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## Updates in Critical Care Medicine: Evidence-based Practice in 2020

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GUEST EDITORS

### INTRODUCTION

Welcome to this issue of the *Rhode Island Medical Journal* titled "Updates in Critical Care Medicine," which offers concise and comprehensive reviews on new and important issues that occur regularly in the critical care setting. Our distinguished Rhode Island colleagues, who are dedicated to improving the care and outcomes of critically ill medical patients, present the following topics:

#### Sepsis

Sepsis management has dramatically evolved over the last two decades. The multi-national Surviving Sepsis Campaign has driven much of the research and recommendations for sepsis care. We are fortunate that one of the campaign leaders is **MITCHELL LEVY, MD**, Chief of Brown's Division of Critical Care, Pulmonary and Sleep Medicine. He and **DR. JISOO LEE** provide an excellent review of the most recent clinical trials related to the management of sepsis and present current recommendations for patient management.

#### Acute Renal Failure

Renal failure is extraordinarily common in the critically ill and has been shown to predict mortality. The correct timing for starting renal replacement in the ICU remains an unanswered question. Recent studies have attempted to better describe appropriate timing of dialysis in patients who develop renal failure. **DR. KATHERINE COX**, et al review some of the most important literature in the field. Of note, Rhode Island and Miriam Hospitals are sites for the current STARRT-AKI trial which aims to better address this issue.

#### Transfusion of red blood cells

Less may be more in the case of the transfusion of red blood cells to critically ill patients. Many patients are anemic or become anemic in the ICU setting, yet multiple studies suggest that transfusion of red blood cells may be overutilized and does not achieve desired goals. **DR. CHANNING HUI**, et al review data regarding red blood cell transfusions and present recommendations for appropriate transfusion triggers in the ICU.

#### End-of-life care in the ICU

Despite clinical advances, ICU mortality remains significant. Communicating with patients and families about a patient's critical condition and facilitating decisions about end-of-life (EOL) are a fundamental aspect of critical care medicine. Over the last two decades there has been a significant increase in knowledge about how to best care for both patients and their families in this situation. **DR. SARAH**

**RHOADS**, et al review current best practices for communicating with and supporting family members and patients, as well as reducing distress during EOL. The authors also discuss the role of the evolving specialty of palliative care in the ICU.

#### Point-of-care ultrasound (POCUS) for patients with acute respiratory failure

Very few things have changed critical care medicine in the recent past than the advent of bedside ultrasound to answer clinical questions in real time. Initially point-of-care ultrasound (POCUS) focused on assistance with vascular access, but currently includes diagnosis of pulmonary conditions. Diagnosing the cause of patients with severe respiratory failure can be a challenging dilemma and POCUS may significantly increase diagnostic accuracy. It is now widely taught in academic critical care medicine programs such as Brown's. **DR. MOHAMMAD ARABIAT**, et al review key findings of lung ultrasound and the evidence for its use in diagnosing patients with dyspnea and acute respiratory failure.

#### Extracorporeal life support (ECLS)

Extracorporeal life support (ECLS) has been rapidly adopted for use in adult patients with severe acute respiratory failure and can help sustain patients refractory to conventional mechanical ventilator support. The Rhode Island and Hasbro Children's Hospital ECLS program is the only one in Southern New England and has been awarded a Gold Center of Excellence by the Extracorporeal Life Support Organization. **DR. COREY VENTETUOLO** is the Medical Director, ECLS program, and **DR. NEEL SODHA** is the Surgical Director, ECMO and Mechanical Circulatory Support, at Rhode Island Hospital. They and **DR. ADEEL ABBASI**, et al provide an excellent state-of-the-art review about ECLS for respiratory failure.

#### Managing high-risk pulmonary embolism

The management of high-risk pulmonary embolism remains a rapidly evolving field in critical care medicine. Medical, interventional and surgical options can all be considered and makes decision-making quite complex. Multi-disciplinary Pulmonary Emergency Response Teams (PERTs) have been recently described as a way to assist in this complex decision-making. **DR. CHRISTOPHER MULLIN** is director of Rhode Island Hospital's PERT team. He and **DR. CHRISTOPHER THEROUX**, et al review the recent literature and treatment options for patients with pulmonary embolism at high risk of clinical decompensation or death.

In conclusion, we very much hope you enjoy this compilation and advance your knowledge about key current topics in critical care medicine both here in Rhode Island and globally.

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# Treatment of Patients with Severe Sepsis and Septic Shock: Current Evidence-Based Practices

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## ABSTRACT

Sepsis remains a field of active research with many unknown and unanswered questions. Over the past few decades, advancements in sepsis management have led to improved mortality and morbidity. This article will review the current evidence-based practices of the treatment of sepsis and septic shock. It will also critically appraise some of the current controversies in sepsis management, such as fluids, steroids, early vasopressors, early goal-directed therapy and immunotherapy.

**KEYWORDS:** sepsis, septic shock, management, controversies

## INTRODUCTION

Sepsis is a common disease entity that is associated with high morbidity and mortality. Globally, it is estimated that over 30 million people are hospitalized for sepsis every year, and sepsis may contribute to up to 5.3 million deaths every year.<sup>1</sup> The terms systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic shock were initially described through a consensus statement in the early 1990s by the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM).<sup>2</sup> Most recently, the terms SIRS and severe sepsis were eliminated, and sepsis is now defined as “life-threatening organ dysfunction due to a dysregulated host response to infection.”<sup>3</sup>

In this review article, the concept of sepsis bundles for management of sepsis and septic shock based on evidence-based practice will be reviewed. Additionally, some of the major controversies in sepsis management will be reviewed, focusing on the roles of steroids, fluids, vasopressors, early goal-directed therapy and immunotherapy.

## MANAGEMENT OF SEPSIS – THE SURVIVING SEPSIS CAMPAIGN (SSC) AND SEPSIS BUNDLE

Unfortunately, there are no specific molecular therapies that have proven to be effective in sepsis treatment. The Surviving Sepsis Campaign (SSC) was initiated in 2002 to provide guidelines for sepsis and septic shock management for clinicians with the goal to reduce mortality. The “sepsis

**Table 1. Hour-3 and Hour-6 Bundles.**

To be completed within 3 hours and 6 hours of time of presentation, respectively. The “time of presentation” is defined as the time of triage in the Emergency Department or, if presenting from another care venue, from the earliest chart annotation consistent with all elements severe sepsis or septic shock ascertained through chart review.

