based scoring systems have undergone rigorous evaluation, optimal therapy for patients with high risk pulmonary emboli is often unclear. The decision to use catheter-based therapies and fibrinolytic medication is based on the patient’s clinical condition and serologic and radiographic studies, most of which are available to Emergency Physicians. This monograph addresses the classification and pathophysiology of PE, including diagnostic modalities and treatment options.

Severity of Pulmonary Embolism

Massive Pulmonary Embolism

Since patient outcomes are related to PE severity, attempts to classify PE using terms such as “massive” and “submassive” are often encountered in the literature. However, these imprecise descriptions often lead to confusion and ambiguity. Classification based strictly on mortality is difficult and is complicated by comorbidities that may make an otherwise low risk embolism a very high risk one in a selected patient population. Conversely, basing a description solely on angiographic clot burden, such as the Miller index, fails to account for physiological variation in patients. Among several large registries, hypotension emerges as a consistent parameter associated with morbidity and mortality. In the Germany-based Management Strategy and Prognosis in Pulmonary Embolism (MAPPET) Registry of 1,001 patients with acute PE, in-hospital mortality was 8.1% for hemodynamically stable patients in comparison to 25% for those with low blood pressure. Similar results were found in the International Cooperative Pulmonary Embolism Registry (ICOPER), where patients with presenting systolic blood pressure of less than 90 mmHg had a 90 day mortality of 52.4% in comparison to 14.7% in those without hypotension. Both the Geneva scoring system and the Pulmonary Embolism Severity Index (PESI and simplified PESI) identify systolic blood pressure of less than 100 mmHg as a high risk clinical feature. Accordingly, a writing group of the American Heart Association (AHA) has proposed that massive PE be defined as: acute PE with sustained hypotension (systolic blood pressure less than 90 mmHg for 15 minutes or requiring inotropic support, not due to a cause other than PE, such as arrhythmia, hypovolemia, sepsis or left ventricular dysfunction), pulselessness, or persistent profound bradycardia (heart rate less than 40 beats per minute with signs or symptoms of shock).

Submassive Pulmonary Embolism

The definition of submassive PE centers on the identification of risk of short term adverse events, such as mortality, recurrent VTE or major bleeding. However, the definition of “short term” varies significantly, ranging from in-hospital events to 30-90 day outcomes to one year mortality. Ideally, the tools used to predict short term risk should be widely available and readily deployed in the emergent evaluation of a patient suspected to have VTE. Such predictors include clinical scoring systems, natriuretic peptides, troponins, cardiac echocardiography, electrocardiography (ECG) and chest CT.

Clinical Scoring Systems

There are validated clinical decision rules to guide the evaluation of patients suspected to have pulmonary embolism. In addition, after a patient has been diagnosed with a pulmonary embolism, several clinical scoring systems have been evaluated and found to be predictive of adverse events independent of radiography and biomarkers. The more common scores include the PESI and simplified PESI (Table 1) and the HESTIA criteria (Table 2). The HESTIA criteria were developed as a tool to identify patients that may be able to be treated as outpatients. These scores incorporate age, physiological parameters and comorbidities into risk stratification. They have most commonly been used to identify PE patients at low risk for short term adverse events that may be candidates for abbreviated hospital stay, placement into clinical decision units (observation units) or direct release from the ED.
Echocardiography

Right ventricular (RV) dysfunction can be identified on cardiac echocardiography using a variety of parameters, such as RV hypokinesis, interventricular septal shift or bowing, McConnell’s sign (regional akinesis of the RV mid free wall with normal septal motion), and elevated RV end diastolic pressure (RVEDP > 30mmHg). The RV to LV end diastolic diameter ratio (RVEDD/LVEDD) of greater than or equal to 0.9 is commonly used to identify RV dysfunction in acute PE and is included in the definition of submassive PE.

Electrocardiography

Although ECG changes in acute PE are highly variable and often nonspecific, RV strain patterns have been shown to be predictive of adverse events. New incomplete or complete right bundle branch block, S1Q3T3, and negative T waves in leads V1-V4 have been found to be associated with clinical outcomes of in-hospital death.
or clinical deterioration (hazard ratio 2.58; 95% confidence interval [CI] 1.05-6.36) independent of echocardiographic findings of RV strain.14

**Computed Tomography Pulmonary Angiography (CT PA)**

Although clot burden on CT does not predict short term adverse events,15 RV dilation does. In-hospital death, 30 day mortality and three month mortality are increased if the RV is dilated. As with echocardiography, several CT measures of RV dilation have been studied, including septal bowing; however, the most consistently reliable parameter reflecting RV dysfunction is RV diameter/LV diameter ratio of greater than or equal to 0.9 in the four chamber view.

**Troponins**

In acute PE patients, both hemodynamically stable and unstable, elevations in cardiac troponin I and T are associated with short term all-cause mortality (odds ratio [OR], 5.24; 95% CI 3.28 to 8.38), death from PE (OR, 9.44; 95% CI 4.14 to 21.49), and adverse outcome events (OR, 7.03; 95% CI 2.42 to 20.43). Adverse outcome events include shock, need for thrombolysis, endotracheal intubation, vasopressor infusion for sustained hypotension, cardiopulmonary resuscitation, or recurrent pulmonary embolism. In the subgroup of hemodynamically stable patients, elevated troponin levels are also associated with a high mortality (OR, 5.90; 95% CI, 2.68 to 12.95).17

**Natriuretic Peptides**

As a marker of ventricular dysfunction, the natriuretic peptides are significantly predictive of short term mortality and adverse events in stable and unstable acute PE patients. The unadjusted risk ratio for predicting death is 9.5 (95% CI 3.2-28.6) for brain natriuretic peptide (BNP) and 5.7 (95% CI 2.2-15.1) for pro-BNP.13

Based on the above tests, the AHA writing group suggests the following definition for **submassive PE**: acute PE without systemic hypotension (systolic BP > 90 mmHg), but with either RV dysfunction or myocardial necrosis. The definitions of RV dysfunction and myocardial necrosis are listed in Table 3.

**Low Risk Pulmonary Embolism**

Although risk stratification based on age, comorbidities, and clinical judgment is warranted for patients who do not meet the criteria of massive and submassive PE, the short term mortality of the subgroup who are normotensive and lack RV dysfunction or marker elevation is estimated to approach 1%. Per the AHA writing group, this cohort of patients is described using the term low risk PE to best characterize their generally good prognosis. Thus, low risk PE is defined as acute PE in the absence of the clinical markers of adverse events that define massive and submassive PE.

<table>
<thead>
<tr>
<th>TABLE 03 Definitions of Severity of Pulmonary Embolism (PE)</th>
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<tbody>
<tr>
<td><strong>Definitions</strong></td>
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<tr>
<td><strong>Massive PE</strong></td>
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<td><strong>Submassive PE</strong></td>
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<td><strong>RV Dysfunction defined by at least one</strong> of the following:</td>
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<td><strong>Myocardial Necrosis defined by either</strong> of the following:</td>
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<td><strong>Low Risk PE</strong></td>
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**Treatment of Pulmonary Embolism**

**Massive Pulmonary Embolism**

Fibrinolytic therapy, in addition to parenteral anticoagulation, is indicated in the treatment of acute massive PE when the risk of bleeding is considered acceptable. The usual absolute and relative contraindications to fibrinolytic therapy are described elsewhere. If there is a high clinical suspicion for massive PE and the patient is too unstable to be safely studied or the study is unavailable, bedside transthoracic echocardiography showing RV dysfunction is an appropriate method of confirming the presence of PE. Administering fibrinolysis in the setting of undifferentiated cardiac arrest is not recommended.19 For patients with acute massive PE who are candidates for fibrinolysis, the American College of Chest Physicians (ACCP) recommends peripheral infusion of alteplase 100 mg over two hours. Tenecteplase 30-50 mg over two hours has been used in recent trials as well. Shorter infusion regimens are acceptable in selected critically ill patients. Prolonged infusions of up to 24 hours are not recommended. The Food and Drug Administration (FDA) recommends that intravenous (IV) unfractionated heparin (UFH) be temporarily suspended while the fibrinolytic is infusing...
and that activated partial thromboplastin time (aPTT) be checked after infusion. If the aPTT < 80 sec, IV UFH should be restarted at the pre-fibrinolytic infusion rate without re-bolus.

**Submassive Pulmonary Embolism**

The use of fibrinolytics in the subgroup of patients who are normotensive, but have objective signs of RV dysfunction, is controversial. Since the short term mortality of US patients presenting with this phenotype is approximately 2%, a trial to study the treatment effects of fibrinolysis using mortality as the primary endpoint is impractical. However, the development of dyspnea, fatigue and exercise intolerance from increased RV systolic pressure and the development of chronic thromboembolic pulmonary hypertension (CTEPH) may serve as a plausible endpoint. Although the development of CTEPH is multifactorial, strong predictors include large thrombus burden, younger age and multiple PE episodes. The Tenecteplase Or Placebo with Cardiovascular Outcomes At Three months (TOPCOAT) Trial used the composite endpoint of survival combined with assessment of functional capacity and patient evaluation of wellness to compare full dose LMWH plus placebo to LMWH plus tenecteplase. Although the trial was terminated early due to non-outcome related factors, TOPCOAT showed that treatment with tenecteplase in submassive PE was associated with an increased positive composite outcome.21

The Pulmonary Embolism Thrombolysis Trial (PEITHO) serves as the largest body of evidence in the study of fibrinolytic therapy for submassive PE.22 A randomized double-blind trial comparing tenecteplase plus heparin to placebo plus heparin, PEITHO enrolled 1,006 subjects with acute PE who were normotensive with signs or RV dysfunction on CT or echocardiogram or with myocardial necrosis, and used a primary outcome of death or hemodynamic collapse within seven days. The safety endpoint was major extracranial or intracranial stroke or hemorrhage within seven days. Patients who received weight based tenecteplase had a significantly lower incidence of the primary outcome (2.6%) vs. standard heparin plus placebo (5.6%, OR 0.44; 95% CI 0.23 to 0.87; P = 0.02). However, extracranial bleeding occurred in 32 patients (6.3%) in the tenecteplase group vs. six patients (1.2%) in the heparin plus placebo group (P < 0.001). The intracranial hemorrhage rate in the tenecteplase arm was 2.0%, which is similar to previous analyses. At day 30, there was no significant difference in mortality. Although the study failed to incorporate functional capacity endpoints, the authors concluded that there was no net clinical benefit to the use of fibrinolysis in the submassive PE population. Subgroup analysis showed a lower risk of bleeding in subjects less than age 75, but the difference was not significant.

A recent meta-analysis that reviewed fibrinolysis in submassive PE and included both PEITHO and TOPCOAT showed a decrease in mortality (number needed to treat, NNT=59) and recurrent PE (NNT=54) at the expense of an increased risk of major bleeding (number needed to harm, NNH=18) and intracranial hemorrhage (NNH=78). However, no increased risk of major bleeding was seen in patients less than age 65.23 An even more recent meta-analysis by European investigators that combined massive and submassive PE found similar results.24 In patients who are hemodynamically stable with evidence of RV dysfunction (submassive PE), the most recent available data is summarized with the recommendation to weigh the risk of hemorrhage with the benefit of improved mortality and recurrent PE, taking into account individual patient characteristics and expectations.25

**Low Risk Pulmonary Embolism**

Patients diagnosed with acute low risk PE are treated with anticoagulant therapy if they have no contraindications. The approved options for acute therapy in this subgroup are UFH, low molecular weight heparin (LMWH), fondaparinux or a Non-vitamin K antagonist Oral Anticoagulant (NOAC) (see Table 4). Guidelines published in 2012 by the American College of Chest Physicians (ACCP) recommend LMWH or fondaparinux over IV or subcutaneous (SC) UFH. They favor once daily over twice daily dosing of enoxaparin.27 The AHA suggests that empiric therapy can be given to patients with an intermediate to high clinical suspicion of PE prior to obtaining a confirmatory study if the patient lacks contraindications to anticoagulation.2 The use of fibrinolytic therapy is NOT recommended for the treatment of low risk PE.

**Catheter-Based Strategies**

Patients with massive and submassive PE should be considered for transcatheter therapies based on the clinical presentation and the capabilities of the institution. These therapies can be deployed in the setting of acute PE if traditional peripherally delivered fibrinolysis fails to improve hemodynamics or is contraindicated. Percutaneous options may also be considered when emergent surgical embolectomy is unavailable or contraindicated. A combination of directed fibrinolytic infusion with mechanical clot disruption is emerging as a viable option. In experienced centers, the pharmaco-mechanical treatment of massive and submassive PE may decrease the hemorrhagic complications seen with peripheral fibrinolysis while more rapidly improving RV hemodynamics and systemic circulation.28

The types of catheter therapies generally fall into the following categories: aspiration thrombectomy, thrombus fragmentation, and rheolytic thrombectomy. Thrombus aspiration catheters deploy a suction-tipped catheter for clot removal and are the oldest of
the mechanical therapies. Fragmentation devices use a variety of 
hardware, such as ultrasound augmentation and rotational devices, 
to morelize the thrombus. Ultrasound destabilizes the fibrin mesh 
making it more susceptible to locally targeted fibrinolytic agents. 
Rheolytic systems deploy a high pressure saline jet to disrupt clot, 
but have come under regulatory scrutiny due to periprocedural 
hemorrhagic complications.

**Clinical Pathway**

The majority of patients with acute PE in US institutions are admitted 
to the hospital. Using risk stratification tools, if feasible to tailor 
treatment and disposition decisions based on individual patient factors.

In patients with acute massive PE who have contraindications to 
fibrinolysis, failed fibrinolysis, or shock that is likely to cause death 
before systemic fibrinolysis can take effect (i.e., within hours), catheter-assisted thrombus removal or surgical thrombectomy is suggested over no such intervention if appropriate expertise and resources are available. Since most pharmaco-mechanical studies have been nonrandomized and had few patients, the ACCP guidelines suggest that the decision to deploy such a strategy be based on local expertise. The use of peripheral fibrinolysis in patients with acute submassive PE, while still the subject of discussion, is generally reserved for those patients with a low risk of bleeding and evidence of clinical instability.

Some patients with low risk PE, adequate social support and outpatient follow-up may have an abbreviated inpatient stay, such as in a clinical decision unit. Some centers advocate direct ED discharge and prospective US studies are ongoing. The European Society of
Cardiology (ESC) advocates further risk stratification of the low risk PE population with the PESI and sPESI scoring systems to triage patients to inpatient or outpatient care. The HESTIA scoring system was specifically designed to risk stratify patients for outpatient therapy.

The most recently drafted treatment algorithm by the ESC, which was published after the PEITHO study, combines risk stratification using the PESI/sPESI scores and treatment options, including pulmonary reperfusion strategies. The algorithm serves as to guide to clinicians in the evaluation and treatment patients with acute PE (Figure 1).

**Conclusion**

In conclusion, emergency physicians, hospitalists, and critical care physicians must be experts in the diagnosis and treatment of PE and DVT. For the critically ill patient, rapid evaluation and appropriate treatment can reduce adverse outcomes and decrease mortality.
References


POST-CARDIAC ARREST IN THE EMERGENCY DEPARTMENT: BEYOND HYPOTHERMIA

Jon C. Rittenberger, MD, MS
Associate Professor
Department of Emergency Medicine
University of Pittsburgh, Pittsburgh, PA

Objectives

1. Summarize literature supporting temperature management in the patient successfully resuscitated from cardiac arrest.
2. Identify neurocritical care interventions that can be initiated during the Emergency Department management of the patient resuscitated from cardiac arrest.
3. Distinguish patient populations likely to benefit from coronary angiography after resuscitation from cardiac arrest.
4. Discuss how the Institute of Medicine Report on Cardiac Arrest will affect Emergency Department care of the patient resuscitated from cardiac arrest.

Introduction

Cardiac arrest is common and deadly, resulting in more than 300,000 deaths annually. Following decades of unchanged outcomes, recent data demonstrate that survival is increasing. The improvement in outcomes is likely due to advances in the treatment of cardiac arrest, including use of critical care bundles that incorporate temperature management and aggressive coronary revascularization, as well as delayed neuroprognosis. The management of these patients is complex, focusing on determining the etiology of arrest as well as the resuscitation of multiple organ systems. In the first 24 hours, the immediate threat is cardiovascular collapse; however, therapy must also be directed toward preventing secondary neuronal injury. Additionally, the pitfall of early withdrawal of support should be avoided in order to optimize outcome. This manuscript will review current treatment strategies, including the use of temperature management, in this population.

First Hours: Determining Illness Severity and Etiology of Cardiac Arrest

The majority of patients resuscitated from cardiac arrest are unable to provide a historical account of prodromal symptoms, allergies, medications and other aspects of the medical history. These may be obtained from family or witnesses to the arrest when available. Critical information that should be obtained either from emergency medical services (EMS) or bystanders include:

- Was the arrest witnessed?
- Was bystander cardiopulmonary resuscitation (CPR) provided?
- What was the duration of CPR?
- Which medications were administered? How many doses were administered?
- What was the primary cardiac rhythm? Alternatively, did the automated external defibrillator (AED) advise a shock?
- Did the patient experience prodromal symptoms, such as chest pain or shortness of breath?