Hour-3 Bundle	Hour-6 Bundle
1. Measure lactate level.	Hour-3 Bundle elements (as seen on the left). Plus,
2. Obtain blood cultures prior to administration of antibiotics.	5. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) $\geq 65$ mmHg
3. Administer broad-spectrum antibiotics.	6. In the event of persistent hypotension after initial fluid administration (MAP $< 65$ mm Hg) or if initial lactate was $\geq 4$ mmol/L, re-assess volume status and tissue perfusion.
4. Administer 30ml/kg crystalloid for hypotension or lactate $\geq 4$ mmol/L.	7. Re-measure lactate if initial lactate elevated.

bundles”, which have gone through multiple iterations in the SSC Guidelines, describe a selected set of interventions that are recommended to be conducted. The hour-3 bundle and hour-6 bundle highlight interventions to be completed within 3 hours and 6 hours of time of presentation, respectively (Table 1). Studies have shown that increased compliance with the sepsis bundle is associated with improved survival.<sup>4</sup>

According to the SSC 2016 guideline recommendations, initial resuscitation should begin immediately, as sepsis and septic shock are medical emergencies.<sup>4</sup> Some of the highlights of the SSC 2016 guidelines include fluid resuscitation of at least 30 mL/kg of intravenous crystalloid fluid to be given in the first three hours, then guiding additional fluid administration by reassessing hemodynamic status. Further hemodynamic assessment such as assessing cardiac function is recommended to determine the type of shock, and dynamic over static variables should be used to predict fluid responsiveness. Targeting mean arterial pressure (MAP) of 65 mm Hg should be an initial target for patients with septic shock requiring vasopressors, and the resuscitation should be continued until lactate is normalized. The SSC guidelines

recommend (best practice statement) hospitals have a performance improvement program to screen for patients for sepsis. Routine microbiologic cultures including at least two sets of blood cultures should be obtained prior to starting broad-spectrum intravenous antimicrobial therapy without causing substantial delay in the therapy.

The 2018 update to the SCC guidelines describes the “hour-1 bundle” (Table 2).<sup>5</sup> This bundle consists of five bundle elements as follows: Measure lactate level; obtain blood cultures prior to administration of antibiotics; administer broad-spectrum antibiotics; rapidly administer 30 mL/kg crystalloid for hypotension or lactate  $\geq 4$  mmol/L; and apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain MAP  $\geq 65$  mm Hg. This hour-1 bundle intends to underscore the urgency to treat patients with sepsis and septic shock, combining the three-hour and six-hour bundles into a single hour to shorten the time to beginning resuscitation and management and improve outcome. Further research is warranted to assess the efficacy of hour-1 bundle implementation.

**Table 2. Hour-1 Bundle.**

To be completed within 1 hour of time of presentation. The “time of presentation” is defined as the time of triage in the Emergency Department or, if presenting from another care venue, from the earliest chart annotation consistent with all elements of sepsis (formerly severe sepsis) or septic shock ascertained through chart review.

Hour-1 Bundle
• Measure lactate level. Remeasure if initial lactate is $>2$ mmol/L.
• Obtain blood cultures prior to administration of antibiotics.
• Administer broad-spectrum antibiotics.
• Rapidly administer 30ml/kg crystalloid for hypotension or lactate $\geq 4$ mmol/L.
• Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain MAP $\geq 65$ mm Hg.

**HOT CONTROVERSIES IN SEPSIS**

There have been many hotly debated controversies in sepsis and septic shock management over the past few decades. While some have robust amount of trials with conflicting results over time, others are in need of more research. We will discuss some of the topics, including the use of steroids, fluid choice, vasopressor choice and timing, early goal-directed therapy, and immunotherapy for personalized medicine.

**Steroids**

Since the first randomized controlled trial published in JAMA in 1963, there have been over 40 randomized controlled trials to determine the use of corticosteroids in severe sepsis and septic shock. The 2016 SSC guidelines suggest against using intravenous corticosteroids to treat septic shock if

adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability. However, it is suggested to use 200 mg of hydrocortisone per day if hemodynamic stability is not achievable.<sup>4</sup> The most two recent trials after these guidelines showed conflicting data regarding corticosteroid use and mortality benefit in septic shock. The ADRENAL trial by Venkatesh *et al.* compared 200 mg of hydrocortisone per day versus placebo for 7 days in patients with septic shock undergoing mechanical ventilation, which showed no difference in 90-day mortality.<sup>6</sup> The APROCCHSS trial by Annane *et al.* evaluated the effect of hydrocortisone-plus-fludrocortisone therapy, drotrecogin alfa, the combination of the three drugs, or their respective placebos.<sup>7</sup> This study showed that the hydrocortisone-plus-fludrocortisone therapy reduced the 90-day mortality compared to the placebo (43.0% versus 49.1%,  $p=0.03$ ). The drotrecogin alfa group was not completed due to the withdrawal of the drug from the market in 2011. Regardless of the difference in the primary outcomes of mortality, both trials demonstrated that corticosteroid treatment group has a shorter time to resolution of shock compared to placebo. Although there is no systematic review and meta-analysis involving these two recent trials, the BMJ Rapid Recommendations, which is a BMJ collaboration that aims to accelerate evidence into practice, incorporated these two trials and made a weak recommendation for corticosteroids with sepsis, concluding that both steroids and no steroids are reasonable management options for refractory septic shock.<sup>8</sup>