The first four questions attempt to determine the severity of ischemic damage experienced, while the last two questions focus on reversible causes for the arrest. For example, a history of ventricular fibrillation following chest pain would direct the clinician to have a lower threshold for emergent cardiac catheterization. Additional testing may include laboratory testing, imaging, and bedside ultrasonography to determine both etiology and organ dysfunction resulting from the cardiac arrest.

Determining Illness Severity

A bedside evaluation of the patient is necessary to determine the severity of the post-cardiac arrest syndrome. This may help elucidate the etiology of arrest, but it also provides important baseline information that can help predict long-term outcome. Illness severity can also aid in determining which patients may derive benefit from interventions such as coronary angiography.

Two illness severity scores are particularly useful in the evaluation of post-cardiac arrest patients. The Full Outline of UnResponsiveness (FOUR) score, developed by Wijdicks, quantifies neurologic status based on motor, brainstem, respiratory, and eye responses, and has comparable inter-rater reliability to the Glasgow Coma Scale (Table 1). The Sequential Organ Failure Assessment (SOFA) score is used to quantify individual organ system dysfunction (Table 2). Based on a brief clinical patient examination and an arterial blood gas, the cardiovascular and respiratory components of the SOFA score and the motor and brainstem portions of the FOUR score can be used to place the patient into one of four categories of illness severity using the Pittsburgh Cardiac Arrest Category (PCAC) [Table 3]. The PCAC is predictive of survival after cardiac arrest (PCAC I: 80% survival; PCAC II: 60% survival; PCAC III: 40% survival; PCAC IV: 10% survival).

Diagnostic Testing

Electrocardiography (ECG) and neuroimaging, along with basic laboratory testing, can be used to help determine the etiology of cardiac arrest, quantify organ system dysfunction, and guide therapies. The 12-lead ECG can help identify primary arrhythmia, acute coronary syndrome and cardiomyopathy as reasons for cardiac arrest. Clinicians should be vigilant in identifying ST-elevation myocardial infarction (STEMI) or acute ST changes suggesting ongoing ischemia.
Similarly, QT prolongation or other evidence of ion channelopathy can guide further diagnostic testing. Evidence of right heart strain may suggest pulmonary embolus.

Computed tomography (CT) imaging of the brain is indicated in patients resuscitated from cardiac arrest who are in a coma on initial examination. Approximately 5% of patients resuscitated from cardiac arrest demonstrate intracranial hemorrhage on initial CT of the brain. The CT may also demonstrate early cerebral edema, which is associated with poor outcomes.

An active area of research is determining which patients are likely to benefit from emergent coronary angiography. Cardiac disease is common in patients resuscitated from cardiac arrest and prior work has demonstrated better functional outcomes in patients who undergo coronary angiography, although the outcomes differ based on initial illness severity. Most patients with STEMI require emergent catheterization, but many interventional cardiologists express concern regarding the high rate of mortality from neurologic causes unique to the cardiac arrest patient. One approach that incorporates neurologic injury into the decision is to emergently catheterize patients with cardiac arrest due to STEMI who are PCAC I-III (Table 4). Those with PCAC IV illness severity require a CT scan of the brain to further risk stratify the patient. If the CT demonstrates intracranial hemorrhage or edema, the team must discuss the low likelihood of overall survival with the family prior to cardiac catheterization.

While patients with cardiac arrest due to STEMI should clearly undergo cardiac catheterization and emergent reperfusion, patients with a suggestive history including chest pain or shortness of breath prior to arrest, cardiac risk factors, or initial shockable rhythm should also be considered for coronary angiography. Additionally, those with ongoing cardiovascular shock, focal wall motion abnormalities, or rising troponin serum levels should prompt re-consideration of coronary angiography. Cardiac catheterization can also be critical in post-arrest patients because a significant number of them require intra-aortic balloon pump placement, left ventricular assist device placement, transplant or emergent bypass grafting.

**Initial Resuscitation Goals**

The care of the patient resuscitated from cardiac arrest is challenging. It requires optimizing hemodynamic and ventilatory parameters with a focus on optimizing cerebral perfusion, while continuing efforts to determine and treat the etiology of the cardiac arrest. Moreover, many patients have significant medical co-morbidities exacerbated by anoxic injury, and most patients resuscitated from cardiac arrest are comatose. Thus, while the first concern of the bedside clinician is to...
optimize the cardiovascular system, preventing secondary neuronal injury is necessary for optimal recovery.

Goal resuscitation parameters differ in the acutely neurologically injured patient. Hypotension exacerbates neuronal injury and should be avoided. Because many patients resuscitated from cardiac arrest have an impaired baroreceptor response to blood pressure, augmented mean arterial blood pressures (>80mmHg) are generally required to maintain adequate cerebral perfusion. Lactic acidosis is common, resulting in compensatory hyperventilation. The chemoreceptor response to PCO₂ remains intact in this patient population, thus the natural response can result in cerebral vasoconstriction and secondary neuronal injury. Hyperventilation can also decrease preload and precipitate hypotension. Thus, normalizing PaCO₂ between 35-45mmHg is recommended. Although prior literature has demonstrated an association between hyperoxia and poor outcome, recent data suggest that the ‘dose’ of hyperoxia (severity and duration of exposure) is important; severe hyperoxia has been associated with decreased survival post-cardiac arrest patients, while moderate hyperoxia has not. While these associations should result in titration of FiO₂, hypoxia clearly exacerbates neuronal injury and should also be avoided.

Temperature Management

Since 2002, temperature management strategies, including therapeutic hypothermia, have been at the vanguard of the neurologic resuscitation plan for patients after cardiac arrest. The Targeted Temperature Management (TTM) Trial demonstrated that temperature management to 36°C, along with a standardized care plan, provides similar results to deeper hypothermia temperatures (32-34°C). Hypothermia decreases cerebral metabolism by 5% for every degree below 37°C. It may decrease free radical production, is an adjunct for decreasing seizures, and decreases cerebral edema. Titrating temperature management based on neurologic injury pattern and risk of seizures or edema may optimize therapy.

Importantly, fever must be avoided during the post-arrest phase, as it has been shown to be associated with worse neurologic outcome. During the TTM Trial, patient temperature was controlled for the first 72 hours after resuscitation, which differed from prior work. Subjects received therapeutic hypothermia or temperature management for a period of 24 hours, followed by temperature control (fever prevention) in all subjects for a total of 72 hours. This prevention of secondary injury may be one reason for the excellent rates of recovery noted in the study. An additional nuance of the TTM Trial was the delay in neurologic prognostication to at least 72 hours following resuscitation. When care is withdrawn early in the post-resuscitation phase, the benefits of aggressive management may be limited. Thus, a critical care bundle, including temperature management and delayed neuroprognostication, is required in the comatose patient resuscitated from cardiac arrest.

Electroencephalography Monitoring

Following resuscitation from cardiac arrest, seizures and other malignant electroencephalogram (EEG) patterns are common. Non-convulsive status epilepticus occurs in 8-20% of patients, but convulsive status epilepticus is less common. Other malignant patterns, such as generalized epileptiform discharges and myoclonic status epilepticus, are also common. Given the frequency of these patterns, EEG monitoring is recommended for all comatose patients resuscitated after cardiac arrest. When possible, evaluating the EEG for reactivity to stimulus should be documented. Malignant EEG patterns are associated with worse neurologic outcome, but improvement in the EEG
over time is associated with recovery. Moreover, some patients with malignant EEG patterns recover with treatment and experience good neurologic recovery. Treating malignant EEG patterns therefore may be a reasonable intervention for at least a proportion of patients. It is currently unknown whether prophylactic antiepileptic agents alter the course of recovery in these patients.

**Specialized Centers for Post-Arrest Care**

Management of the post-arrest patient is resource intensive, and collaborative care teams are frequently needed given the heterogeneity of illness. As with trauma, stroke and STEMI care, increased exposure to post-arrest patients may improve patient outcomes. Currently, most hospitals care for approximately 12 cardiac arrest patients each year that may benefit from comprehensive post-arrest care.

Specialized centers should have expertise in cardiovascular resuscitation including coronary angiography, electrophysiology, mechanical assist devices, neurologic resuscitation including brain imaging, EEG monitoring, temperature management protocols, and rehabilitation available at all times, 24 hours per day, 7 days a week. Each of these is critical to the care and recovery of these patients. Such services may not be available in all hospitals, so protocols to determine indications and logistics of transfer should be developed for each facility. Specialized centers should also offer organ donation and procurement services for those patients who do not survive.

Existing data show that prehospital transport time does not impact outcome after cardiac arrest, supporting EMS decisions to transport farther to a specialized center. Additionally, a study of aeromedical transport of post cardiac arrest patients to tertiary care facilities (median transport time 63 minutes) demonstrated that the rate of critical events such as hypotension or hypoxia during transport was not significantly different, but that re-arrest was less common (6%). Approximately one-fourth of all events occurred prior to transport. Important ly, the rate of events did not differ over the transport interval; median transport time was the same in those who experienced a critical event such as hypotension or hypoxia during transport was significant (23%), but that re-arrest was less common (6%). Approximately one-fourth of all events occurred prior to transport. Importantly, the rate of events did not differ over the transport interval; median transport time was the same in those who experienced a critical event and those who did not. Clinicians should weigh the risks and potential benefits for each patient when considering transport of the post-arrest patient. These data do suggest that transport of the post-arrest patient should occur with a critical care transport team ready to prevent or respond to cardiopulmonary critical events.

**Conclusion**

Continued resuscitation and critical care of patients after cardiac arrest significantly improves survival and neurologic outcomes, even in comatose patients. Aggressive resuscitation should include temperature management, coronary angiography and reperfusion, optimization of hemodynamic status and ventilator settings, and delayed neuroprognostication in order to achieve the best outcomes.

**References**


ATRIAL FIBRILLATION: ADVANCED MANAGEMENT OF THE CRITICALLY ILL PATIENT IN THE EMERGENCY DEPARTMENT AND INTENSIVE CARE UNIT

Evie G. Marcolini, MD
Assistant Professor, Departments of Emergency Medicine and Neurology, Divisions of Neurocritical Care and Emergency Neurology; Medical Director, SkyHealth Critical Care, Yale University School of Medicine, New Haven, CT

Objectives
1. Describe the treatment options for atrial fibrillation in the critically ill patient.
2. Contrast and compare the roles of anticoagulation therapy using non-vitamin K antagonist oral anticoagulants (NOACs) and warfarin for atrial fibrillation.
3. Discuss the complications of ischemic and hemorrhagic stroke in the critically ill patient with atrial fibrillation.
4. Summarize the treatment options for critically ill patients requiring reversal of anticoagulation for atrial fibrillation.

Introduction
Atrial fibrillation (AF) afflicts over two million people, or 0.95% of the United States population. The prevalence of AF is age-associated, affecting 3.8% of people over age 60 and 9% of those over age 80. Although there are different types and etiologies of AF (Table 1), this monograph will address acute, new-onset AF in the critically ill patient because it presents a different paradigm with respect to epidemiology as well as treatment. Unfortunately, most existing data on AF in critically ill patients is observational, and often combines AF with a wide spectrum of other supraventricular arrhythmias.

Etiology
Many physiologic factors predispose a patient to AF, including cardiac diseases such as hypertension, coronary artery disease (CAD), cardiomyopathy, valvular disease, cardiac surgery, myocarditis, pericarditis, and other supraventricular tachycardias, as well as non-cardiac disorders, such as excessive alcohol intake, hyperthyroidism, pulmonary embolism, obstructive sleep apnea, metabolic syndrome and vagal or sympathetic mechanisms. In the critically ill patient, the incidence of AF ranges from 6-20%. In patients with acute CAD, the highest incidence of AF (30-40%) occurs in patients after cardiac surgery, especially mitral valve surgery and coronary artery bypass grafting. The highest incidence of new-onset AF in non-cardiac post-operative patients occurs after vascular, abdominal and thoracic surgery. In general, most patients have at least one modifiable risk factor such as electrolyte abnormalities, fluid balance and hypotension. Patients with new-onset AF who develop hemodynamic instability are more likely to have been receiving vasoressors, to have had congestive heart failure (CHF) with pulmonary edema, and to have a rapid ventricular response greater than 150 beats per minute (bpm) than those without hemodynamic instability. It is still undetermined whether AF is related to contiguous inflammation or these modifiable factors.

The most common correlate in critically ill patients with AF is sepsis, with some evidence that c-reactive protein plays a role; fueling the theory that inflammation could be a target for prophylaxis and treatment. In a review of almost 50,000 hospitalized patients with severe sepsis, 26% had AF, one-quarter of which were new-onset. Sepsis patients with new-onset AF have an increased risk of in-hospital stroke and mortality. Risk factors for AF in sepsis include age, Caucasian race and severity of sepsis, but not many of the traditional risk factors, such as CHF, myocardial infarction (MI), hypertension.

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxysmal AF</td>
<td>AF that terminates spontaneously or with intervention within 7 d of onset.</td>
</tr>
<tr>
<td></td>
<td>Episodes may recur with variable frequency.</td>
</tr>
<tr>
<td>Persistent AF</td>
<td>Continuous AF that is sustained &gt;7 d.</td>
</tr>
<tr>
<td>Long-standing persistent AF</td>
<td>Continuous AF &gt;12 mo in duration.</td>
</tr>
<tr>
<td>Permanent AF</td>
<td>The term “permanent AF” is used when the patient and clinician make a joint decision to stop further attempts to restore and/or maintain sinus rhythm.</td>
</tr>
<tr>
<td></td>
<td>Acceptance of AF represents a therapeutic attitude on the part of the patient and clinician rather than an inherent pathophysiological attribute of AF.</td>
</tr>
<tr>
<td></td>
<td>Acceptance of AF may change as symptoms, efficacy of therapeutic interventions, and patient and clinician preferences evolve.</td>
</tr>
<tr>
<td>Nonvalvular AF</td>
<td>AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair.</td>
</tr>
</tbody>
</table>

diabetes mellitus and valve disease. Blunt thoracic trauma also carries a high risk for new-onset AF.12

Some of the evidence from research into the etiology of AF in critical illness would suggest that it is a marker of illness severity or a result of the physiology of the critical illness itself, although still conferring future risk for stroke and mortality. Genetic and environmental risk factors have been implicated as well.13 There is a lack of correlation between new-onset AF and ischemic heart disease, thus obviating the need for admission to rule out MI based on AF alone.1

**Pathophysiology**

The critically ill patient typically starts with physiologic disadvantages, including volume shift, anemia, electrolyte imbalance, sepsis and/or the requirement for adrenergic vasoactive agents. A sudden increase in heart rate will drive an increase in right and left atrial pressures, and a decrease in end-diastolic volume and stroke volume. If the decrease in stroke volume is offset by the increased heart rate, cardiac output could be maintained; otherwise it, too, will decrease.14 Myocardial oxygen demand, vulnerable to changes in heart rate, afterload and left ventricular end diastolic pressure, will increase as cardiac output deteriorates. Subsequent resulting hypotension leading to a diminution in coronary perfusion, ischemia, heart failure and organ dysfunction can create a cycle of deterioration. Patients with pre-existing diastolic dysfunction are particularly vulnerable to these events.7 The development of AF can also cause a rise in pulmonary artery pressures, pulmonary hypertension and pulmonary edema.

In addition to the pathophysiology of AF contributing to critical illness, stroke risk is increased as a result of atrial inactivity, coagulopathy of critical illness, and decreased cardiac output. Pathophysiologic components contributing to thrombus formation are complex and include arrhythmia-induced stasis in the left atrium, atrial dilation and endothelial damage, causing changes in hemostasis such as platelet activation.15

**Treatment Options**

There are little prospective, randomized data regarding treatment modalities for AF in the critically ill. Most recommendations are derived from data in ambulatory patients and are adapted according to critical illness factors including contraindications to anticoagulation due to recent surgery, trauma or thrombocytopenia, or contraindications to chemical rate or rhythm control because of pre-existing comorbidities.