**Fluids**

Early fluid resuscitation is one of the key recommendations for sepsis and septic shock management, and there have been many controversies regarding the types of fluid. In the SSC guidelines, crystalloids have been recommended as the first line of fluids for resuscitation, and these are most widely available. More recently, a great deal of attention has been focused on balanced fluids. The most commonly used isotonic crystalloid, 0.9% normal saline, has high chloride concentration (154 mmol per liter) compared to human plasma (94 to 111 mmol per liter), and is thought to worsen kidney function due to the excess chloride. Unlike normal saline, balanced fluids such as lactated Ringer’s solution and Plasma-Lyte A have electrolyte compositions that are closer to that of plasma, with chloride concentration of 109 mmol per liter and 98 mmol per liter, respectively. The SPLIT trial published in 2015 compared a buffered crystalloid solution (Plasma-Lyte 148) with saline on their effect on acute kidney injury (AKI) among patients admitted to the intensive care unit.<sup>9</sup> The study did not show any significant difference in the risk of AKI, the use of renal replacement therapy, or hospital mortality. However, there was a signal towards improved outcome with the buffered crystalloid solution, which prompted the need for further studies. The SMART trial published in 2018 compared balanced crystalloids

(lactated Ringer's solution or Plasma-Lyte A) with saline and looked at a composite of death from any cause, new renal-replacement therapy, or persistent renal dysfunction within 30 days.<sup>10</sup> This study showed that the use of balanced crystalloids resulted in a lower rate of the composite outcome, favoring its use over saline. Most recently, a single center, multi-crossover trial compared balanced crystalloids with saline among adults in the emergency department who were hospitalized outside an ICU.<sup>11</sup> This study did not show any difference in the number of hospital-free days in the two groups; however, the balanced crystalloids group had less major adverse kidney events within 30 days compared to the saline group.

Other types of fluids have been studied as well. Colloids such as albumin have also been evaluated for its effect on fluid resuscitation. The SAFE trial looked at 4% albumin or normal saline for fluid resuscitation in a heterogeneous population of ICU patients.<sup>12</sup> The CRISTAL trial compared colloids (gelatins, dextrans, hydroxyethyl starches, 4% or 20% albumin) to crystalloids (isotonic or hypertonic saline or Ringer lactate solution) in critically ill patients with hypovolemic shock.<sup>13</sup> Both the SAFE and CRISTAL trials showed no significant difference in the primary outcome of 28-day mortality.

### Vasopressors

Vasopressors are one of the essential medications used in shock; however, the choice of vasopressor and the optimal timing of vasopressor initiation remain controversial. Norepinephrine is the most commonly used first-line vasoactive medication in shock, as it has shown to have lower mortality and lower risk of arrhythmias when compared with dopamine.<sup>14</sup> Vasopressin and epinephrine are reasonable second-line agents in order to lower the amount of norepinephrine, and the use of phenylephrine does not have enough data to support its use in septic shock currently.<sup>4</sup> The optimal timing of vasopressor initiation is unknown. Early vasopressor therapy might lead to faster achievement of the target MAP and thereby facilitate tissue perfusion. It may also prevent deleterious effects from fluid overload. However, a fine balance will need to be established as it may also be harmful to initiate vasopressor therapy when the intravascular fluid resuscitation has not been adequately achieved. This concept is currently being tested in an ongoing trial.<sup>15</sup> The 2018 update to the SSC bundle recommends vasopressor therapy within the first hour to achieve mean arterial pressure (MAP) of 65 mm Hg or greater if blood pressure is not restored after initial fluid resuscitation of 30 mL/kg.<sup>5</sup>

### Early goal-directed therapy (EGDT)

EGDT involves optimizing tissue perfusion by giving crystalloid fluid boluses to achieve central venous pressure (CVP) 8-12 mm Hg, initiating vasopressors to maintain MAP of at least 65 mm Hg, and maintaining central venous

oxygen saturation (ScvO<sub>2</sub>) at greater than 70% with red blood cell transfusion and/or dobutamine administration. In 2001, Rivers *et al.* showed that a significant improvement in mortality by 15% when patients with severe sepsis or septic shock were treated using six-hour EGDT compared to standard therapy.<sup>16</sup> This study has since promoted best practice guidelines for early management of sepsis and septic shock. However, limitations of this study, including that it was a single-center trial lacking external validity, and the complexity and resourceful demand of the protocol, prompted further research. A little over a decade later, three multi-center clinical trials were published – ProCESS from the United States, ARISE from Australasia, and ProMISe from England. These trials compared protocol-based EGDT to standard therapy and all failed to show a difference in 90-day mortality.<sup>17,18,19</sup> It is important to acknowledge that the mortality rates were lower in the newer trials compared to the Rivers *et al.*'s study, and there has been overall improvement in the management of initial sepsis management in the past 15 years. However, it must be concluded that mandated central lines targeting CVP and ScvO<sub>2</sub> are no longer supported by the current literature.

### Targeted Immunotherapy

Although decades of effort and multiple, large international RCTs have been conducted on promising immunomodulatory therapeutics, all of these trials have been negative and there is no current immunotherapy that is in clinical use for sepsis and septic shock. Various agents including anti-cytokines (e.g. anti TNF- $\alpha$ ), anti-virulence factors (e.g. monoclonal antibody against lipopolysaccharide and gram negative endotoxins), anticoagulation agents (e.g. activated protein C, antithrombin III, heparin) and immune stimulators (e.g. G-CSF) have been studied without yielding significant results.<sup>20</sup> The heterogeneity of the patients with sepsis and septic shock, clinical trial design, variable pathways that lead to sepsis, as well as the complexity of sepsis pathophysiology, among other factors, may account for the failure of these trials. Overcoming these challenges will be crucial to advance to precision medicine and enable successful, targeted immunomodulatory therapy.

### CONCLUSION

Management of sepsis and septic shock involves early interventions to achieve hemodynamic stability. Due to the heterogeneity and complexity of sepsis pathophysiology, there is no perfect therapy for sepsis that "fits for all." However, implementation of best-practice guidelines based on evidence-based medicine has shown to improve mortality associated with sepsis and septic shock. Many elements of the guidelines remain controversial and more research is needed to address these important unanswered questions.

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# Acute Renal Failure in Critically Ill Patients: Current Evidence-Based Practices

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## ABSTRACT

Acute kidney injury (AKI) is a common condition amongst critically ill patients in the medical intensive care unit (ICU) and is associated with increased morbidity and mortality. There are several areas of ongoing debate regarding management of AKI, specifically the initiation and timing of renal replacement therapy (RRT). In this review, we aim to concisely discuss epidemiology, current evidence with regards to optimal vascular access, timing of initiation and modality of renal replacement therapy in acute kidney injury in critically ill patients.