Resolution of pre-existing modifiable risk factors is the first step toward preventing or treating new-onset AF in the critically ill patient (Table 2). Treating these risk factors also increases the success of cardioversion or rate control. It is important to restore and maintain perfusion pressure and minimize inflammation and/or cat-

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Etiology</th>
<th>Specific Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial stretch (atrial hypertension, atrial dilatation, reduced contractility)</td>
<td>• Fluid overload</td>
<td>• Fluid removal (restrictive fluid administration, diuretics, renal replacement therapy)</td>
</tr>
<tr>
<td></td>
<td>• Acute mitral insufficiency</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Mitral stenosis</td>
<td></td>
</tr>
<tr>
<td>Inappropriate oxygen delivery to the myocardium</td>
<td>• Myocardial ischemia</td>
<td>• Revascularization</td>
</tr>
<tr>
<td></td>
<td>• Hypovolemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Anemia</td>
<td></td>
</tr>
<tr>
<td>Electrolyte disturbances (risk factors: diuretics, dialysis)</td>
<td>• Hypokalemia</td>
<td>• Substitution of potassium (goal K⁺ 4.5–5.5 mmol/L)</td>
</tr>
<tr>
<td></td>
<td>• Hypomagnesemia</td>
<td></td>
</tr>
<tr>
<td>Systemic and local inflammation</td>
<td>• Heart-lung machine</td>
<td>• Steroids; off-pump cardiothoracic techniques</td>
</tr>
<tr>
<td></td>
<td>• Sepsis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Myocarditis</td>
<td></td>
</tr>
<tr>
<td>Adrenergic overstimulation</td>
<td>• Inotropic support</td>
<td>• Reduction of inotropes</td>
</tr>
<tr>
<td></td>
<td>• Stress (pain, anxiety)</td>
<td></td>
</tr>
<tr>
<td>Endocrine disorder</td>
<td>• Elevated thyroid hormones</td>
<td>• Betablockers; thyreostatic drugs</td>
</tr>
<tr>
<td></td>
<td>• Pheochromocytoma</td>
<td></td>
</tr>
<tr>
<td>Various</td>
<td>• Hypothermia</td>
<td>• Correction of hypothermia</td>
</tr>
</tbody>
</table>

echolamines. Volume status, sepsis, use of catecholamine-based vasoactive agents and generalized stress contribute to development of AF and should be addressed early in an effort to minimize the development of arrhythmia, or be remedied upon development of the arrhythmia. Providing sedation and pain control also contributes to success because it reduces the catecholamine response.7

After addressing the modifiable risk factors, rate control is most important, with anticipation that spontaneous conversion may occur. If AF has been ongoing for greater than 48 hours cardioversion is recommended, either by electrical or pharmacological mechanisms. Prior to cardioversion, the patient should undergo transesophageal echocardiography (TEE) to rule out existing left atrial thrombus, and/or three weeks of anticoagulation prior to cardioversion and four weeks after cardioversion.3 This may not be practical in the critically ill patient for many reasons, one of which is coagulopathy and the driving mechanisms for AF. If the duration of AF is less than 48 hours, cardioversion can be performed with consideration for anticoagulation due to increased risk of thrombus post-conversion.3

Cardioversion

Rhythm control by electrical cardioversion, the first line therapy, or pharmacological cardioversion is the priority for treating hemodynamic instability resulting in angina pain, ST-segment changes or hypotension.13 Caution should be taken in converting AF to sinus rhythm if the patient has been in AF for greater than 48 hours due to the potential for left atrial thrombus; however, in patients with hemodynamic instability secondary to AF, cardioversion may be necessary even if an atrial thrombus has not been excluded.3

In ambulatory patients, electrical or pharmacologic cardioversion for new-onset AF is generally safe and effective with success rates of approximately 90%. In contrast, success rates for electrical cardioversion are as low as 30% in the critically ill patient.7 Strategies for higher success rates with electrical cardioversion include sedation and analgesia to decrease catecholamine surge, starting with higher energy joules (200 J biphasic) to overcome increased impedance, and careful adjustment of electrode placement due to wounds or dressings. Anterior-posterior (AP) paddles are best for supraventricular tachycardias (SVTs). Even with electrical conversion there is a high rate of recurrence in this population.8 If cardioversion is not possible, then anti-arrhythmic or nodal slowing agents may be used.

Rate Control

Hemodynamic stability may be restored by using agents to slow atrioventricular (AV) nodal conduction such as beta antagonists or calcium channel blockers, or with antiarrhythmic agents such as amiodarone; these medications may precipitate hypotension which could worsen the clinical picture. Heart rate control can also be helpful in increasing ventricular filling and stroke volume, thus preventing tachycardia-induced cardiomyopathy which typically occurs with protracted rapid AF. The current treatment goal for heart rate is <110 bpm.16,17 There are no data to recommend any one agent over the others in the critically ill patient, therefore the treatment strategy should be tailored to the particular patient’s clinical situation.19,20-21

The commonly used medications for rate control in AF are listed in Tables 3 and 4.

Beta antagonists are effective for rate control because they slow the ventricular rate and reduce myocardial excitability. Less desirable effects include negative inotropy and vasodilatation, which may be counterproductive in the setting of decreased cardiac output. In the intensive care unit (ICU) setting, esmolol is used most commonly due to its short half-life and the ability to titrate based on effect.

Calcium channel blockers are effective and have been studied in comparison to other agents. Diltiazem has been shown to be superior to digoxin for rapid control of tachycardia associated with AF in the ambulatory setting and more effective than metoprolol in postsurgical patients, excluding cardiac and thoracic surgery. It is not inferior to amiodarone in rate control in critically ill patients; however, the downside to diltiazem is hypotension which may not be tolerated in critically ill patients.19,21 Negative inotropic effect is more pronounced with verapamil than diltiazem. Verapamil also has an increased incidence of conduction disorders. Therefore diltiazem is preferred, but both require caution in the setting of heart failure unless left ventricular function is preserved.

Digoxin is not typically a first line agent for rate control in the ICU due to its long onset of action (>1 hour) and time to peak concentration (6 hours). It acts by directly affecting the AV node and through centrally mediated vagal stimulation. Its value is that it does not have a negative inotropic effect so it can be combined with other nodal slowing agents. Digoxin is less effective in settings of high adrenergic stress, making it less useful in the ICU setting.22 It is important to follow digoxin levels closely because renal dosing is required. Its metabolism can be affected by agents commonly used in this setting such as amiodarone and non-dihydropyridine calcium channel blockers.

Caution should be taken with all agents that block the AV node in the setting of pre-excitation syndromes such as Wolfe-Parkinson-White due to the potential for decreasing the refractoriness of the bypass tract and creating a worsening tachycardia with subsequent decrease in cardiac output. Amiodarone has antagonistic effects on adrenergic receptors as well as potassium and calcium channels. In addition to slowing the ventricular rate it has shown high conversion rates in the setting of critical illness.8 Amiodarone’s advantages over beta and calcium channel blockers are that it causes less negative inotropy. Amiodarone has a very long half-life and pertinent side effects in critical care settings include bradycardia, hypotension and local phlebitis. If used in a more prolonged fashion, significant side effects include thyroid disturbances, neurologic, pulmonary, and hepatic toxicity, as well as multiple interactions with other medications.3,23,24
### TABLE 04: Common Medication Dosage for Rate Control of Atrial Fibrillation

<table>
<thead>
<tr>
<th>Substance</th>
<th>Intravenous Administration</th>
<th>Usual Oral Maintenance Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beta blockers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metoprolol tartrate</td>
<td>2.5–5.0 mg IV bolus over 2 min; up to 3 doses</td>
<td>25–100 mg BID</td>
</tr>
<tr>
<td>Metoprolol XL (succinate)</td>
<td>N/A</td>
<td>50–400 mg QD</td>
</tr>
<tr>
<td>Atenolol</td>
<td>N/A</td>
<td>25–100 mg QD</td>
</tr>
<tr>
<td>Esmolol</td>
<td>500 mcg/kg IV bolus over 1 min, then 50–300 mcg/kg/min IV</td>
<td>N/A</td>
</tr>
<tr>
<td>Propranolol</td>
<td>1 mg IV over 1 min, up to 3 doses at 2-min intervals</td>
<td>10–40 mg TID or QID</td>
</tr>
<tr>
<td>Nadolol</td>
<td>N/A</td>
<td>10–240 mg QD</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>N/A</td>
<td>3.125–25 mg BID</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>N/A</td>
<td>2.5–10 mg QD</td>
</tr>
<tr>
<td><strong>Nondihydropyridine Calcium Channel Antagonists</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verapamil</td>
<td>0.075–0.15 mg/kg IV bolus over 2 min; may give an additional 10.0 mg if no response; then 0.005 mg/kg/min infusion</td>
<td>180–480 mg QD (ER)</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>0.25 mg/kg IV bolus over 2 min, then 5–15 mg/h</td>
<td>120–360 mg QD (ER)</td>
</tr>
<tr>
<td><strong>Digitalis Glycosides</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>0.25 mg IV with repeat dosing to a maximum of 1.5 mg over 24 h</td>
<td>0.125–0.25 mg QD</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiodarone*</td>
<td>300 mg IV over 1 h, then 10–50 mg/h over 24 h</td>
<td>100–200 mg QD</td>
</tr>
</tbody>
</table>

*Multiple dosing schemes exist for the use of amiodarone.
BID, twice daily; ER, extended release; IV, intravenous; N/A, not applicable; QD, once daily; QID, 4 times a day; and TID, 3 times a day.

Magnesium increases atrial and AV nodal refractory periods. It has been suggested to be as effective as amiodarone and diltiazem in rate control for AF. These data are of limited strength, but reinforce the point that hypomagnesemia, present in nearly half of AF patients, should be addressed in conjunction with any agent chosen for treatment of acute AF.

Complications of Atrial Fibrillation

Although cardioversion for new-onset AF in ambulatory patients is generally effective, AF does not seem to be as transient or benign in the critical care setting. Even if cardioversion is accomplished, AF often recurs with other morbidity and mortality effects associated with new-onset AF. The AF after cardiac surgery confers a three-fold greater risk of stroke and a higher risk of MI, heart failure, and respiratory failure. New studies are now examining the existence of AF in other postoperative and critically ill patients to try to identify predisposing factors and hopefully improve outcomes through prevention and treatment.

Stroke Risk

Critically ill patients have an increased risk of in-hospital and out-of-hospital stroke in the setting of new-onset AF, in part because of the contributions of inflammation and a pro-coagulation state. The presence of AF alone increases the risk of stroke nearly five-fold, and the only prophylactic treatment is anticoagulation. Anticoagulation can affect a 60% decrease in the incidence of stroke in the ambulatory setting. Many factors make anticoagulation a risky proposition in the ICU patient, however, including possible thrombocytopenia, renal and hepatic insufficiency, and anticipation of invasive procedures. The risk of stroke must therefore be balanced with the risk of hemorrhagic complications due to anticoagulation which increases in the critically ill patient and with the challenge of maintaining a therapeutic international normalized ratio (INR). In one study of ICU patients, only 16% of patients with new-onset AF and 19% of patients with pre-existing AF received anticoagulation while in the ICU. There were no acute ischemic stroke events but 9% of patients had a significant bleeding event, while still in the ICU.

Perioperative stroke has an incidence of 0.05-7% in non-cardiac, non-neurosurgical patients, and carries a mortality twice that of stroke in ambulatory patients. Postoperative arterial thrombotic events, in general, carry up to 33% mortality; however, only 3% of postoperative bleeding events are fatal. Unfractionated heparin, although not studied conclusively, may be a safer option because it is not eliminated by the kidneys and is easily reversible.

New-onset AF in critical illness is associated with in-hospital and long term risk of recurrent AF, stroke, heart failure and mortality. There is also evidence from ongoing research on the cause of cryptogenic stroke (stroke without identifiable cause) that some patients who have had transient AF during hospitalization for sepsis have developed stroke after hospitalization without evidence of recurrent AF.

Risk Assessment

Currently, decisions regarding anticoagulation in critically ill patients with AF are made using published recommendations for preventing stroke in ambulatory patients with AF and adapting these to critically ill patients by estimating the risk of bleeding.

The CHADS2 and CHA2DS2-VASc scoring systems predict the risk of future ischemic stroke events in the ambulatory patient with AF and have been validated in the ICU setting, although there is some disagreement as to how to set the threshold for anticoagulation (Table 5). The recommendations for antithrombotic therapy in the ambulatory AF patient are based on multiple factors including patient preference, age, classification of AF, CHA2DS2-VASc score, presence of mechanical valve, and prior stroke or transient ischemic event (TIA) (Table 6). The American Heart Association/American College of Cardiology/Heart Rhythm Society recommendations propose using a CHA2DS2-VASc score of two or more as threshold for anticoagulation but this is a general recommendation, and does not take into account critically ill patients. Some recommend considering a CHADS2 score of four or higher, significant mitral stenosis, or previous stroke as criteria for anticoagulation in critically ill patients.

The American Association for Thoracic Surgery (AATS) recommends anticoagulation in post-operative thoracic surgery patients whose CHA2DS2-VASc score is two or more, and consider anticoagulation therapy if the score is one (Figure 1). This Society recommends using warfarin but suggests that the non-vitamin K antagonist oral anticoagulants (NOACs) are a reasonable alternative for those without a prosthetic heart valve, valve disease, renal impairment or risk of gastrointestinal bleeding. These recommendations are based on evidence from patients in the ambulatory setting.
### TABLE 06  Summary of Recommendations for Risk-Based Antithrombotic Therapy

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithrombotic therapy based on shared decision making, discussion of risks of stroke and bleeding, and patient’s preferences</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Selection of antithrombotic therapy based on risk of thromboembolism</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>CHA$<em>{DS}</em>{2}$-VASc score recommended to assess stroke risk</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Warfarin recommended for mechanical heart valves and target INR intensity based on type and location of prosthesis</td>
<td>I</td>
<td>B</td>
</tr>
</tbody>
</table>

*With prior stroke, TIA, or CHA$_{DS}_{2}$-VASc score ≥2, oral anticoagulants recommended. Options include:

- **Warfarin**

  - Warfarin recommended for mechanical heart valves and target INR intensity based on type and location of prosthesis
  - Warfarin
  - With warfarin, determine INR at least weekly during initiation of therapy and monthly when stable
  - With warfarin, determine INR at least weekly during initiation of therapy and monthly when stable
  - Direct thrombin or factor Xa inhibitor recommended if unable to maintain therapeutic INR
  - Reevaluate the need for anticoagulation at periodic intervals
  - Bridging therapy with UFH or LMWH recommended with a mechanical heart valve if warfarin is interrupted.
  - For patients without mechanical heart valves, bridging therapy decisions should balance risks of stroke and bleeding
  - Evaluate renal function before initiation of direct thrombin or factor Xa inhibitors, and reevaluate when clinically indicated and at least annually
  - For atrial flutter, antithrombotic therapy is recommended as for AF
  - With nonvalvular AF and CHA$_{DS}_{2}$-VASc score of 0, it is reasonable to omit antithrombotic therapy
  - With CHA$_{DS}_{2}$-VASc score ≥2 and end-stage CKD (CrCl <15 mL/min) or on hemodialysis, it is reasonable to prescribe warfarin for oral anticoagulation
  - With nonvalvular AF and a CHA$_{DS}_{2}$-VASc score of 1, no antithrombotic therapy or treatment with oral anticoagulant or aspirin may be considered
  - With moderate-to-severe CKD and CHA$_{DS}_{2}$-VASc scores ≥2, reduced doses of direct thrombin or factor Xa inhibitors may be considered
  - For PCI,* BMS may be considered to minimize duration of DAPT
  - After coronary revascularization in patients with CHA$_{DS}_{2}$-VASc score ≥2, it may be reasonable to use clopidogrel concurrently with oral anticoagulants but without aspirin
  - Direct thrombin dabigatran and factor Xa inhibitor rivaroxaban are not recommended in patients with AF and end-stage CKD or on dialysis because of a lack of evidence from clinical trials regarding the balance of risks and benefits
  - Direct thrombin inhibitor dabigatran should not be used with a mechanical heart valve

*See the 2011 PCI guideline for type of stent and duration of DAPT recommendations.

AF indicates atrial fibrillation; BMS, bare-metal stent; CHA$_{DS}_{2}$-VASc, Congestive heart failure, Hypertension, Age ≥75 years (doubled), Diabetes mellitus, Prior Stroke or TIA or thromboembolism (doubled), Vascular disease, Age 65 to 74 years, Sex category; CKD, chronic kidney disease; COR, Class of Recommendation; CrCl, creatinine clearance; DAPT, dual antiplatelet therapy; INR, international normalized ratio; LMWH, low-molecular-weight heparin; LOE, Level of Evidence; PCI, percutaneous coronary intervention; TIA, transient ischemic attack; and UFH, unfractionated heparin.

Multiple scoring systems have been published to assess for bleeding risk in the anticoagulated patient. The HAS-BLED score has been shown to be superior in predictive value as well as simplicity (Table 7). These scoring systems have not been validated in critically ill patients who have many other factors contributing to a high risk of bleeding if anticoagulated.