**KEYWORDS:** acute kidney injury (AKI), critically ill, renal replacement therapy (RRT)

## EPIDEMIOLOGY

AKI is defined as a sudden decrease in renal function and is conventionally diagnosed utilizing the Kidney Disease: Improving Global Outcomes (KDIGO) criteria. KDIGO defines AKI as an increase in serum creatinine by  $\geq 0.3$  mg/dL within 48 hours, or an increase in serum creatinine  $\geq 1.5$  times baseline, known to have occurred within the prior seven days or urine volume  $< 0.5$  mL/kg/hour for at least six hours (Table 1).<sup>1</sup> Accepted alternate criteria exist and include those proposed by the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) group and criteria posed by the Acute Kidney Injury Network (AKIN) (Tables 1, 2).

AKI affects up to half of medical intensive care unit patients and is associated with increased length of ICU stay, increased hospital stay, development of chronic kidney disease and increased short-term and long-term mortality.<sup>2</sup> In fact, more than 13% of critically ill patients will receive RRT within the first week of their ICU stay.<sup>2</sup> Mortality rates in critically ill patients with AKI is quoted to be around 50% and is associated with a six-fold increased risk of dying in the hospital.<sup>2,3</sup> A multinational cross-sectional study on the epidemiology of AKI in ICU patients meeting KDIGO criteria revealed an incidence of 57% with little variation in AKI occurrence and mortality between different parts of the world.<sup>2</sup> Sepsis is among the most common causes of admission to the ICU and is frequently associated with AKI. The pathophysiology of AKI and sepsis is poorly understood,

**Table 1.** KDIGO and AKIN criteria for diagnosis of AKI

KDIGO	AKIN
Increase in serum creatinine by $\geq 0.3$ mg/dL within 48 hours or	Increase in serum creatinine of $\geq 0.3$ mg/dL
Increase in serum creatinine to $\geq 1.5$ times baseline, known to have occurred within the prior seven days	Increase in serum creatinine of $\geq 50\%$ within 48 hours
Urine volume $< 0.5$ mL/kg/hr for six hours	Urine output of $< 0.5$ mL/kg/hr for $> 6$ hours

**Table 2.** KDIGO, AKIN and RIFLE staging for AKI.<sup>1,19</sup>

RIFLE	KDIGO	AKIN
<b>Risk:</b> Increase in serum creatinine x 1.5 or decrease in GFR $> 25\%$ or UOP $< 0.5$ mL/kg/hr for 6-12 hours	<b>Stage 1:</b> Increase in serum creatinine of $\geq 0.3$ mg/dL or 1.5-1.9 x baseline or UOP of $< 0.5$ mL/kg/hr for 6-12 hours	<b>Stage 1:</b> Increase in serum creatinine of $\geq 0.3$ mg/dL or increase in serum creatinine x 1.5-2.0 or UOP $< 0.5$ mL/kg/hr for 6-12 hours
<b>Injury:</b> Increase in serum creatinine x2 or decrease in GFR $> 50\%$ or UOP $< 0.5$ mL/kg/hr for 12-24 hours	<b>Stage 2:</b> Increase in serum creatinine of 2.0-2.9 x baseline or UOP $< 0.5$ mL/kg/hr for 12-24 hours	<b>Stage 2:</b> Increase in serum creatinine $> 200-300\%$ or UOP $< 0.5$ mL/kg/hr for 12-24 hours
<b>Failure:</b> Increase in serum creatinine x 3 or GFR $> 75\%$ or increase in serum creatinine by $> 0.5$ mg/dL if baseline creatinine is $> 4.0$ mg/dL or UOP of $< 0.3$ mL/kg/hr for $> 24$ hr or anuria for $> 12$ hours or initiation of RRT	<b>Stage 3:</b> Increase in serum creatinine of 3.0 x baseline or increase in serum creatinine to $\geq 4.0$ mg/dL or UOP of $< 0.3$ mL/kg/hr for over 24 hours or anuria for over 12 hours or initiation of RRT	<b>Stage 3:</b> Increase in serum creatinine $> 300\%$ or increase in serum creatinine by $> 0.5$ mg/dL if baseline is $\geq 4.0$ mg/dL or UOP of $< 0.3$ mL/kg/hr for $> 24$ hours or anuria for $> 12$ hours or initiation of RRT
<b>Loss:</b> Need for RRT for $> 4$ weeks		
<b>End Stage:</b> Need for RRT $> 3$ months		

UOP: urine output.

**Table 3.** Summary of the sentinel trials regarding timing of initiation of RRT in critically ill patients with AKI.

Clinical Study	Patients	Study design	N	Study Endpoints	Statistical Significance
<b>ELAIN</b>	Critically ill patients with AKI (KDIGO Stage 2 and higher), mostly surgical	Single center RCT. Early RRT (within 8 hours of KDIGO 2) versus delayed RRT (within 12 hours of KDIGO stage 3 or no initiation)	231	Mortality at 90 days after randomization	Early RRT compared with delayed reduced 90-day mortality
<b>AKIKI</b>	Critically ill medical patients with AKI (KDIGO stage 3)	Multicenter RCT. Early RRT started immediately after randomization, delayed started if patients developed urgent indications or oliguria >72h	620	Overall survival at day 60	Mortality did not differ significantly between early and delayed strategies
<b>IDEAL-ICU</b>	Critically ill patients with early-stage septic shock and AKI (RIFLE)	Multicenter RCT. Early RRT within 12 hours after documentation of failure-stage AKI or delayed at 48 hours if renal recovery had not occurred	488	Death at 90 days	No significant difference in overall mortality at 90 days

though animal models suggest that initially, septic AKI may be caused by a combination of microvascular shunting and tubular cell stress.<sup>4</sup> With resolution of sepsis, the majority of patients with AKI in the context of sepsis have renal recovery though remain at increased risk for developing chronic kidney disease.<sup>4</sup>