**Oral Anticoagulants**

Warfarin, a vitamin K antagonist (VKA), has been the mainstay for prophylactic anticoagulation in the AF patient but has been underused due to its many food and drug interactions, patient noncompliance, and hesitancy of many physicians to prescribe this drug because of patient risk factors including fall potential, dementia and history of bleeding. Antiplatelet agents have been considered as an alternative, but aspirin may carry a higher risk of bleeding than warfarin with no significant protection against cardio-embolic events. Clopidogrel has not been approved for use in stroke prevention. The combination of aspirin and clopidogrel has also been shown to increase bleeding risk without providing cardio-embolic protection, and would not be an appropriate choice for risk prevention in the critically ill patient due to length of therapeutic effect.
The NOACs are advantageous because, as opposed to warfarin, they do not require frequent laboratory evaluation to ensure target therapeutic goals. These agents, which are sometimes called direct oral anticoagulants (DOAC), or target specific anticoagulants (TSAOC), have been approved in phase III trials for stroke prevention in patients with nonvalvular AF. \(^{39,40}\) Apixaban, dabigatran and rivaroxaban have been shown to have greater efficacy than VKAs in preventing combined stroke, systemic embolism, all-cause mortality, vascular mortality and decreasing the risk for intracranial hemorrhage, although rivaroxaban had a higher risk for gastrointestinal hemorrhage.\(^{41}\) In 2010, dabigatran was the first NOAC to be approved in the United States to reduce stroke or systemic embolism, after being shown to have a similar rate of major bleeding and a lower rate of intracranial hemorrhage than warfarin.\(^{42}\) Rivaroxaban and apixaban approval closely followed, and all three agents are options to be considered for stroke reduction in AF patients in the ambulatory patient. These must be considered within the limitations of renal function, fall risk, bleeding risk and valvular heart disease (Table 6).

The question remains whether or not these agents are suitable for use in the critically ill patient. One of the most concerning drawbacks to the NOACs is the lack of reversibility. Although NOACs have a shorter half-life than VKAs, there are no specific reversal agents. However, it should also be considered that reversal of coagulopathy, although it seems intuitively protective, has not been shown to improve outcome in significant hemorrhage.

In general, it is important for clinicians taking care of critically ill patients with AF to discriminate which require anticoagulation, due to the lack of direct evidence in this population that improved outcomes outweigh the risk of complications.\(^{28,43}\)

**Alternative Approaches**

Newer methods of reducing ischemic stroke risk in patients with AF have been studied, although none of them in the setting of critical illness. Left atrial appendage (LAA) closure has been performed for decades in patients with AF primarily using a surgical approach at the time of mitral valve replacement to reduce the area of origin for most known cardio-embolic strokes, but this has not been studied in a randomized fashion. In addition, many ischemic strokes do not have thrombus originating in the LAA so anticoagulation is still considered after the procedure.\(^{44}\) Catheter ablation is another alternative to chemotherapy for AF, with success being dependent on factors such as patient selection and operator experience. Catheter ablation is typically used for those patients who are intolerant of or symptomatic despite medication, but is not used in the setting of critical illness.\(^{45}\)

**Conclusion**

In summary, AF is a significant issue in the critically ill patient with increased rates of morbidity and mortality. The physiology of the critically ill patient predisposes to AF, and morbidity and mortality are more significant than in the ambulatory setting in which most of the data regarding treatment and stroke prophylaxis have been obtained. The consideration for treatment, whether for rate control, rhythm conversion, or anticoagulation must include the unique circumstances of the critically ill patient who is at higher risk of complication. The astute clinician will apply existing data judiciously to the patient situation, closely balancing risk and benefit. The emergency physician will be seeing more critically ill patients with AF, due to the aging population and increased therapies evolving to extend life. More research is necessary to assess the safety of chemical and other therapies to treat the critically ill patient with AF.

**References**


MANAGEMENT OF MAJOR BLEEDING FOR PATIENTS TREATED WITH NON-VITAMIN K ANTAGONIST ORAL ANTICOAGULANTS

Charles V. Pollack, Jr., MD
Associate Provost for Innovation in Education; Director, Jefferson Institute of Emerging Health Professions; Associate Dean for CME and Strategic Partner Alliances; Professor, Department of Emergency Medicine, Thomas Jefferson University, Philadelphia, PA

Objectives

1. Assess the likely contribution of anticoagulation with non-vitamin K antagonist oral anticoagulants (NOACs) to acute hemorrhagic presentations to the Emergency Department.
2. Demonstrate a working knowledge of various general management strategies in the NOAC-treated bleeding or pre-procedural patient.
3. Formulate an action plan to manage specific cases of NOAC-related bleeding or pre-procedural presentations.
4. Describe the mechanism of action of various specific reversal agents to the NOACs and explain how this informs their clinical use.

Introduction

Non-vitamin K antagonist (formerly “novel”) oral anticoagulants (NOACs, sometimes also called direct oral anticoagulants [DOACs] or target-specific oral anticoagulants [TSOACs]) include the direct Factor Xa inhibitors rivaroxaban, apixaban, and edoxaban and the direct thrombin (Factor IIa) inhibitor dabigatran etexilate. These agents are approved for the prevention and treatment of venous thromboembolism (VTE) and for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF).

NOACs vs. Warfarin

For decades, the indications for NOACs were met only by vitamin K antagonists (VKAs), such as warfarin. However, warfarin is often viewed more as a problem than as a solution, given the drug’s inter-individual variation in efficacy and safety, multiple drug–drug and drug–diet interactions, and the need for frequent coagulation monitoring and dose adjustments to ensure that the international normalized ratio (INR) remains within the therapeutic range of 2.0–3.0. Such monitoring is burdensome, costly, and many would say (after the approval of four NOACs based on head-to-head comparisons with VKAs) that it is often no longer necessary. Conversely, the NOACs have a predictable anticoagulant response that allows for fixed dosing without routine coagulation monitoring. In Phase III trials that enrolled more than 150,000 patients globally, NOACs were at least as effective as VKAs for VTE treatment1–4 and for stroke prevention in patients with NVAF,5–10 while providing safety advantages. Subsequent real-world studies have supported the efficacy and safety of these agents in routine clinical practice (Figure 1).11,12

FIGURE 01 Comparison of Non-Vitamin K Antagonist Oral Anticoagulants (NOACs) versus Vitamin K Antagonists (VKAs)

**NOACs Overcome Many Practical Limitations of Warfarin**

- Rapid onset of action
- Short half-lives compared with warfarin
- Predictable and consistent anticoagulant effects
- Low potential for drug-drug interactions
- No drug-food interactions
- No requirement for routine coagulation monitoring

Despite their beneficial attributes, the “market uptake” of NOACs has been less robust than many medical experts and business estimates had predicted. This is likely due to a number of issues, including resistance to change in entrenched practice patterns, hesitancy to adopt new therapies “early,” and initial problems with health insurance coverage. A major reason, however, for the slow growth of NOAC use seems to be the lack of specific reversal agents for use in those occasional patients who present with serious bleeding while taking a NOAC, or in those who require urgent surgery and therefore need prompt restoration of hemostasis while taking a NOAC.13 There are validated approaches, promulgated by specialty societies and hospital pharmacy and therapeutics committees, and based on the quantitative guidance provided by rapid turnaround INR values, for handling such patients in the context of warfarin use. Although there is a lack of evidence that providers scrupulously follow such protocols—the comfort seems to be simply in having them and in having something to measure at baseline and serially. Because the anticoagulant effect of the NOACs cannot be readily measured, effecting “reversal” in NOAC-treated patients seems more abstract, demands an appreciation of some basic pharmacology as opposed simply to pulling out a protocol, and perhaps may create a bit of insecurity for the provider.

Bleeding Risk

There are, in fact, validated general approaches to managing NOAC-related bleeding complications (Figure 2), and specific approaches are being developed. Before discussing those, it is important to place NOAC-related bleeding into context (Figure 3). Across the four Phase III trials of NOACs versus VKAs in stroke prevention in NVAF, rates of major bleeding ranged from 1.6% to 3.6% per year for the NOACs and from 3.1% to 3.6% per year for warfarin.5–10 Intracranial hemorrhage (ICH) is the most-feared complication of VKA therapy, contributing to the majority of VKA-associated deaths and severe functional
CARE OF CRITICALLY ILL AND INJURED PATIENTS IN THE EMERGENCY DEPARTMENT

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Disabilities; therefore, the significant reductions in the rates of ICH (by ~30–70 %) and fatal or life-threatening bleeding episodes seen among NOAC-treated patients in these NVAF trials (in which the typical patient is elderly and has multiple comorbidities) are particularly reassuring. The only important exception is major gastrointestinal (GI) bleeding, for which incidences were higher with rivaroxaban and the higher doses of dabigatran and edoxaban compared with warfarin in Phase III studies. Of note, apixaban and the lower edoxaban and dabigatran doses were not associated with higher incidences of GI bleeding.

There are some populations that are generally viewed as being at higher risk of bleeding complications. Their outcomes are no worse and in fact are sometimes better with NOACs than with warfarin. For example, in the pooled analysis of the EINSTEIN-DVT and EINSTEIN-PE Trials, there was a significant 73% relative risk reduction in major bleeding on rivaroxaban compared with low-molecular-weight heparin (LMWH) bridging to VKA among “fragile” patients—those with two of three characteristics: (1) age > 75 years, (2) creatinine clearance (CrCl) < 50 ml/min, or (3) body weight < 50 kg.

Although patients with severe renal insufficiency were excluded in all Phase III studies of NOACs, VTE studies revealed that patients with mild renal insufficiency (CrCl 50–79 ml/min) receiving NOACs experienced significantly lower rates of major or clinically relevant non-major (CRNM) bleeding than those receiving other anticoagulants, and there was also a trend toward lower rates of major or CRNM bleeding with NOACs in moderate renal insufficiency (CrCl 30–49 ml/min). The impact of renal function on NOAC-related bleeding rates is, not surprisingly, related to the degree to which each drug is excreted by the kidneys. In a meta-analysis of data from patients with renal impairment (CrCl < 50 ml/min) enrolled in studies of NOACs in patients with VTE and NVAF, there was a significantly greater relative reduction in major bleeding in patients receiving NOACs that have < 50 % renal excretion (rivaroxaban, apixaban and edoxaban) than in those receiving dabigatran.

This information is not intended and must not be considered as a specific recommendation from Boehringer Ingelheim. Each treating physician should determine what medical treatment and/or bleeding management measures should be taken on a case by case basis, based on their medical experience and judgement. Idarucizumab is currently in development and is not approved for use in the EU.

EHRA: European Heart Rhythm Association; GI: gastrointestinal; RBC: red blood cell; FFP: fresh frozen plasma; PCC: prothrombin complex concentrate; aPCC: activated prothrombin complex concentrate; rFVIIa: recombinant activated clotting factor VII

Although the NOACs have many fewer drug-drug and drug-diet interactions than warfarin, some concomitant medications may increase the risk of bleeding in patients taking NOACs; these concerns apply to VKAs as well. Non-steroidal anti-inflammatory drugs (NSAIDs), aspirin, and other antiplatelet medications (such as clopidogrel, ticagrelor, prasugrel, and dipyridamole) not only increase the risk of major bleeding when taken with NOACs, but also complicate the restoration of hemostasis when major bleeding occurs.21,22

Since approval of the NOACs, multiple real-world registries have demonstrated that the safety and efficacy of the NOACs seen in Phase III trials is replicated in practice, including the reduction in ICH and the concern for GI bleeding. In the Dresden NOAC Registry, for example, the rate of major bleeding was 3.4% per year, and GI bleeding was the most common site.12 It is also reassuring to note that most of these bleeding episodes were successfully managed conservatively.

A retrospective analysis of patients with AF receiving rivaroxaban or dabigatran in the United States showed low rates of major bleeding, ICH, and fatal bleeding.23 Data collected for the Food and Drug Administration (FDA) on more than 134,000 Medicare patients with newly diagnosed AF showed that, compared with warfarin, dabigatran was associated with a lower risk of ischemic stroke, ICH, and death, but an increased risk of major GI bleeding;24,25 all of these findings are consistent with the Phase III data for dabigatran.

Emergency physicians may also be faced with NOAC-treated patients who require urgent or emergent invasive procedures or surgery for which hemostasis is required. The inability to rapidly assess the extent of anticoagulation in these patients increases clinical anxiety. It is vital to obtain an accurate report of time since last dose, because the short half-life of all the NOAC agents is helpful in these situations. In fact, in cases of invasive interventions in the RE-LY Trial, the incidence of major bleeding was significantly lower in patients taking dabigatran than in those taking warfarin when the time between the last dose and surgery was no more than 48 hours.26 Knowledge of time of last dose can be coupled with quick assessment of renal function to assess how much anticoagulant effect is likely to be on board when the patient is in the Emergency Department (ED) or operating room. For the most part, a therapeutic anticoagulation effect can be excluded if the activated partial thromboplastin time (aPTT) is normal in dabigatran-treated patients or if the prothrombin time (PT) is normal in patients being treated with rivaroxaban or edoxaban (Figure 4). There are no such reliable “qualitative” tests for apixaban.

Managing NOAC-Related Bleeding

When patients taking NOACs do present with major or life-threatening bleeding, there are basic principles to keep in mind (again, Figure 2 provides a summary):

1. Discontinue the NOAC.
2. If resuscitation is needed, start resuscitation! The ABCs always take priority! If the patient is hypotensive, then rapid crystalloid infusion should immediately be initiated; blood products should be given as indicated. Send type-and-crossmatch specimens. Keep in mind that septic or multi-injured patients may develop coagulopathy that goes beyond simple inhibition of the activity of one factor in the clotting pathway. Patients taking antiplatelet agents may need platelet transfusion.
3. Address treatable sites of bleeding with direct pressure, appropriate vascular clamps, or stabilization of fractures.
4. Decontamination – for any of the NOACs, if the previous dose was taken within the past 2-4 hours, give activated charcoal. Adsorption is least effective for rivaroxaban, because it is so rapidly absorbed and then highly protein-bound. For dabigatran, emergency hemodialysis, while time-consuming and logistically challenging, is effective.22,28 The anti-Xa agents are too tightly protein-bound for dialysis to be effective.

5. Initiate appropriate diagnostic procedures (such as computed tomography [CT] scan in the patient with suspected ICH, endoscopic procedures for GI bleeding, etc.).

For patients who remain unstable due to coagulopathy or ongoing hemorrhage after these general steps are taken, and for patients with bleeding into closed spaces such as the head, pericardium, or retroperitoneum, emergent factor repletion may be considered. There are scant objective data to support such an approach, and the logic behind it is likewise limited. In warfarin-related coagulopathy there is an actual absence of functional coagulation factors including Vitamin K-dependent Factors II, VII, IX, X, and Proteins C and S. For these patients, repletion is necessary to restore the physiologic mechanism of hemostasis. In patients treated with NOACs, there are no “missing” factors. In dabigatran-treated patients, there are normal circulating levels of thrombin (Factor IIa), but dabigatran binds thrombin more avidly than thrombin binds fibrinogen. Giving additional Factor IIa might be helpful, but only to the extent that it overcomes the body load of dabigatran; in any event Factor IIa cannot be given alone. Fresh frozen plasma (FFP) or prothrombin complex concentrates (PCCs) such as FEIBA or Kcentra® may be administered. In doing so, Factors IX and X are also given and, depending on the preparation, Factor VII and other clotting proteins may be included as well. There is understandable concern that such an approach actually might create more of a sustained, prothrombotic state than is desired in treating dabigatran-associated bleeding. With apixaban, edoxaban, or rivaroxaban-associated bleeding, FFP or 3- or 4-factor repletion does much more than overwhelm the inhibition of normal levels of Factor Xa. For these rare cases, a specific reversal strategy is desirable.

Reversal Agents

At least three specific reversal agents have been developed, and two are in Phase III trials currently. Idarucizumab is an antibody fragment directed against dabigatran (Figure 5).29 This Fab fragment binds dabigatran with at least 350 times the affinity with which dabigatran binds to thrombin, and has no intrinsic anticoagulant or procoagulant activity. Phase I and II results have shown complete and sustained reversal of dabigatran-induced anticoagulation in healthy volunteers with normal renal function and in older subjects with mild-to-moderate renal impairment.30,31 The FDA granted breakthrough therapy designation to idarucizumab in June 2014, and a phase III study is currently ongoing (RE-VERSE AD, clinicaltrials.gov NCT02104947). Two types of patients are being studied in RE-VERSE AD – those with serious bleeding and those requiring urgent surgery or intervention that cannot be delayed at least eight hours.

Interim results of RE-VERSE AD, reflecting experience with 90 of an expected 300 subjects, were published earlier this year.32 The primary endpoint of the study is the maximum percentage reversal of the anticoagulant activity of dabigatran as measured by either dilute thrombin time (dTT) or ecarin clotting time (ECT). Among the evaluable patients in the interim analysis cohort, the median maximum percentage reversal was 100% (95% confidence interval, 100 to 100). Idarucizumab normalized the test results in 88% to 98% of the patients, an effect that was evident within minutes. Concentrations of unbound dabigatran remained below 20 ng per milliliter at 24 hours in 79% of the patients. Among 35 patients in the bleeding cohort who could be assessed, hemostasis, as determined by local investigators, was restored at a median of 11.4 hours (Figure 6). Among 36 of 39 patients in the pre-procedure group who underwent a procedure, normal intraoperative hemostasis was reported in 33, and mildly or moderately abnormal hemostasis was reported in two patients and one patient, respectively (Figure 7).32 The study is being completed, but both the FDA and the European Medicines Agency (EMA) are reviewing regulatory packages based on the interim data. On October 16, 2015, the FDA approved idarucizumab for use in the U.S.

Andexanet alfa is a universal Factor Xa reversal agent. It is a biologically inactive recombinant analogue of Factor Xa that binds to direct Factor Xa inhibitors and antithrombin. Andexanet alpha has the potential to neutralize the effect of apixaban, edoxaban, rivaroxaban, enoxaparin, dalteparin, fondaparinux, and tinzaparin. In preclinical studies, andexanet alfa, in a dose-dependent fashion, reversed Factor Xa inhibition. Full results from the phase II trials are pending (clinicaltrials.gov NCT01758432). In interim results, andexanet alfa was shown to reverse the anticoagulant effects of rivaroxaban and apixaban in a dose-dependent manner as assessed using pharmacodynamic markers.33,34 In November 2013, the development of andexanet alfa as a reversal agent for Factor Xa inhibitors
MANAGEMENT OF MAJOR BLEEDING FOR PATIENTS TREATED WITH NON-VITAMIN K ANTAGONIST ORAL ANTICOAGULANTS

**Interim Results From Hemorrhaging Patients in RE-VERSE AD Trial**

**Group A interim results:** reversal of dabigatran anticoagulation with idarucizumab based on dTT

- **Group A:** Uncontrolled bleeding
  - Idarucizumab 2x 2.5 g
  - No idarucizumab-related safety concerns identified to date in the analysis
  - Assay upper limit of normal

**Interim analysis includes data for the first 90 patients
Adapted with permission from Pollack et al. N Eng J Med 2015.

**Interim Results From Pre-Procedural Patients in RE-VERSE AD Trial**

**Group B interim results:** reversal of dabigatran anticoagulation with idarucizumab based on dTT

- **Group B:** Emergency surgery or procedure
  - Idarucizumab 2x 2.5 g
  - CLINICAL OUTCOMES
    - 33 patients had normal intraoperative hemostasis (as judged by the physician)
    - 2 mildly abnormal
    - 1 moderately abnormal

**Assay upper limit of normal
Adapted with permission from Pollack et al. N Eng J Med 2015.**

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was granted breakthrough therapy designation by the FDA. A cohort study of andexanet alfa in rivaroxaban treated or apixaban treated patients who present with serious bleeding is underway (clinicaltrials.gov NCT02329327).

Finally, aripazine is a cationic small molecule designed to bind unfractionated heparin, LMWH and fondaparinux, as well as all of the NOACs. Its binding to heparins is charge-dependent and interferes with NOACs via a hydrogen bond-mediated mechanism. It is being billed as a potential “universal antidote.” An initial human study showed that, at doses of 50–300 mg, aripazine reversed the anticoagulant effect of 60 mg edoxaban.25

Reversal agent development is exciting and clearly addresses an unmet need. Due to the favorable bleeding profiles of NOACs compared with VKAs, and their short half-lives, clinical data show that NOAC-associated bleeding can largely be managed using conservative measures. Just as with warfarin, restoration of coagulation may not necessarily lead to better clinical outcomes. This will likely limit the use of the reversal agents to patients with catastrophic bleeding. For dire situations, such as immediate life-threatening bleeding, ICH, the need for rapid reversal prior to emergency surgery, or when other measures fail or if the NOAC cannot be cleared because of renal failure, specific reversal agents will be indicated.

**Conclusion**

Severe or life-threatening bleeding complications on NOAC therapy, in which emergency reversal may be necessary, are rare, and therefore the current lack of specific reversal agents should not deter physicians from using NOACs. At the same time, emergency management protocols should be established to guide evaluation of the severity of the bleeding event, and all EDs should have management pathways to deal with bleeding in patients receiving anticoagulants, including both VKAs and NOACs. Non-specific reversal agents (such as PCCs) may be considered in exceptional cases of severe or life-threatening bleeding if other measures prove unsuccessful. Agents such as PCC should be available in the ED for the management of life-threatening bleeding (including ICH) with VKAs and NOACs, and if indicated, should be given as soon as possible. In the near future, specific reversal agents for NOAC treated patients with severe bleeding complications or the need for emergency surgery will be available.

**References**


Thromboelastography (TEG) – Understanding the Patient’s Ability to Clot Blood

Jordan B. Bonomo, MD
Associate Professor, Emergency Medicine; Director, Division of Critical Care, Department of Emergency Medicine; Associate Professor, Neurosurgery/Neurocritical Care; Director, Neurocritical Care Fellowship, University of Cincinnati College of Medicine, Cincinnati, OH

Natalie E. Kreitzer, MD
Assistant Professor of Emergency Medicine
Fellow, Neurovascular Emergencies and Neurocritical Care Department of Emergency Medicine, University of Cincinnati College of Medicine, Cincinnati, OH

Christopher R. Zammit, MD
Assistant Professor of Emergency Medicine and Neurology
Department of Emergency Medicine, Critical Care Division, University of Cincinnati College of Medicine, Cincinnati, OH

Objectives
1. Describe the emerging role of thromboelastography (TEG) in resuscitation in the Emergency Department and Critical Care environment.
2. Discuss how TEG informs a practitioner about correctible causes of bleeding during critical illness and injury, allowing differentiation between diminished hemostatic capacity and active fibrinolysis.
3. Describe the value of TEG as a marker of global hemostasis and inflammation in critical illness and emergency medicine.

Introduction
Thromboelastography (TEG), an assay of the viscoelastic properties of blood, provides a comprehensive real-time analysis of hemostasis, from initial thrombin burst to fibrinolysis, permitting improved transfusion strategies that result in the potential for goal-directed therapy of coagulation abnormalities following injury. TEG was first described in 1948 in Germany by Dr. Hellmut Hartert, and the process was automated and computerized in the late 20th century. There are two commercially available TEG systems, both of which are types of viscoelastic hemostatic assays (VHA): the rotational thromboelastometry (ROTEM®; Tem International GmbH, Munich, Germany) and the modified traditional thromboelastography (TEG®, Hemoscope Corporation, Niles, IL), which is the most prevalent system in use in North America. VHA technology is currently used and well validated in trauma, liver transplant surgery, cardiac surgery, obstetrics, bedside extracorporeal membrane oxygenation (ECMO) management, diagnosis of hypercoagulable states, major surgeries, hemophilia, and monitoring of antithrombotic therapy. In order to monitor antithrombotic therapy, TEG platelet mapping (TEM/PM) is also used. TEG/PM compares the patient’s platelet inhibition percentage against maximum platelet function measured by the assay, allowing relative changes in platelet contribution to clot formation to be clearly detected. Within the specialty of Emergency Medicine, TEG has seen its most prolific and validated use in trauma patients, but recent expansion of use has included traumatic brain injury, severe sepsis and septic shock. More recently, TEG has been described in the realm of acute coronary syndrome and hypothermia.

Clot Formation
In order to best understand TEG, a basic yet modern understanding of the process by which a clot forms is important. The most common scenario in which a clot forms occurs when damaged endothelium exposes underlying collagen and tissue factor to platelets. Platelets combine with von Willebrand factor (vWF) to link the platelets and collagen. Further platelet activation occurs and leads to strongly adhered platelets. The resulting coagulation cascade, which consists of the activation of previously inactivated circulating zymogens, sets off an exquisite and intricate reaction in which downstream pro-coagulant factors are activated by one another. At the same time, tissue factor pathway inhibitor (TFPI) is activated. The resulting reaction leads to the final common pathway, in which thrombin cleaves fibrinogen into fibrin. Thrombin also activates multiple other proteins, including protein C, which is inhibitory to clotting. The clot is concurrently amplified when Factors VIII and V accelerate thrombin formation exponentially, which is known as the “thrombin burst.” Thrombin subsequently activates Factor XIII, which leads to cross-linking of the fibrin fibers. Thus, in order to describe the clot formation and simultaneous breakdown, the function of multiple interacting proteins must be known. TEG is able to describe this balance both qualitatively (via the tracing) and quantitatively (via the measured values). A brief overview of the coagulation cascade is represented in Figure 1, and demonstrations of the qualitative tracings of VHAs (TEG and ROTEM) are shown in Figure 2 and Figure 3.

The VHA allow for unique product driven, goal-oriented resuscitation in the bleeding patient. In particular, TEG facilitates a global assessment of a patient’s coagulation status by evaluating factors that are difficult and time consuming to assess otherwise, such as platelet function and the state of fibrinolysis. The benefit of this capability is that a patient can receive timely workup and potential treatment of complex, multifocal coagulation disorders secondary to relatively common presentations in the emergency setting.

FIGURE 01 Overview of the Coagulation Cascade

The balance between hemostasis and fibrinolysis is intricate and TEG offers insightful information about that balance. One example is in the multisystem trauma patient who presents to the Emergency Department (ED) in shock. He or she likely has components of clotting and fibrinolysis simultaneously, and these components are difficult to capture with traditional assays of coagulation. TEG is more suited to providing understanding of clot lysis than traditional markers of fibrin degradation such as d-dimer, fibrin degradation products, or fibrin split products, which are non-specifically elevated in many states of inflammation other than bleeding or clotting. Recently, Carroll and colleagues addressed the acute post-traumatic coagulopathy, reported by Brohi et al., by VHA analyses of samples obtained at the scene of accident and upon arrival in the ED in 161 trauma patients. Interestingly, they found that the clot forming parameters demonstrating hypocoagulability correlated with fatality, whereas none of the routine coagulation tests like PT and aPTT demonstrated such a correlation. This indicates that VHA is more sensitive in reflecting clinically relevant coagulopathies than routine coagulation tests.

One particularly useful measurement provided by modern TEG is the so-called LY30, which reports the percent of fibrinolysis that has taken place in 30 minutes, with a standardized reference range of 0 – 8%. In the acute setting, an elevated LY30 percentage likely signifies a hyperfibrinolytic state and some authors have advocated administering antifibrinolytic therapy, such as transaxenic acid to these patients. While no consensus exists currently on the effectiveness of this strategy, clinical trials are underway to explore the benefit of targeting acute antifibrinolytic therapies in these hyperfibrinolytic patients.

**Understanding Viscoelastic Hemostatic Assays and TEG**

TEG analysis is conducted on aliquots of citrated whole blood, rather than separated blood and plasma components. In the most commonly employed TEG analyzer, a 0.36 mL sample of whole blood is placed into a cup, which is then incubated to 37 degrees. Calcium is then added to the sample to counteract the citrate, and the cup is continuously rotated through 4°-45° while a strain gauge pin, linked to a torsion wire, connects to a mechanical-electrical transducer. As changes in force are detected by the strain gauge during clot formation and degradation, the signal is translated into measurable data that is plotted in real time through automated signal translation (Figure 4 and Figure 5). As changes in force are detected by the strain gauge during clot formation and degradation, the signal is translated into measurable data that is plotted in real time through automated signal translation. As the blood clots in the cup, the degree of torque is increased. The amount of torque is measured electronically, and is representative of the degree to which clot formation has taken place. An activating solution consisting of kaolin, phospholipids, and buffered stabilizers is often used to help initiate the coagulation process in TEG, although this still takes several minutes. This process can be further expedited in the setting of hemorrhagic shock by the addition of tissue factor, resulting in a “rapid-TEG” (rTEG). rTEG allows a faster clotting profile to be created because the additional reagents activate both the intrinsic and extrinsic clotting systems simultaneously, and the earliest tracings of rTEG can be viewed within ten minutes. Real time changes that are seen in the TEG profile represent the strength and speed of clot formation, and allow assessment of which clotting factors are contributing appropriately or inappropriately, thereby informing targeted blood product delivery in the bleeding or coagulopathic patient. While there were initial concerns to the contrary, it appears as though the addition of accelerants to the rTEG assay does not bias the resulting data.
and colleagues described the rTEG evaluation of 1,996 consecutive severe trauma patients, and 41 (2%) of those patients demonstrated hyperfibrinolysis at admission. This subset had a 76% mortality rate, in contrast to 10% in the entire group. This study also demonstrated that prehospital crystalloid fluid administration resulted in a statistically significantly higher hyperfibrinolysis score, defined as more than 7.5% amplitude reduction at 30 minutes after maximal amplitude. Ultimately, if a higher percentage of hyperfibrinolysis is noted in patients who have had crystalloid administration, and this TEG abnormality is associated with higher mortality, then blood products may ultimately be proven to be preferential to crystalloids in the setting of acute traumatic hemorrhage.

The benefit of testing whole blood, rather than testing coagulation pathways piecemeal with separate complete blood count (CBC), PT, and aPTT tests, is that dynamics of clot formation are visualized, such that thrombosis and fibrinolysis are both represented in sequence. Traditionally, PT and aPTT are utilized as markers to screen trauma patients for coagulation deficits during trauma. These lab values are, in reality, indirect markers of coagulopathy, in that they do not directly evaluate the quantity or function of coagulation factors, despite classic training to the contrary. These traditional coagulation tests do not measure every coagulation factor, nor the process of clot formation as a whole. Specifically, PT/INR and aPTT describe the time to the start of thrombus formation, but all activity in the clotting cascade beyond that point remains unknown with these standard assays. It is of critical importance to remember that PT and aPTT do not account for fibrinolysis and may remain normal even in a hyperfibrinolytic state; additionally, PT and aPTT do not provide information regarding the interaction of platelets and other clotting factors, the final critical step in creating stable clots.

Platelet Function

TEG is also able to provide direct information about platelet function. Traditional coagulation testing only tests for platelet counts, which may be normal even in the setting of severe platelet dysfunction. This is helpful in the management of patients who are taking anti-platelet medications such as salicylates or clopidogrel, which inhibit platelet function but do not alter platelet counts. TEG platelet mapping can be utilized to determine if patients are therapeutic on or are currently taking aspirin or clopidogrel if that information is unknown.

How to Interpret TEG

Broadly speaking, reported TEG variables include coagulation time (CT), clot formation time (CFT), the angle of clot formation, the maximum clot firmness, and lysis time. Typically, these are described in the automated TEG report as reaction time (R, in seconds), clot kinetics (K, in seconds), the angle of the curve (α), maximum amplitude (MA, measured in mm), coagulation index (CI, measured in dynes/sec), lysis at 30 minutes (a percent of clot lysis), and clot firmness (G, measured in dynes/sec). Individual results may be compared to normative TEG values, allowing for an assessment of the derangements in clotting that are present. Please see Table 1 for more information.

The MA value represents clot strength, R indicates the time until there is evidence of clot, and K describes the time from R until the clot is 20 mm in size. The angle is the angle formed by the horizon and a line from the start of the TEG tracing to the point of clot reaction time; this demonstrates the speed of clot formation and is dependent on platelet number, platelet activity,
and fibrinogen concentration and activation. The CI describes the global coagulation state as derived from an equation utilizing the other variables. TEG is modified by sex, age, and other factors, as demonstrated in Figure 6. Please see Table 1 and Table 2 for interpretation and description of TEG variables.

### Table 1: Common Measurements in TEG

<table>
<thead>
<tr>
<th>Description</th>
<th>TEG term</th>
<th>ROTEM term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to clot initiation</td>
<td>R time</td>
<td>CT (coagulation time)</td>
</tr>
<tr>
<td>Rate of clot formation</td>
<td>k time</td>
<td>CFT (coagulation formation time)</td>
</tr>
<tr>
<td>Angle of clot formation</td>
<td>a (slope between R and K)</td>
<td>a (Angle of tangent at 2mm amplitude)</td>
</tr>
<tr>
<td>Maximum strength of clot</td>
<td>MA (Maximum amplitude)</td>
<td>MCF (Maximum clot formation)</td>
</tr>
<tr>
<td>Amplitude (at set time in min)</td>
<td>A30, A60</td>
<td>AS, A10, A15, A20, A30</td>
</tr>
<tr>
<td>Maximal lysis</td>
<td>-</td>
<td>ML</td>
</tr>
<tr>
<td>Clot lysis (at set time in min)</td>
<td>CL30, CL60</td>
<td>LY30, LY60</td>
</tr>
<tr>
<td>Time to lysis</td>
<td>TTL (2-mm drop from MA)</td>
<td>LOT (lysis onset time, 85% of MCF)</td>
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</table>


### Table 2: Utilizing Thromboelastography (TEG) Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Interpretation</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased reaction time (R)</td>
<td>Slow initiation of clot</td>
<td>Give fresh frozen plasma (FFP)</td>
</tr>
<tr>
<td>Decreased angle (a)</td>
<td>Slow rate of clot formation</td>
<td>Give cryoprecipitate, consider platelets</td>
</tr>
<tr>
<td>Decreased maximum amplitude (MA)</td>
<td>Decreased strength of clot</td>
<td>Give platelets</td>
</tr>
<tr>
<td>Percentage of decrease in amplitude at 30 minutes (A30 or LY30) is elevated</td>
<td>Fibrinolysis</td>
<td>Give tranexamic acid, aprotinin or aminocaproic acid</td>
</tr>
</tbody>
</table>

### Figure 6: Preanalytical Variables Affecting the Viscoelastic Hemostatic Assay (VHA) Trace

- **Anticoagulants**
- **Increased time to clot**
- **Increased rate of clot formation**
- **Neutrophils vs. < 2 yrs and adults**
- **Reduced PLT count**
- **Reduced HCT**
- **Reduced WBC**
- **Increased fibrinogen**
- **Fibrinolytic drugs**
- **HCT, hematocrit; PLT, platelet; WBC, white blood cell count.**


### TEG in the Emergency Department (ED)

There is increasing evidence that TEG is valuable in the emergency setting, particularly during resuscitations that involve massive transfusion. Massive transfusion is defined as the requirement of 10 units of packed red blood cells (pRBC) during the first 24 hours of admission and is consistently associated with increased morbidity and mortality in trauma patients. Damage control surgery is used in conjunction with damage control resuscitation, and using balanced blood products, including fresh frozen plasma and platelets in fixed ratios is considered standard of care to correct the coagulopathy of trauma by many experts. This is consistent with numerous descriptions of the benefits of damage control resuscitation, born of retrospective military data, in which lower mortality rates were noted when transfusions were given in such a way as to mimic whole blood rather than simply transfusing pRBCs. TEG is most useful in guiding damage control resuscitation and blood product administration and allowing decisions regarding the necessity for repeat or continued damage control surgery. In a 2012 study, Pezold and colleagues found that for the endpoints of death and massive transfusion, clot strength (G) was found to independently predict massive transfusion and death in the early part of resuscitation. The clot strength G had the greatest adjusted area under the receiver operating characteristic curve (AUC ROC) when compared to base deficit (BD) (0.87, P = 0.05), INR (0.88, P = 0.11), and PT (0.89; P = 0.19), meaning that it is a better predictor of morbidity and mortality than more traditional markers of severity commonly employed in the ED. In 2011, Nystrup et al. reviewed 89 subjects in the trauma registry who had a reduced clot strength defined as maximal amplitude < 50 mm on TEG. They demonstrated a higher injury severity score (ISS, p = 0.006) compared with those who had a normal MA, a higher need for transfusion of packed red blood cells (p = 0.01), fresh frozen plasma (p = 0.04), and platelets (p = 0.03) during the first 24 hours of resuscitation, and a remarkably increased 30-day mortality (47% vs. 10%, P < 0.001). These authors hypothesized that TEG could be used to target patients to receive selected blood products preferentially in the setting of trauma-induced coagulopathy.