The decision regarding whether to start RRT, optimal timing for initiation, modality used, and frequency of RRT in acutely ill patients is an area of ongoing investigation and remains controversial. Many patients will have spontaneous renal recovery and premature initiation of RRT may expose patients to risks such as complications of anticoagulation, hypotension, allergic reactions to system components, and complications of vascular access without conferring meaningful benefit.<sup>5</sup>

**TIMING**

It is universally accepted that urgent indications for RRT in patients with AKI include severe refractory metabolic acidosis, signs of uremia such as pericarditis or severe encephalopathy, severe refractory hyperkalemia, refractory volume overload, and certain intoxications. In the absence of these clinical scenarios, the optimal timing for initiating RRT among ICU patients remains unclear as there are poor prognostic tools to determine which patients will go on to renal recovery. Some postulate that early removal of uremic toxins and avoidance of hypervolemia may be beneficial in patients who are critically ill, while others contest the risks of vascular access, hemodynamic effects and anticoagulation outweigh the benefits of early initiation. Three large randomized clinical trials comprise the majority of evidence in this arena (Table 3).

The ELAIN trial, published in 2016, was a randomized single center parallel group trial, which randomized 231 ICU patients with AKI to early RRT within eight hours of confirmation of KDIGO stage 2 AKI or delayed RRT which was defined as initiation of RRT within twelve hours of either KDIGO stage 3 criteria (Table 2) or absolute indications. All

patients who received RRT received continuous venovenous hemofiltration (CVVH). The primary outcome of 90-day all-cause mortality was 39.3% in the early group when compared with 54.7% in the delayed group. They also found increased renal recovery at 90 days, a small decrease in median duration of RRT, decreased mechanical ventilation and decreased length of hospital stay in the early group. While striking, this study was limited in that it was single center, almost all patients were surgical patients, and groups were un-blinded.<sup>6</sup>

Within the same year, the AKIKI trial was published. In a large multicenter, open-label randomized trial, 620 ICU patients either mechanically ventilated, or on catecholamine infusions or both, were randomized to receive either early or delayed RRT. When compared with the ELAIN trial, patients were randomized once they developed KDIGO stage 3 AKI (Table 2). The early group was randomized and treated within 6 hours of confirming KDIGO stage 3 AKI and the delayed group was treated once acute indications were met based upon laboratory abnormalities or if oliguria or anuria lasted over 72 hours after randomization. There was no significant difference in all-cause mortality at 60 days. Of note, there was a higher incidence of catheter-related blood stream infections in the early RRT group. When compared with the ELAIN trial, these patients were mostly medical ICU patients and over 50% of patients received intermittent hemodialysis and only 30% of patients received CVVH. Also of note, half of the delayed-group patients never received RRT. Post-hoc analysis found the lowest mortality rate among patients who never underwent RRT as compared with those who underwent RRT.<sup>7</sup>

More recently, the IDEAL-ICU trial was published, supporting the results of AKIKI. This was a multicenter randomized trial in which 488 ICU patients with septic shock and AKI were randomized to early initiation of RRT (within 12 hours of onset of RIFLE end-stage kidney disease) (Table 2) or delayed initiation (after 48 hours if renal function did not spontaneously recover and if no condition meeting criteria for emergent RRT developed). The primary outcome was

90-day mortality and there was no statistically significant difference between the two groups. There was no significant difference in ICU days between the two groups though fewer patients in the delayed group received RRT and had more RRT free days. The trial was stopped early for futility. Again, post-hoc analysis showed the lowest mortality in patients who never received RRT.<sup>8</sup>

These three major trials all have important differences including number of patients and centers, differences in triggers for early or delayed RRT, and RRT modality. To add to the growing body of literature on the subject, there is an ongoing large phase three trial called STARRT-AKI, in which Rhode Island Hospital is a participating site. STARRT-AKI is including critically ill ICU patients randomized to standard RRT initiation versus accelerated RRT initiation and is due to be published at the end of 2019. A recent meta-analysis of ten randomized controlled trials suggested no additional benefit of early initiation of RRT for critically patients with AKI on 30- 60- or 90-day mortality, though studies included in the meta-analysis had a significant amount of heterogeneity with variable definitions of early versus late RRT.<sup>9</sup> Overall, optimal timing remains unclear but seems to favor delayed RRT with close observation to avoid urgent or emergent indications.

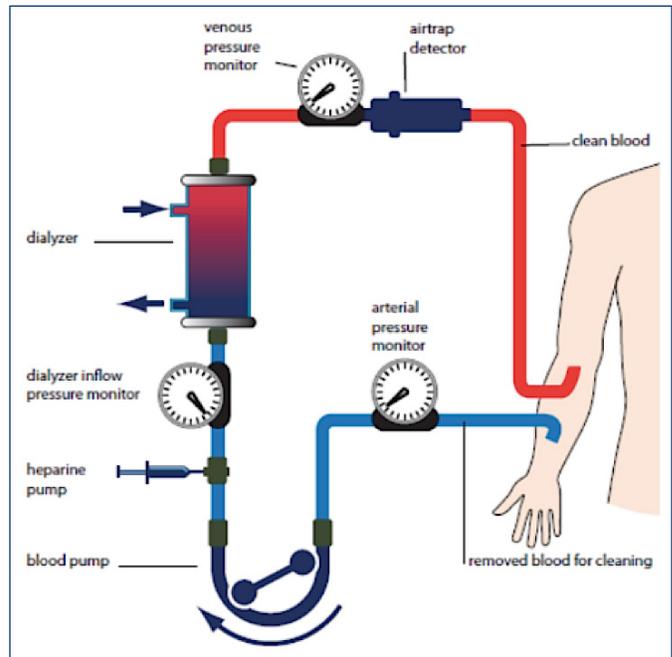
**ACCESS**

Initial vascular access for patients newly on RRT is usually temporary as the average duration of RRT dependence for patients with AKI is less than two weeks.<sup>5</sup> Historically, femoral access was thought to be associated with an increased risk of catheter-associated line infection; however, more recently a systematic review comparing the rate of catheter-associated line infections in patients with femoral, internal jugular and subclavian lines suggested that there is no significant difference between the three.<sup>10</sup> One exception to this may be among obese patients with a BMI >28.4 where femoral lines have been associated with increased risk of infection.<sup>11</sup> Placement of multiple catheters, longer duration, subclavian access and left internal jugular access are all associated with increased risk of development of central vein stenosis which can compromise the future of arterio-venous fistula and graft placement in the ipsilateral extremity if needed.<sup>12</sup> Tunneled cuffed catheters should be placed in patients who will require long-term RRT (until an arterio-venous fistula or graft can be used) due to the decreased rate of catheter-associated infection.