Hyperfibrinolysis and post-traumatic coagulopathy are major risk factors for severe morbidity and mortality. In a prospective study of 161 trauma patients, decreased TEG MA values correlated with fibrinogen <100mg/dL, which also correlated with higher mortality (p = 0.013). In the 14 fatalities found in this study, both the TEG R time and MA times were significantly higher than in non-fatalities (R time was 3.703 +/- 11.618 vs. 270 +/- 393 seconds [P = < 0.001], and MA was 46.4 +/- 22.4 vs. 64.7 +/- 9.8 mm [p < 0.001]).

TEG, along with platelet count and hemoglobin count, may be the most accurate method to assess the need for blood product requirement in trauma patients. When viewed in the context of damage control resuscitation, it is appropriate to assume that the ratio of blood, plasma, and platelets likely differ from one patient to another. For instance, it may be harmful for some patients to receive a 1:1:1 ratio of plasma, pRBCs, and platelets, especially if they receive inappropriate and potentially harmful amounts of each product. By utilizing TEG appropriately, patients may receive only the products that they would likely require during damage control resuscitation.

Another benefit to having TEG in the ED is the fact that results typically can be obtained within ten minutes, compared to 30-60 minutes for PT, aPTT, fibrinogen, and platelet counts. Although initiating transfusion therapy rapidly improves patient care when necessary, TEG may also be helpful in deter-
mining when transfusion may not be useful, since it provides a rapid, global assessment of a patient’s coagulation status. For example, a clinician may be able to avoid using blood products in a normotensive trauma patient with a normal TEG. This is important, given the risks associated with the administration of all blood component therapy, including allergic reactions, infection transmission, transfusion associated acute lung injuries (TRALI), transfusion associated cardiac overload (TACO), and acute respiratory distress syndrome (ARDS). These risks are low, but it is important to remember that platelets and FFP carry the highest risk of TRALI and platelets have been reported to carry a risk of bacterial contamination, usually from the donor’s skin.22

TEG, like any laboratory test, is not without pitfalls. Values may be different when one machine is compared to another machine. When a patient has serial TEG studies, they should be run on the same machine with the same kind of activator.15 The machine requires calibration 2-3 times per day, and personnel using TEG require additional training. The advantages of TEG are presented in Table 3.

### Current Data and TEG Applications

TEG is being studied increasingly in areas other than traumatic conditions and the surgical realms. One of these areas is in acute coronary syndrome, where TEG may be used to identify patients with impaired endogenous fibrinolysis, aspirin or clopidogrel resistance, or at risk for thrombosis following percutaneous coronary intervention (PCI).

Gur et al. demonstrated that increased thrombogenesis after PCI, as measured by TEG, was an independent risk factor for thrombosis within three years following PCI in one of the largest series of patients on this topic.23 Fu et al. described similar results later in a series of 861 consecutive patients who had routine TEG platelet mapping following PCI.24 Of these, 249 patients developed in stent restenosis (ISR). The frequency of clopidogrel hyporesponsiveness in the ISR group was significantly higher than that in non-ISR group (p < 0.01), and the authors concluded that clopidogrel hyporesponsiveness, as measured by TEG, was an independent risk factor for ISR.

Despite these findings and the ability of TEG platelet mapping to identify aspirin and clopidogrel non-responders, the clinical benefit of routine platelet mapping after PCI has not yet been demonstrated. Xu et al. randomized patients following high risk PCI to a control group or to a group in which clopidogrel dosing was adjusted based on TEG results.25 There was no difference between the two groups at six months for the endpoints of myocardial infarction, emergency target vessel revascularization, stent thrombosis, or death. Another avenue where the diagnosis and treatment of coagulopathy using TEG is being pursued is in hypothermia, where initial studies have surprisingly not demonstrated hypothermia induced coagulopathy. The interim analysis of the Cooling And Surviving Septic shock (CASS) study, which prospectively enrolled 100 patients with severe sepsis or septic shock to mild induced hypothermia (32°C to 34°C) vs. control (no temperature regulation), demonstrated that coagulopathy based on TEG MA and R parameters actually improved in the mild hypothermia group, but was not corrected in the control group.26 The Targeted Temperature Management (TTM) Trial compared normothermia (36°C) to mild induced hypothermia (33°C) following cardiac arrest.27 A predefined sub study of this trial compared TEG parameters of both groups, given that there is concern related to induced hypothermia and coagulopathy. They demonstrated no significant difference in TEG parameters between the two groups or with respect to adverse bleeding or clotting.

TEG is being explored in a diverse number of disease states at this time. Current trials are describing the use of TEG to assist in cesarean deliveries, hemostasis after coronary artery bypass grafting (CABG), fat emboli, traumatic brain injury, and acute ischemic stroke.

### Cases

#### Case 1:

A 34 year old previously healthy male presents to the emergency department after falling off his roof. His blood pressure is 85/40 and his heart rate is 124 beats per minute (bpm). On initial assessment he has an obvious femur fracture. His chest x-ray demonstrates multiple rib fractures and he has a positive focused assessment with sonography for trauma (FAST). A TEG is performed and he has an LY30 of 12%. In addition to giving him blood products for his hemorrhagic shock, what other drug should you give him?

This patient should receive tranexamic acid (TXA) or aminocaproic acid. He demonstrates an elevated degree of fibrinolysis, which puts him at an increased risk of mortality following trauma.

#### Case 2:

A 65 year old male presents to the ED three days after undergoing a left heart catheterization and left circumflex stent placement following an ST-segment elevation myocardial infarction (STEMI). He has a large groin hematoma secondary to the procedure. He feels lightheaded and his initial blood pressure is 82/40. A TEG is performed and demonstrates a prolonged K time and decreased MA time. A CBC, PT, and PTT are all within normal limits. What are these values reflective of?

These values reflect platelet dysfunction, likely secondary to anti-platelet medications he is taking after having a stent placed. It is worth noting that although the more traditional laboratory tests that are used to assess coagulopathy (CBC, PT, PTT) are normal, the TEG is abnormal, offering insight into platelet function.

### Table 3: Advantages of TEG

<table>
<thead>
<tr>
<th>Advantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Can be used at point of care (POC) to provide rapid results</td>
</tr>
<tr>
<td>Evaluates global hemostatic function</td>
</tr>
<tr>
<td>Allows the physician to assess for hyperfibrinolysis and monitor treatment in patients who are given recombinant activated factor VII or tissue plasminogen activator (tPA)</td>
</tr>
<tr>
<td>Detects low factor XIII activity</td>
</tr>
<tr>
<td>Small sample volume, which is attractive for pediatrics (requires only .33 mL of blood)</td>
</tr>
</tbody>
</table>

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**THROMBOELASTOGRAPHY (TEG) – UNDERSTANDING THE PATIENT’S ABILITY TO CLOT BLOOD**
Case 3:
A 72 year old male with a history of a STEMI and stent placement three weeks ago presents to the ED with chest pain. He reports that he has been compliant in taking the clopidogrel and aspirin prescribed to him. Although data are still preliminary, how might TEG platelet mapping help in management of this patient?

TEG platelet mapping can be used to identify patients who are aspirin or clopidogrel nonresponders and hyporesponders. At this time, clinical benefit has not been established by performing routine platelet mapping once anti-platelet therapy is started to identify these patients. However, in the setting of in stent restenosis, TEG platelet mapping should be considered to help determine the cause of the event.

Further abnormal scenarios are represented in Figure 7.

Conclusion
In summary, TEG is a promising technology that offers remarkable insight into the delicate balance between thrombosis and fibrinolysis, does so in real time, and is broadly applicable in the emergency and critical care environments. While further research is needed to clarify exact roles for utilization of TEG, clinical experience to date has demonstrated that TEG has remarkable potential in the care of the critically ill and injured and should become more routine in the near future.

References
9. Nystrup KB, Windelov NA, Thomsen AB, Johansson PI. Reduced clot strength upon admission, evaluated by thrombelastography (TEG), in trauma patients is independently associated with increased 30-day mortality. Scan J Trauma Resusc Emerg Med. 2011;19:52.


ADVANCED RESUSCITATION OF SEPTIC SHOCK IN THE EMERGENCY DEPARTMENT AND INTENSIVE CARE UNIT

Christopher M. Palmer, MD
Assistant Professor of Anesthesiology and Emergency Medicine, Department of Anesthesiology, Division of Critical Care, Division of Emergency Medicine, Washington University School of Medicine, St. Louis, MO

Trenton C. Wray, MD
Critical Care Fellow, Division of Emergency Medicine, Washington University School of Medicine, St. Louis, MO

Objectives

1. Describe the need for early identification of sepsis.
2. Describe early, aggressive treatment of shock, including assessment of preload responsiveness and cardiac function, volume loading, and use of vasopressors, steroids, and inotropes.
3. Describe how to minimize the functional burden associated with ICU treatment of sepsis.

Introduction

Hospitalizations due to severe sepsis and septic shock have increased over the past two decades, and now represent up to 12% of emergency department (ED) admissions and 11-30% of admissions to the intensive care unit (ICU) worldwide. In 2001, Emmanuel Rivers published a landmark randomized controlled trial (RCT) of Early Goal-Directed Therapy (EGDT) for severe sepsis and septic shock. This introduced the concepts of early, aggressive identification of sepsis and goal-directed hemodynamic optimization in patients with sepsis and evidence of “tissue hypoperfusion.” Using the EGDT approach, the primary focus of which was to deliver hemodynamic interventions within six hours, a 16% reduction in 28-day mortality was seen. “Bundled Therapy,” which is based on goals described in the trial rapidly became the standard of care. Mortality has steadily improved from an average of 47% from 1991-1995 to 29% from 2006-2009, and now to as low as 18% in 2012.

In an unprecedented collaboration, three recent trials compared modern “usual care” to protocol-based EGDT. In the EGDT groups, goal-driven resuscitation was used. In the “usual care” groups, the treating physician directed resuscitation. The use of invasive monitoring techniques such as CVP, ScvO₂, and arterial catheters (AC), was not mandated. Some important comparisons between the four studies are highlighted in Table 1. The ProCESS, ARISE, and ProMISe Trials were unable to reproduce the difference in mortality seen with EGDT over the “standard care” group in the Rivers Trial. In the more recent trials, the primary intervention differences were that the EGDT groups received slightly more fluid, blood transfusions, and inotropic therapy than the “usual care” groups. These interventions were likely to achieve hemodynamic goals as assessed by monitoring of CVP, hematocrit, and ScvO₂ respectively.

Overall, the ProCESS, ARISE, and ProMISe Trials highlight the evolution of “standard care” and the overall mortality improvement over the past decade. The EGDT approach was extremely successful in reducing mortality by emphasizing the importance of early recognition and shock reversal in critically ill patients with sepsis, and may remain useful in select cases. However, the application of invasive “bundled therapy” to all patients with severe sepsis and septic shock in the modern era is likely unnecessary.

Modern Early Goal-Directed Therapy

Based on their presentation and trajectory, some patients will need more invasive care than others. “Modern” EGDT is based on the same principles as the predecessor Rivers Trial, but is applied to the individual needs of the patient. At the bedside, this means meeting three primary goals: 1) early identification of sepsis, 2) early, aggressive treatment of septic shock, and 3) minimizing the functional burden of illness.

1. Early Identification of Sepsis

The systemic effects of sepsis are time-dependent. Early intervention and early identification are required. Because signs of infection can be nonspecific, rapidly determining whether a bacterial infection exists can be difficult. The Systemic Inflammatory Response Syndrome (SIRS) Criteria (Table 2), which were developed primarily for research purposes, were proposed in 1992. Since then, most of the evidence regarding outcomes in patients with severe sepsis and septic shock has been based on these criteria, which remain widely used. Even at the time of their proposal, the diagnostic limitations of the SIRS Criteria were well recognized. In order to develop SIRS Criteria a patient must have an intact inflammatory and catecholamine response to physiologic stress. Numerous other conditions may cause these aspects of the EGDT bundles have come under scrutiny. Chief among these is the placement of a central venous catheter (CVC) for the purpose of monitoring central venous pressure (CVP) and central venous oxygen saturation (ScvO₂).
responses without infection, which limits the specificity of the criteria. Further, if a patient is immunosuppressed, takes a beta-blocker, is elderly or diabetic, progression to shock or even organ failure can occur without developing any of the SIRS criteria. As a result of these limitations, the Surviving Sepsis Guidelines which emphasize clinical judgment in the diagnosis of sepsis were established in 2003. The clinician should first decide whether an infection exists, then evaluate for evidence of a systemic burden of infection. This may or may not include traditional SIRS diagnostic criteria which may not be present in up to one in eight patients admitted to the ICU with severe sepsis. If a bacterial, fungal, or protozoan infection exists in a critically ill patient, rapid antimicrobial administration to decrease microbial burden is necessary to improve outcome. If such an infection does not exist, the treatment is unnecessary and may be harmful. As noted previously, determining whether or not an antimicrobial susceptible infection exists can be difficult, even in critically ill patients. A diagnostic “test” for sepsis of bacterial, fungal, or protozoan etiology of infection has been explored but has not become routine. The most widely studied is procalcitonin (PCT) which has been evaluated for the identification of sepsis of bacterial origin. The PCT assay has not

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**TABLE 01** Data From 4 Randomized Trials Comparing Early Goal-Directed Therapy (EGDT) to “Usual” or “Standard” Care

<table>
<thead>
<tr>
<th>Factor</th>
<th>Rivers 2001</th>
<th>ProCESS 2014*</th>
<th>ARISE 2014</th>
<th>PRoMISe 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>263</td>
<td>1351</td>
<td>1591</td>
<td>1251</td>
</tr>
<tr>
<td># Centers</td>
<td>1</td>
<td>31</td>
<td>51</td>
<td>56</td>
</tr>
<tr>
<td>Location</td>
<td>USA</td>
<td>USA</td>
<td>Australia, New Zealand, Europe, Hong Kong</td>
<td>England</td>
</tr>
<tr>
<td>Center Type</td>
<td>Academic</td>
<td>Academic</td>
<td>Academic, Nonacademic</td>
<td>Academic, Nonacademic</td>
</tr>
<tr>
<td>EGDT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>130</td>
<td>439</td>
<td>793</td>
<td>625</td>
</tr>
<tr>
<td>% arterial catheter (0-6 hrs)</td>
<td>100</td>
<td>NR</td>
<td>91</td>
<td>74</td>
</tr>
<tr>
<td>% CVC (0-6 hrs)</td>
<td>100</td>
<td>90</td>
<td>90</td>
<td>92</td>
</tr>
<tr>
<td>Volume IVF (0-6 hrs)</td>
<td>4981 mL</td>
<td>2805 mL</td>
<td>1964 mL</td>
<td>2226 mL</td>
</tr>
<tr>
<td>% Vasopressor (0-6 hrs)</td>
<td>27.4</td>
<td>55</td>
<td>67</td>
<td>53</td>
</tr>
<tr>
<td>% Inotrope (0-6 hrs)</td>
<td>14%</td>
<td>8</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td>% PRBCs (0-6 hrs)</td>
<td>64.1</td>
<td>14</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>28 day mortality</td>
<td>33.3%</td>
<td>NR</td>
<td>14.8%</td>
<td>24.8%</td>
</tr>
<tr>
<td>60 day mortality</td>
<td>44.3%</td>
<td>21%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>90 day mortality</td>
<td>NR</td>
<td>31.9%</td>
<td>18.6%</td>
<td>29.5%</td>
</tr>
</tbody>
</table>

| “Standard/Usual Care”   |             |               |            |              |
| n                       | 133         | 456           | 798        | 626          |
| % arterial line (0-6 hrs) | 100       | NR            | 76         | 62           |
| % CVC (0-6 hrs)         | 100         | 60%           | 61.9       | 51           |
| Volume of IVF (0-6 hrs) | 3499 mL     | 2279 mL       | 1401 mL    | 2022 mL      |
| % Vasopressor (0-6 hrs) | 30.3        | 44.1          | 57.8       | 47           |
| % Inotrope (0-6 hrs)    | 8           | 0.9           | 2.6        | 4            |
| % PRBCs (0-6 hrs)       | 18.5        | 8             | 7          | 4            |
| 28 day mortality        | 49.2%       | NR            | 15.9%      | 24.5%        |
| 60 day mortality        | 56.9%       | 18.9%         | NR         | NR           |
| 90 day mortality        | NR          | 33.7%         | 18.8%      | 29.2%        |

*The ProCESS trial also included a group of 446 patients randomized to “protocol-based standard therapy”. This group was excluded from this table for simplicity.