**MODALITY**

There are several different types of RRT available for use including intermittent hemodialysis (IHD), continuous renal replacement therapy (CRRT), peritoneal dialysis (PD), and hybrid therapies including sustained low-efficiency

Figure 1. Schematic of a hemodialysis circuit.



From Bode, A.S. & Tordoir, Jan. (2013). Vascular Access For Hemodialysis Therapy. Studies in Computational Intelligence. 404. 235-303. 10.1007/978-3-642-27458-9-5)20.

hemodialysis (SLED) (a combined modality where dialysis is administered for hours longer than traditional IHD with slower blood flows but still delivered on a daily basis as opposed to continuously) (Figure 1).

In a prospective randomized multicenter study including critically ill patients with acute renal failure, 60-day mortality was not different between patients who received IHD when compared with CRRT.<sup>13</sup> Additionally, CRRT is associated with higher costs when compared with IHD.<sup>14</sup> A recent systematic review and meta-analysis of 21 studies comparing mortality, dialysis dependence and length of stay among critically ill patients receiving CRRT, IHD or SLED for AKI did not reveal an advantage for any specific RRT modality.<sup>14</sup> KDIGO practice guidelines for AKI recommend using intermittent and continuous RRT modalities as complementary therapies as studies have shown similar survival and recovery of renal function with use of both modalities.<sup>1</sup>

There may be certain circumstances for which a particular modality of RRT may be most beneficial. IHD may be preferential when used for clearance of certain toxicities as poison clearance with CRRT is 50-80% less than that achieved with intermittent modalities.<sup>15</sup> CRRT, on the other hand, is recommended in patients with acute brain injury in whom changes in plasma solute concentration may worsen intracranial hypertension and in concert with systemic hypotension can lead to cerebral hypoperfusion.<sup>16</sup> Additionally, in patients with acute hepatic failure with associated hyperammonemia and high grade encephalopathy, one multi-center cohort study suggested an associated with decreased

ammonia levels and improved 21-day transplant free survival in patients who underwent CRRT as compared with no RRT and IHD.<sup>17</sup> In our center, we have found that when fluid removal is the main purpose of RRT, CRRT allows for increased ultrafiltration as compared with IHD. While used more frequently in the pediatric patient population, there is a paucity of well-designed adult studies comparing the use of PD compared with other RRT modalities in AKI. One prospective, randomized, controlled trial comparing high volume PD with IHD in patients with AKI due to acute tubular necrosis found that mortality rate and renal function recovery were similar in both groups.<sup>18</sup>

## CONCLUSIONS

Acute kidney injury in acutely ill adults is associated with high morbidity and mortality and RRT remains an important part of management. Optimal criteria for and timing of initiation remain controversial though the current body of evidence favor delayed initiation with close observation to avoid urgent or emergent indications and minimize the risks of catheter related infection and intradialytic hypotension. Practice guidelines recommend using intermittent and continuous RRT modalities as complementary therapies as studies have shown similar survival and recovery of renal function in the general ICU population.

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# Red Blood Cell Transfusions in the ICU

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## ABSTRACT

Red blood cells are commonly administered to critically ill patients, yet the desired benefit of improving oxygen delivery and overall outcome may not be achieved in many scenarios. In addition, blood products are of limited supply and there are clear risks associated with blood transfusion. Despite this, studies show that almost half of all ICU patients receiving blood transfusions do so in the setting of stable anemia, suggesting that many critically ill patients in the ICU may receive unnecessary transfusions. Critical illnesses can lead to increased rates of anemia, even without active blood loss. The benefits of transfusion in these situations are unclear. Clear indications for blood transfusions, including uncontrolled hemorrhage, symptomatic anemia, and possibly acute coronary syndrome, are met in the minority of patients receiving red blood cell transfusions. This review discusses current evidence regarding the use of red blood cell transfusions in the ICU. Two major categories are examined, transfusion in patients noted to be anemic, but not clearly actively bleeding or symptomatic, and patients with aggressive bleeding who are critically ill or require massive transfusions.

## INTRODUCTION

Anemia is a common phenomenon in the ICU, with approximately 30% of patients having a hemoglobin concentration less than 10 g/dL.<sup>1</sup> In critically ill patients, the controversy to transfuse stems from a conflict of physiological principles and the results of randomized trials. As the oxygen carrier in blood, increased hemoglobin levels theoretically increase oxygen delivery and support the patient in shock.<sup>1</sup> However, the benefit of transfusing liberally to a higher hemoglobin concentration in non-bleeding, anemic patients is unproven, and in certain cases may be harmful. Randomized trials have demonstrated that transfusing to a lower target may have lower complication rates and decreased mortality in particular groups of patients. It remains unclear if red cell transfusions themselves are the reason for worse clinical outcomes or the result of being critically ill with anemia.

## CONSEQUENCES OF ANEMIA AND EFFECTS OF TRANSFUSION

Anemia has been clearly associated with poor outcomes in many instances, including with elderly patients, acute myocardial infarction, chronic kidney disease and acute respiratory failure. The causes of anemia in the critically ill are multifactorial and include acute blood loss (including recurrent phlebotomy), poor red cell production (from nutritional deficiencies, renal insufficiency, medications or decreased bone marrow response), hemolysis or sepsis.<sup>2</sup> Transfusions of packed red blood cells are meant to increase oxygen delivery and reduce tissue hypoxia; however, multiple studies have failed to show improvement in oxygen delivery after transfusion. This may be due to various factors associated with stored blood, including low levels of 2,3-diphosphoglycerate (which shifts the oxygen dissociation curve to the left and decreases the ability of the transfused hemoglobin to unload oxygen in the tissues), structural problems with the stored RBCs which may lead to increased aggregation or hemolysis and the inflammatory response to the transfusion.<sup>3</sup> Attempts to mitigate some of these causes of poor oxygen delivery by using “fresh” blood (mean age 6–12 days) versus older red cells (mean age 22 days) have not shown any improvements in outcome.<sup>4,5</sup>

The risks for complications of transfusion are varied and increase with larger volume transfusion. These can vary from very minor (fever) to severe (anaphylaxis). Due to extensive screening and testing, the risk of transferring a blood-borne infection (like HIV, hepatitis B or C) remains extremely low. Transfusion-related Lung Injury (TRALI) is an inflammatory-mediated non-cardiogenic pulmonary edema leading to hypoxia and potentially respiratory failure. It is the second leading cause (after anaphylaxis) of acute mortality due to blood transfusion.

Coagulation abnormalities are also commonly seen from RBC transfusions due to direct dilutional effects (due to a lack of coagulation factors in RBC transfusions). Furthermore, massive transfusions can cause potentially dangerous metabolic and electrolyte abnormalities. Packed RBC units contain citrate anticoagulant that induces hypocalcemia from citrate binding to ionized calcium. Citrate itself metabolizes into bicarbonate and causes metabolic alkalosis, which can lead to hypokalemia. On the other hand,

hyperkalemia may also be noted as a result of the storage and lysis of blood products, with higher potassium levels observed when using blood stored for >12 days.<sup>6</sup>

### RBC TRANSFUSIONS IN STABLE CRITICALLY ILL PATIENTS

Multiple studies have demonstrated increased mortality with RBC transfusion, yet rates of transfusion remain high. The CRIT Study described transfusion practices in the intensive care unit by examining 4892 critically ill patients.<sup>1</sup> The mean pre-transfusion hemoglobin was 8.6 g/dL and the most common reason for transfusion was “low hemoglobin” (90% of all cases). Other clinically relevant indications, such as active bleeding and hemodynamic instability, were seen in much fewer cases of transfusion (24 and 21%, respectively). In a more recent single-center study of 10,642 ICU patients in Canada, the rate of RBC transfusions during an ICU stay was noted to be 38.3%.<sup>7</sup> These data describe a high, possibly excessive rate of blood cell transfusion in the ICU and suggest that defining appropriate transfusion thresholds is an important goal.

Prospective studies establishing appropriate thresholds for transfusing red blood cells in critically ill anemic patients have trended towards a more restrictive approach. The Transfusion Requirements in Critical Care (TRICC) trial randomized non-bleeding, anemic ICU patients without active heart disease to either a “liberal” (<9 mg/dL) or “restrictive” (<7 mg/dL) transfusion trigger. The restrictive strategy showed a trend towards mortality benefit in all patients, and demonstrated a statistically significant mortality benefit in pre-determined subgroups of younger patients (<55 years old) and in less critically ill patients (APACHE II score <20).<sup>8</sup> After the publication of the TRICC trial, a hemoglobin of 7g/dL became the widely accepted and recommended threshold for transfusion in non-bleeding critically ill patients, but questions regarding applicability relating to other subgroups persisted.<sup>9</sup>

In the Transfusion Requirements in Septic Shock (TRISS) study, patients with a diagnosis of septic shock were similarly assigned to two different transfusion thresholds. The comparison of transfusion thresholds of less than 7g/dL (lower threshold) and less than 9g/dL (higher threshold) did not show significant differences in 90-day mortality. In the subgroup analysis, patients with chronic cardiovascular disease also did not have a significant difference in relative risk of death by day 90.<sup>10</sup> Another study examined patients with recent, treated acute upper-gastrointestinal bleeding, which demonstrated a higher probability of survival at six weeks if transfusions were administered at a lower threshold of 7g/dL when compared to 9 g/dL.<sup>11</sup> The primary outcome results from both trials are similar to the TRICC trial, which further support the use of a restrictive approach with blood transfusions. In both studies, patients with acute coronary syndrome (ACS) were excluded.

Anemia may worsen myocardial ischemia, induce arrhythmias, and increase infarct size during acute myocardial infarction. In patients with ACS or heart failure, anemia increases morbidity and mortality.<sup>12</sup> In patients undergoing cardiac surgery, the Transfusion Requirements in Cardiac Surgery (TRICS III) trial demonstrated that a restrictive approach utilizing a hemoglobin threshold of 7.5 g/dL was noninferior to a liberal approach 9.5 g/dL. The primary outcome was a composite outcome of mortality, myocardial infarction, stroke, and new-onset renal failure requiring dialysis.<sup>13</sup> Therefore, the 7.5 g/dL threshold is probably acceptable for post-cardiac surgery patients.

To our knowledge, there are no randomized trials that examine transfusion thresholds in patients with active cardiac ischemia or acute coronary syndrome. These patients have generally been excluded from randomized studies that compared transfusion thresholds. So while overall the trend with blood transfusions favors a lower threshold goal, there is no clear evidence that lower thresholds can be applied to patients with acute coronary syndrome.

### RBC TRANSFUSION IN UNSTABLE CRITICALLY ILL PATIENTS/MASSIVE TRANSFUSION

The data discussed thus far pertains only to non-bleeding ICU patients with anemia. In the unstable, acutely hemorrhaging patient, large volumes of blood products may be necessary and restrictive transfusion triggers do not apply. The most commonly seen causes of severe acute bleeding stem from trauma, surgery, obstetrical bleeding and GI bleeding.<sup>14</sup> Classic definitions of massive blood transfusion encompassed 10 units of PRBCs or a patient’s whole blood volume within 24 hours. Additional proposed definitions include three units of PRBCs within one hour<sup>15</sup> and four units of total blood products within the first 30 minutes.<sup>16</sup> The need to deliver blood products quickly and appropriately in the acute setting has led to the development of massive transfusion protocols.

There are several proposed methods to massive blood transfusion using different ratios of blood products. When large volumes of RBCs are delivered, dilutional coagulopathy can develop, therefore concurrent transfusion of plasma and platelets are recommended. The best available evidence for the optimal ratios of these various blood products has been described in trauma patients. The use of fresh frozen plasma (FFP), platelets, and PRBCs in a 1:1:1 ratio was compared to a group with 1:1:2 ratio in the Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial. There was no significant difference in mortality at 24 hours or 30 days between the two groups. However, there was better hemostasis achieved in the 1:1:1 group with fewer deaths by exsanguination within 24 hours.<sup>17</sup> This ratio of blood products is most commonly advocated for use as part of massive transfusion protocols and is utilized at Rhode Island Hospital’s Level I Trauma Center.