CVC: central venous catheter; IVF: intravenous fluids; PRBCs: packed red blood cells; NR: not reported
proven accurate when used alone. A recent meta-analysis, which reviewed studies with varying cutoff values and marked heterogeneity, noted an overall sensitivity and specificity for PCT in the 75-80% range. Although the Surviving Sepsis Campaign Guidelines list an elevated PCT as potential evidence of sepsis, the cumulative data do not support its use in isolation to guide the initiation of antimicrobial therapy. In some cases, PCT may be drawn in the ED as a baseline and followed in order to help guide the duration of antibiotics during the inpatient stay.

With no rapid, accurate diagnostic test for bacterial infection, critically ill patients with suspected infection must be treated presumptively with broad-spectrum antibiotics as soon as possible. Every attempt should be made to obtain cultures from the patient prior to antibiotic administration as appropriate de-escalation of antibiotics can improve patient outcome as well.

### Early Antibiotic Administration

The 2012 Surviving Sepsis Campaign Guidelines recommend that empiric antibiotics be administered within three hours of ED presentation (Grade 1C). In patients with sepsis, delays in administering antimicrobial therapy proportionately increases mortality. Initial antimicrobial choice in undifferentiated patients with severe sepsis or septic shock should target both gram positive and gram negative bacteria common to the respiratory and urinary tract which account for 55-84% of sites of infection. Some variation in this protocol may be necessary due to patient or environmental factors. Although anaerobic and fungal pathogens are rare (<2%), they are associated with high mortality and so appropriate therapy should be given in select patients with specific risk factors. Attention should be paid to adequate dosing, particularly for antibiotics with renal clearance such as vancomycin, beta-lactams, and aminoglycosides as sepsis may result in both a higher volume of distribution and augmented renal clearance, resulting in subtherapeutic drug levels. It is important to dose antibiotics aggressively early in the patient’s course.

Controlling the source of infection is likely as important as early antibiotic administration in improving mortality. Infected tissues and implanted devices need to be removed as soon as feasible. Although the methods of source control vary and have been infrequently studied, the Surviving Sepsis Guidelines recommend using the intervention with the “least physiologic insult possible,” understanding the added inflammatory burden that can occur with major surgery.

### 2. Early, Aggressive Treatment of Septic Shock

Following the recognition of a microbial pathogen by the innate immune system, a complex pro-and anti-inflammatory cascade occurs. This results in multiple changes at the level of the glycocalyx, including increased permeability, loss of vascular tone, microthrombosis, and local blood pooling. If limited to the formation of a local response to an invading pathogen, this event would be beneficial. When it occurs systemically, however, loss of intravascular volume and an imbalance between global oxygen delivery (DO2) and oxygen demand (VO2) occurs. As this hemodynamic process progresses, physiologic compensation (catecholamine tone) maintains perfusion to the brain and heart, though this may lead to impairment of other organ systems. Over time, if left untreated, compensatory mechanisms become taxed and decompensation may occur, leading to a fall in mean arterial pressure (MAP) and ultimately death due to cardiovascular collapse. If early hemodynamic support is provided, macrocirculatory parameters may improve, but there may still be microcirculatory dysfunction, which can lead to multi-organ failure and death. In general, the faster this is reversed, the better. Patients may present anywhere along this continuum and thus require individualized therapies.

### Identifying Septic Shock

Septic shock is recognized as the most severe aspect of the sepsis syndrome. It is important to recognize, however, that patients with severe sepsis (maintaining physiologic compensation) may have a mortality approaching that of those in overt septic shock. Patients should be triaged and assessed for signs of severe sepsis as quickly as possible. Lactate, which correlates strongly with disease severity and outcome, should be checked as early as possible in the triage process, and then, if abnormal, rechecked during resuscitation to assess for clearance.

### Reversing Septic Shock

Any patient with a low MAP, elevated lactate, or clinical evidence of tissue hypoperfusion should be aggressively managed. A potential algorithm for resuscitation is shown in Figure 1. The overall goal is to restore adequate tissue perfusion and oxygenation as quickly as possible without causing volume overload; however, the methods for accomplishing this are the subject of considerable study and debate. The two primary resuscitation goals are MAP > 65 mmHg and adequate tissue perfusion.

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>SIRS*</td>
<td>(must have ≥ 2)</td>
</tr>
<tr>
<td></td>
<td>• Body Temperature ≥ 38°C or ≤ 36°C</td>
</tr>
<tr>
<td></td>
<td>• Heart Rate ≥ 90 beats per minute</td>
</tr>
<tr>
<td></td>
<td>• Respiratory Rate ≥ 20 breaths per minute or PaCO2 &lt; 32 mmHg</td>
</tr>
<tr>
<td></td>
<td>• White Blood Cell Count &gt; 12x10^9/mm^3 or &lt; 4x10^9/mm^3 or ≥ 10% bands</td>
</tr>
<tr>
<td>Sepsis</td>
<td>SIRS + suspected or documented infection</td>
</tr>
<tr>
<td>Severe Sepsis</td>
<td>Sepsis + tissue hypoperfusion, organ dysfunction or hypotension</td>
</tr>
<tr>
<td>Septic Shock</td>
<td>Sepsis + hypotension despite fluid resuscitation + tissue hypoperfusion</td>
</tr>
</tbody>
</table>

*About 88% of patients with severe sepsis or septic shock will meet these criteria within 24 hours of ICU admission. The diagnosis of sepsis is based on clinical judgment and should not be limited to these criteria.
**Goal 1 - MAP > 65 mmHg**: Although a normal MAP does not guarantee adequate organ perfusion, MAP does reflect drive pressure at the tissue level. The majority of evidence suggests a higher mortality with a MAP target of ≤ 65 mmHg, and no definitive improvement in organ function with higher goals. A recent randomized trial comparing a lower MAP goal (65-70 mmHg) to a higher MAP goal (80-90 mmHg) did not demonstrate an overall benefit in mortality or any other measured parameter. However, in the subset of patients with pre-existing hypertension, there was an 11% decrease in the need for renal replacement therapy (RRT) in the group with the higher MAP goal. Therefore, it is reasonable to target a MAP ≥ 65 in most patients, but this should be individualized, and a higher MAP may be necessary in patients with pre-existing hypertension to decrease the risk of renal failure.

**Goal 2 - Adequate Perfusion**: Recognizing the risk of “occult shock,” the patient should be monitored frequently for evidence of hypoperfusion and increasing disease severity, regardless of the MAP. Physical exam findings, such as delayed capillary refill, skin temperature, decreased urine output, and altered mental status are accurate predictors of tissue hypoperfusion and correlate with disease severity if present. However, their absence alone should not be used to rule out inadequate perfusion.

Lactate should be checked early in the patient’s course and, if elevated, monitored intermittently for clearance. It is unclear whether elevation of lactate in sepsis is the result of tissue hypoperfusion, “cytopathic stress” from oxidative injury, adrenergic tone, or lack of clearance. Regardless, its elevation closely correlates with disease severity in a variety of conditions, including sepsis. A cutoff value of 4 mmol/L appears...
to be appropriate in predicting in-hospital mortality in patients with sepsis, although indeterminate levels (2.3-4 mmol/L) have also been associated with poor outcomes. Additionally, patients with septic shock, even without hyperlactatemia, may have a high mortality as well. Thus, lactate should not be used alone to predict disease severity.

Lactate normalization is strongly associated with survival. However, lactate clearance as a target of resuscitation is less clear, as its normalization could simply be a marker of improving disease severity. One RCT that targeted a lactate clearance of ≥ 20% per two hours demonstrated improved outcomes using this approach vs. controls. Other than this, evidence of lactate clearance as a target for hemodynamic management is lacking. The Surviving Sepsis Campaign recommends checking a lactate within three hours of presentation. If it is elevated, the patient should be resuscitated, and it should be checked again within six hours of presentation. If lactate has not decreased, the reason should be investigated. Usually, this will involve ensuring adequate tissue perfusion and oxygenation (as noted below), assessing for excessive oxygen demand such as fever, shivering, and increased work of breathing, and ensuring adequate source control.

If a central venous catheter (CVC) is present, \( \text{ScvO}_2 \) may be followed. The \( \text{ScvO}_2 \) is often considered a reflection of the oxygen extraction ratio at the tissue level, which in normal patients is about 22-32%. Since the average arterial oxygen saturation (\( \text{SpO}_2 \)) is about 95-100% in normal individuals, the “normal” \( \text{ScvO}_2 \) is usually greater than 70%. If oxygen extraction increases, \( \text{ScvO}_2 \) theoretically decreases indicating tissue hypoperfusion. Indeed, a low \( \text{ScvO}_2 \) is correlated with an increased mortality. However, oxygen extraction at the tissue level can be impaired due to microcirculatory shunting or mitochondrial dysfunction, so an abnormally high \( \text{ScvO}_2 \) (> 89%) may also correlate with increased mortality, which limits its effectiveness as a target for therapy. Regardless, low values do correlate with impaired perfusion, so targeting \( \text{ScvO}_2 \) ≥ 70% is reasonable, particularly when inotropic therapy is needed. Still, the clinician should not be falsely reassured by a normal or high value in the setting of sepsis.

**Volume Loading**

If MAP is low or signs of hypoperfusion exit, fluids are considered first line therapy. But an average of 1.7-3.7 liters over the first six hours has been associated with improved mortality. The goal of fluid therapy is to establish enough preload for adequate cardiac output, particularly early in the patient’s course.

The type of fluid that should be used during resuscitation for septic shock is subject to debate. Excessive use of normal saline, which contains supraphysiologic chloride levels, is independently associated with mortality. So-called “balanced solutions,” which are created to more closely resemble physiologic pH and electrolyte levels, have been associated with lower mortality when compared to saline in patients with sepsis. The quality of this evidence is still debated, and a large RCT comparing the two is underway (ACTRN12613001370796). Until these results are available, it is difficult to recommend one type of crystalloid over another.

Starch solutions (e.g., hydroxyethyl starch, dextrans, gelatins) increase the need for RRT and increase mortality, and should not be routinely used. Although albumin has not demonstrated harm in patients with sepsis, it also has not demonstrated a consistent, definitive benefit over crystalloid resuscitation. Further, depending on location, albumin may be up to 25 times more expensive. Therefore, crystalloid resuscitation is recommended as initial therapy, but albumin may be used in most patients with at least equal efficacy.

Volume may also be given in the form of blood products. Although transfusion of packed red blood cells may be beneficial in some patients with impaired oxygen delivery, a recent RCT comparing a hemoglobin goal of 9 mg/dL vs. 7 mg/dL in patients with septic shock showed no mortality benefit. In the vast majority of patients, a hemoglobin level of 7 mg/dL is an appropriate target.

**Assessing Preload-Responsiveness**

If MAP and tissue perfusion are not restored following initial volume loading, the clinician should avoid giving further empiric fluid until an assessment of “volume responsiveness” (an increase in cardiac output in response to the administration of fluid volume) has occurred. This can be difficult, as the clinical exam alone can be unreliable and wide practice variation exists.

Central venous pressure (CVP), which is a “static measurement,” is used as a surrogate for filling pressure of the right atrium and ventricle. When used in isolation, it does not correlate well with volume responsiveness. However, when used as part of EGDT, CVP does not increase mortality, and it is still an optional measurement recommended by the Surviving Sepsis Campaign Guidelines. Because of this, it is still widely used by clinicians, and may be helpful if more accurate (dynamic) measures are not available.

The lack of efficacy of CVP monitoring is not surprising, as it is a static measurement in a dynamic system. Dynamic tests, where a change in preload occurs and the response is measured, should be used when possible. The gold standard for this is a fluid challenge, during which 250-500 mL of crystalloid volume is given and the patient is observed for a response. An increase in stroke volume of 15% in response to this challenge predicts fluid responsiveness. Since administering any unnecessary volume is undesirable, changes in preload can also be observed using the respiratory cycle or position changes in order to predict volume responsiveness. The following are methods of assessing volume responsiveness:

**Ultrasound:** Ultrasound is noninvasive, readily available, and accurate in a variety of patients. Variations in the diameter of the inferior vena cava (IVC) during the respiratory cycle can be used to estimate pre-
load. If the patient is spontaneously breathing, IVC collapse of ≥15% during inspiration is correlated with volume responsiveness. In mechanically ventilated patients, the IVC distends during inspiration, and distension of ≥12% has a cutoff sensitivity and specificity of 93% and 92%, respectively. The measurement does not have to be quantitative, as qualitative assessment by clinicians at the bedside has been shown to correlate relatively well. Quantitative or qualitative assessment of left ventricle (LV) filling may also be performed at this stage. Quantitatively, a low LV end-diastolic area in addition to decreased flow velocity across the LV outflow tract with a grossly normal right ventricle may indicate hypovolemia. However, a brief, qualitative assessment of LV filling in combination with a qualitative assessment of IVC collapsibility is most often used. An “underfilled” LV often has a small chamber size during diastole with close approximation of the ventricular walls during systole, sometimes even making contact (“kissing ventricles”). In the presence of a normal (not distended) right ventricle, this may also indicate hypovolemia. Further, hyperdynamic features may be noted, such as contact of the mitral valve with the LV septum during diastole. It should be emphasized that a single assessment of LV filling is a static measurement. Although echocardiography does not provide continuous hemodynamic monitoring, serial assessments of both IVC collapsibility/distensibility, LV filling, and changes in stroke volume in response to fluid challenges may be considered dynamic measurements. Serial assessments should be performed as resuscitation continues.

Vasopressors

If MAP does not increase with initial fluid loading, vasopressors should be considered simultaneously with the above assessments for preload responsiveness. Placement of a CVC and AC should be considered at this point, but lack of a CVC should not delay the administration of vasopressors. A delay in vasopressor administration has been associated with increased mortality, and the short-term administration of vasopressors (including norepinephrine) through a reliable peripheral IV is likely safe. The properties and use of vasopressors and inotropes in septic shock are reviewed in Table 3.

Steroids

Low-dose corticosteroids (≤300 mg/day of hydrocortisone or equivalent) in septic shock have long been controversial. The physiology and debate regarding their use is well beyond the scope of this review. What is known is that the two primary trials evaluating the use of steroids, while demonstrating a consistent benefit in septic shock reversal, have been inconsistent in regards to any benefit in mortality. The trials were heavily criticized for a variety of reasons (including patient acuity, the use of the adrenocorticotropic hormone [ACTH]-stimulation test, and the use of etomidate), and a new trial evaluating for a mortality benefit in patients with septic shock is ongoing (NCT01448109). For now, noting the benefit in shock reversal, it is reasonable to administer corticosteroids to patients with refractory hypotension. If given, a dose of 200-300 mg/day (usually 50 mg every six hours, but may be given continuously) should be used and continued for seven days, or 24 hours after discontinuation of vasopressor therapy.

Assessment of Cardiac Function

If signs of hypoperfusion are present, regardless of MAP, and the patient has been deemed “volume unresponsive,” an assessment of cardiac function should be obtained. Pulmonary artery catheters have been the traditional gold standard for hemodynamic monitoring, but they are no longer routinely used for patients with sepsis. Noninvasive means of assessing cardiac function are now favored.

Bedside Echocardiography: As noted above, bedside echocardiography does not generally provide continuous hemodynamic data, but is arguably the most beneficial tool for assessment of cardiac function. It is noninvasive, easily learned, and is now widely used by ED physicians and intensivists. It can be used to assess for anatomical abnormalities of the heart, preload responsiveness, left and right-ventricular function, cardiac output, and response to interventions. Although quantitative measures can be used to calculate hemodynamic parameters, qualitative measures of biventricular function and IVC collapsibility/distensibility are also accurate, allowing for rapid assessment at the bedside. Transesophageal echocardiography (TEE) is most commonly used; however, transesophageal echocardiography (TEE) is becoming more widely available as well, and has been used for hemodynamic guidance in patients with sepsis. For these reasons, echocardiography is often recommended as the preferred method for initial hemodynamic assessment.

Pulse Pressure Variation: Pulse pressure variation (PPV) is used as a surrogate for Stroke Volume Variation (SVV). An arterial catheter is needed, and the change in pulse pressure with the respiratory cycle is measured. In mechanically ventilated patients with a tidal volume of at least 8 mL/kg, PPV of ≥12% with the respiratory cycle has a sensitivity and specificity of 89% and 84%, respectively, when predicting volume responsiveness. Its use may be limited in spontaneously breathing patients, however, as well as in patients with arrhythmias or severe valvular disease.

Passive Leg Raise: A passive leg raise (PLR) test is likely the most accurate method to predict volume responsiveness. It simulates a volume challenge by using a change in position, which mobilizes fluid from the splanchic and lower extremity circulation. The method for performing a PLR is as follows: The patient begins in a semi-recumbent position; the patient is then laid flat with the legs raised, and a measurement of cardiac output is required, and an increase in cardiac output of 15% by direct measurement indicates volume responsiveness. Because PLR simulates an actual volume challenge, it maintains accuracy across cardiac rhythms and variations in ventilation. However, conditions that anatomically compromise venous return (e.g., intraabdominal hypertension) and changes in adrenergic tone (e.g., pain, anxiety) limit its accuracy.
Esophageal Doppler: Esophageal Doppler monitoring measures flow velocity in the descending aorta through the esophagus, enabling calculation of the stroke volume and cardiac output. Its more prominent use has been in guiding fluid therapy during surgery. However, it has been used as part of a more general strategy of limiting fluid administration in the ICU. It is relatively noninvasive, although the patient must be intubated for use. The primary drawback is that, because it is a doppler probe placed blindly, small position changes can change the vector and impact measurements. Its effect on patient-oriented outcomes during early resuscitation in the general ED and ICU population is unknown.

Bioreactance: Bioreactance, which is employed by the Noninvasive Cardiac Output Monitor (NICOM), measures “phase shifts” in voltage across the thorax in response to pulsatile blood flow through the aorta. This is translated to flow, then to stroke volume, and can be used to calculate cardiac output and associated parameters. It is entirely noninvasive, as only large pads are attached to the patient. It has demonstrated variable correlation with more invasive techniques of cardiac monitoring, but has not demonstrated a consistent, patient-oriented benefit.

Inotropic Therapy

If inadequate perfusion is still present and assessment reveals poor ventricular function, inotropic therapy is warranted. There is currently no definitive data to support one particular agent over another (Table 3). Once inotropic therapy begins, it can be titrated to cardiac index (if measured) or a combination of lactate normalization, ScvO₂, and clinical exam parameters of improved perfusion.

<table>
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<tr>
<th>Vasopressor / Inotrope</th>
<th>Property</th>
<th>Effect/Use</th>
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| *Norepinephrine (NE)  | α⁺, β⁻, β⁺ | - Arterial VC, vasoconstriction  
- Increases preload and systemic vascular resistance  
- Increases renal blood flow and urine output in patients with sepsis  
- Minimal splanchnic and pulmonary vasoconstriction at doses <0.5 mcg/kg/min  
- Inotropic + chronotropic effects at higher doses  
- Vasopressor of choice |
| **Vasopressin (VP)     | AVPR1a (peripheral)  
AVPR1b (central)  
AVPR2 (renal) | - Neurohypophyseal hormone  
- Vasostichonstraction, water retention, HPA-axis (among others)  
- Levels increase early in sepsis, then fall for ≥7 days (stores deplete)  
- Used as adjunct to NE – no overall mortality improvement  
- May improve mortality if used + steroids or if NE <0.15 mcg/kg/min  
- Current trial assessing use as primary vasopressor (ICNISRCTN20769191)  
- For now, may use as adjunct to NE if 2nd vasopressor needed |
| Epinephrine (E)        | α⁺, β⁻, β⁺ | - Vasopressor, inotropic, chronotropic effects  
- No advantage over NE if used as primary vasopressor  
- May be safely added to NE and may improve MAP, but no overall advantage over NE + DBA in normotensive or hypotensive patients  
- May be less well-tolerated than NE due to lactic acidosis, splanchnic VC, and tachyarrhythmias  
- Can be “1st line alternative” to NE |
| Phenylephrine (P)      | α⁺ | - Less effective than NE at raising MAP  
- May decrease cardiac output, increase pulmonary vasoconstriction  
- No direct comparison with NE for mortality  
- Should be 2nd line agent for most patients with sepsis |
| #Dopamine (DA)         | α⁺, β⁻, β⁺ | - Arterial VC, inotropic, chronotropic effect  
- Increased mortality compared with NE  
- Use only if NE unavailable or in patients with severe bradycardia |
| Dobutamine (DBA)       | β⁺, β⁻ | - Inotropic, chronotropic, vasodilation  
- Use with NE if hypotensive – may be more well-tolerated than E  
- Use for patients with poor LV function with evidence of poor perfusion |

*Norepinephrine should be the first choice in most circumstances.  
**Vasopressin can be added as an adjunct if needed, though an ongoing trial is evaluating its use as a first-line vasopressor in sepsis.  
#Dopamine should not be used unless norepinephrine is not available, or in patients at very low risk of arrhythmias  
AVPR: Arginine-Vasopressin Receptor; VC: vasoconstriction; HPA: hypothalamic-pituitary-adrenal; MAP: mean arterial pressure; LV: left ventricular
3. Minimizing the Functional Burden of Illness

Up to 25% of patients discharged from the hospital after a diagnosis of severe sepsis will be readmitted within 30 days and nearly half will be readmitted within six months, resulting in an estimated $9 billion in annual costs. Further, cognitive dysfunction and a profound decrease in exercise capacity persist for months to even years after hospitalization.

ICU-acquired weakness can lead to long-term disability after hospitalization. It has been associated with various factors during the ED and ICU stay, including poor glycemic control, bed rest, the use of corticosteroids, and duration of mechanical ventilation. Depth of sedation, benzodiazepine use, and sleep deprivation have been associated with long-term cognitive dysfunction. Further, the inflammatory changes associated with sepsis may independently contribute to some of these processes. Surviving sepsis, it turns out, can result in substantial morbidity.

Determinants of functional and neurocognitive impairment following hospitalizations are still being elucidated. Still, aggressive efforts are being made to minimize the effect of the illness and hospitalization on the patient’s functional status, and these efforts should start in the ED. In general, this means minimizing time receiving mechanical ventilation by using lung protective ventilation and avoiding deep sedation when possible, minimizing duration of immobility, and aggressively treating sepsis to prevent multi-organ failure. Early mobilization protocols that specifically target patients with sepsis are currently being studied and implemented. Although mortality continues to decrease, it is likely that many significant advances in sepsis care will focus on minimizing not just mortality, but also the functional burden of the disease after hospitalization.

Conclusion

Although the care of critically ill patients with sepsis has evolved since the initial publication of EDGT, the principles of EGDT are still relevant. How the “goals” are met, however, should be determined according to individual patient needs. At the bedside, the ED physician should aim to meet the three “primary objectives” outlined in this review in order to minimize morbidity and mortality.

References


TREATMENT OF CRITICAL RESPIRATORY ILLNESS IN THE EMERGENCY DEPARTMENT AND INTENSIVE CARE UNIT – Brian M. Fuller, MD, and Nicholas M. Mohr, MD

1. A 37-year old woman presents to the emergency department in respiratory distress and is intubated secondary to asthma. The ventilator’s graphics display is shown below. What does this flow-time waveform represent?

A. Auto-PEEP
B. A normal flow-time waveform
C. Trigger dysynchrony
D. Flow dysynchrony

2. A 60-year old man presents to the emergency department with an exacerbation of chronic obstructive pulmonary disease (COPD). His peak airway pressure is 42 cm H2O and his plateau pressure is 14 cm H2O.

A. True
B. False

3. In patients with acute respiratory distress syndrome (ARDS), which one of the following is likely to most improve survival?

A. Inhaled nitric oxide
B. Lung-protective ventilation aimed at limiting tidal volume and plateau pressure
C. High frequency oscillatory ventilation (HFOV)
D. Immediate referral for extracorporeal membrane oxygenation (ECMO)

4. In patients without acute respiratory distress syndrome (ARDS), but at risk for it, there is no benefit in providing lung-protective ventilation.

A. True
B. False

5. Which of the following statements are true?

A. In volume-targeted ventilation, the clinician prescribes the tidal volume and rate (guaranteeing minute ventilation), and airway pressures vary with compliance and resistance
B. Patients should be placed on VC/AC as outcomes are superior with this mode of ventilation
C. In pressure-targeted ventilation, inspiratory:expiratory ratio is determined by tidal volume and flow rate
D. Tidal volume does not vary in PC/AC

6. Which of the following has emerged as the most reliable predictor of adverse outcome in patients with acute pulmonary embolism?

A. Clot burden
B. Tachycardia
C. Hypoxia
D. Hypotension

7. All of the following are clinical scoring systems that can be applied to the risk stratification of patients with pulmonary embolism EXCEPT:

A. PESI
B. TIMI risk score
C. sPESI
D. HESTIA

8. Which of the following is NOT considered in the American College of Cardiology/American Heart Association definition of SUBMASSIVE pulmonary embolism?

A. RV/LV diameter ratio > 0.9
B. Elevated cardiac troponin
C. Renal failure
D. Elevated natriuretic peptide

9. Which of the following is NOT appropriate therapy for patients with low risk acute pulmonary embolism who lack contraindications to anticoagulation?

A. Aspirin
B. Unfractionated heparin
C. Rivaroxaban
D. Enoxaparin

10. All of the following are acceptable pulmonary reperfusion strategies for patients with massive pulmonary embolism EXCEPT?

A. Alteplase 100 mg over 2 hours peripherally
B. Surgical thrombectomy
C. Alteplase 100 mg over 24 hours peripherally
D. Pharmaco-mechanical therapy

DEEP VENOUS THROMBOSIS AND PULMONARY EMBOLISM: OPTIMAL THERAPY AND PREVENTION FOR THE CRITICALLY-ILL PATIENT – Gregory J. Fermann, MD

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POST-CARDIAC ARREST IN THE EMERGENCY DEPARTMENT: BEYOND HYPOTHERMIA – Jon C. Rittenberger, MD

11. All of the following are reasons to obtain computed tomography (CT) imaging of the brain following resuscitation from cardiac arrest EXCEPT:

A. The incidence of intracranial hemorrhage is approximately 5%
B. Identification of the presence of early cerebral edema can decrease enthusiasm for invasive procedures such as coronary angiography
C. The patient is awake, alert, and has a non-focal neurologic examination
D. All patients, regardless of neurologic examination, should receive a CT of the brain
12. Which of the following statements regarding temperature management in the post-arrest patient is TRUE?
A. No temperature management is needed
B. All patients should have temperature management to 32-34°C
C. Only patients who follow commands should have temperature management to 32-34°C
D. Fever should be prevented in all comatose patients

13. Which of the following statements regarding neurologic status in the post-arrest patient is TRUE?
A. Seizure development during the post-arrest period portends a universally poor neurologic outcome
B. A persistently flat, unreactive electroencephalogram (EEG) portends a good neurologic outcome
C. Malignant EEG patterns are common in the comatose post-arrest patient
D. There is no need for EEG monitoring in the post-arrest patient

14. Which neurologic examination components are needed to determine initial illness severity as determined by the Pittsburgh Cardiac Arrest Category (PCAC)?
A. Motor response, oculocephalic reflex, respiratory rate, gag reflex
B. Verbal response, pupillary reflex, corneal reflex, cough reflex
C. Motor response, pupillary reflex, corneal reflex, cough reflex
D. Motor response, verbal response, corneal reflex, cough reflex

15. Specific resuscitation goals for the comatose post-arrest patient include all of the following EXCEPT:
A. Maintaining a mean arterial blood pressure (MAP) of > 80mmHg
B. Hyperventilation to prevent cerebral edema
C. Temperature management and avoidance of fever
D. Avoidance of severe hyperoxia

16. Modifiable risk factors for atrial fibrillation in the critically ill patient include all of the following EXCEPT:
A. Hypokalemia
B. Hypotension
C. Seizures
D. Fluid overload

17. A physiologic response to atrial fibrillation in the critically ill patient typically includes:
A. Increase in end-diastolic volume and stroke volume
B. Increased myocardial oxygen demand
C. Increased cardiac output
D. Bradycardia

18. Which of the following statements regarding cardioversion for atrial fibrillation in the critically ill patient is TRUE?
A. Pharmacologic methods result in better outcomes than electrical cardioversion
B. Electrical cardioversion should be first line therapy in the symptomatic, unstable patient
C. In the stable patient with atrial fibrillation for greater than 48 hours, electrical cardioversion is safe
D. If cardioversion is successful, no subsequent anticoagulation is necessary

19. Which of the following is NOT a component of the CHA2DS-VASc stroke risk stratification score?
A. Hypertension
B. Age < 50
C. Diabetes
D. Vascular disease

20. All of the following are good first-line pharmacologic agents for treating atrial fibrillation in the critically ill patient EXCEPT:
A. Diltiazem
B. Esmolol
C. Amiodarone
D. Digoxin

21. Which of the following is NOT an advantage of non-vitamin K antagonist oral anticoagulants (NOACs) as compared with vitamin K antagonists (VKA) such as warfarin?
A. Longer half-life
B. More predictable pharmacokinetics
C. Lower risk of intracranial bleeding
D. Fewer drug-drug and drug-diet interactions of clinical concern

22. The risk of which of the following major bleeding complications is higher for dabigatran, rivaroxaban, and edoxaban than for VKA?
A. Intracranial
B. Intraocular
C. Retroperitoneal
D. Gastrointestinal

23. Which of the following factors does NOT increase the risk of major bleeding associated with any ongoing oral anticoagulation?
A. Advancing age
B. Chronic kidney disease
C. Increasing body weight
D. Concomitant dual antiplatelet therapy

24. Which of the following drugs is being investigated as a specific reversal agent for the anti-Xa NOACs?
A. Idarucizumab
B. Andexanet alfa
C. 4-Factor prothrombin complex concentrate
D. Recombinant activated Factor VIIa

25. Which of the following is NOT true of idarucizumab as studied in RE-VERSE AD?
A. It effected prompt reversal of dabigatran’s anticoagulation effects
B. It was studied in hemorrhaging patients taking dabigatran
C. It was studied in pre-procedural patients taking dabigatran
D. It was not studied in patients with intracranial bleed or with other high-mortality complications at presentation
26. Thromboelastography (TEG) provides the clinician with insight into all of the following components and settings of hemostasis, except:
   A. Sluggish venous flow
   B. Platelet activity
   C. High shear stress
   D. Fibrinolysis

27. A decreased maximum amplitude (MA) on TEG (or maximum clot firmness on ROTEM) may be the result of all of the following except:
   A. Qualitative platelet defect
   B. Tissue factor dysfunction
   C. Fibrinogen deficiency
   D. Factor XIII deficiency

28. In trauma patients, abnormal values recorded on the TEG are associated with increased mortality, even if other measures of coagulation are normal (e.g., prothrombin time [PT], partial thromboplastin time [PTT], international normalized ratio [INR], platelet count):
   A. True
   B. False

29. Randomized control trials have definitively proven that TEG-guided blood product administration in trauma patients reduces mortality.
   A. True
   B. False

30. TEG has been shown to objectively identify abnormal coagulation in patients undergoing mild therapeutic hypothermia.
   A. True
   B. False

31. Which vasopressor is associated with increased arrhythmias in patients with septic shock?
   A. Norepinephrine
   B. Phenylephrine
   C. Dopamine
   D. Vasopressin

32. Compared with normal saline, balanced intravenous fluids such as Lactated Ringer’s are associated with which of the following?
   A. Increased mortality
   B. Decreased incidence of acute kidney injury
   C. Increased incidence of hyperkalemia
   D. Increased need for renal replacement therapy

33. In patients with septic shock, targeting a mean arterial pressure (MAP) > 70 results in a decrease in mortality.
   A. True
   B. False

34. Based on the results of the ProCESS, ARISE and Promise Trials, the Surviving Sepsis Guidelines regarding central venous pressure (CVP) and central venous oxygen saturation (ScvO2) measurement were modified in which of the following ways?
   A. CVP and ScvO2 monitoring are now optional to assist in resuscitation
   B. CVP and ScvO2 monitoring remain mandatory as part of bundled therapy
   C. CVP and ScvO2 monitoring have been removed from the guidelines due to futility
   D. None of the above

35. In patients with severe sepsis and septic shock, early broad-spectrum antibiotics and adequate source control have been shown to lead to which of the following outcomes?
   A. No change in outcomes, including mortality
   B. Decreased mortality
   C. Increased resistance with more complications
   D. None of the above
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