There is far less evidence to target specific massive blood transfusion ratios in the non-trauma setting, for example, in medical bleeding patients. To our knowledge, there are no randomized studies examining massive transfusions in medical patients. However, a retrospective analysis of massive transfusion in non-trauma patients examined 30-day and 48-hour mortality. Patients were stratified to higher (>1:2) or lower (<1:2) ratios of FFP to RBC, and of platelets to RBC. The investigators found no associated difference in 30-day mortality with either groups of FFP to RBC or platelets to RBC ratios. In terms of shorter term, 48-hour mortality, there was an association of decreased mortality in the higher ratio of platelet to RBC group.<sup>18</sup> Overall, further research is necessary to better define transfusion ratios in non-trauma bleeding patients and no specific recommendations regarding massive transfusions or ratios of blood products can be made in non-trauma actively bleeding patients.

As previously discussed, administering large amounts of blood products can cause significant derangements. In trauma care, the classic lethal triad includes hypothermia, acidosis, and coagulopathy. Although the sensitivity and specificity of each of these factors to prognosis are variable, the failure to correct physiological derangements can be detrimental.<sup>19</sup> In severe trauma, restricting surgical interventions to the minimum necessary initially has led to the term “damage control surgery” (DCS). Similarly, the term “damage control resuscitation” (DCR) entails restricting of fluids, tolerating permissive hypotension, and administering specific ratios of blood products. Active patient rewarming, and massive transfusion protocol implementation are also part of these protocols.<sup>20</sup> The combination of DCS and DCR has shown to be associated with an improvement in 30-day survival in trauma patients and remains a potentially promising strategy in other patient groups.<sup>21</sup>

## CONCLUSIONS

RBC transfusions remain a common intervention in the ICU; however, they may not result in the desired improved oxygen delivery or clinical outcomes. In the critically ill patient with exsanguination from traumatic injuries or uncontrolled bleeding, it is clear that blood products are necessary. However, in patients without active hemorrhage, the evidence suggests a more conservative approach with blood transfusions. Based on the current evidence, the transfusion threshold of 7.0 mg/dL is recommended for the majority of critically ill patients in the ICU. Patients with coronary artery disease or acute coronary syndrome may need a more liberal threshold; however, more research is necessary to elucidate the appropriate transfusion threshold for this population.

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# Communication at the End-of-Life in the Intensive Care Unit: A Review of Evidence-Based Best Practices

SARAH RHOADS, MD; TIM AMASS, MD, ScM

## ABSTRACT

This article summarizes current data and recommendations regarding the care of patients in an intensive care unit (ICU) at the end of life. Through analysis of recent literature and society guidelines, we identified three areas of focus for practitioners in order to deliver compassionate care to patients and their families at this critical time – family communication, caregiver support, and palliative care involvement. Attention to these topics during critical illness may reduce stress-related disorders in both patients and family members, as well as increase satisfaction with the care delivered.

**KEYWORDS:** end-of-life, family support, goals of care

## INTRODUCTION

For patients who are hospitalized in an intensive care unit (ICU), there is an average mortality of 10–29% depending on age and medical condition prompting ICU admission.<sup>1</sup> In comparison, overall mortality for hospitalized patients not in an intensive care unit was 2% in 2010.<sup>1</sup> Navigating a patient’s end-of-life (EOL), and addressing family needs and concerns, is a crucial component of care in the ICU. A growing body of literature seeks to address how clinicians can best address these issues in a way that supports the patient’s wishes as well as the needs of their loved ones.

We will examine three primary areas of focus surrounding care around EOL - communicating with families, supporting family members/caregivers of patients and reducing distress, and involving palliative care.

## COMMUNICATION WITH FAMILIES

Having a critically ill loved one in an ICU is an immensely stressful experience for families. Numerous studies have demonstrated significant residual trauma and emotional distress for caregivers following admission to the ICU, regardless of patient outcome.<sup>2</sup> In order to best support families during an ICU admission, existing data supports the early and frequent use of interdisciplinary teams.<sup>3</sup> While current data regarding the emotional impact of interdisciplinary team use is equivocal, there is a significant positive impact on family perceptions of care.<sup>3</sup>

**Figure 1.** VALUE mnemonic to guide family communication – This mnemonic is presented by SCCM as a guide to help clinicians in communicating with families during end-of-life and difficult conversations.

<b>V.A.L.U.E.</b>
<b>A 5-step mnemonic to improve ICU clinician communication with families</b>
<b>V</b> = Value comments made by the family
<b>A</b> = Acknowledge family emotions
<b>L</b> = Listen
<b>U</b> = Understand the patient as a person
<b>E</b> = Elicit family questions

“VALUE” developed by University of Washington End-of-Life Care Research Program at Harborview Medical Center

Regular communication with caregivers is the cornerstone of caring for patients at the end-of-life. Several studies have demonstrated the potential impact of structured discussions regarding care for critically ill patients. There should be particular emphasis on spending time addressing specific concerns and understanding the patient as an individual, including their goals and values. The Society for Critical Care Medicine (SCCM) 2017 guidelines recommend the use of the VALUE mnemonic (**Figure 1**) to guide discussions with families of critically ill patients.<sup>2</sup> Data regarding the implementation of structured VALUE mnemonic has demonstrated decreased rates of PTSD, anxiety, and depression scores amongst family members.<sup>4</sup> VALUE can help providers address family concerns appropriately and empathically.

Interestingly, the use of standardized patients to facilitate better communication skills among physicians does not appear to impact families in a positive manner, bringing into question how young physicians in training can best be prepared to discuss end-of-life care with families.<sup>5</sup> Designated nurse facilitators to help ensure that communication runs smoothly and that families feel their concerns are addressed may be one way of addressing potential gaps in communication. The use and inclusion of nurse facilitators in family meetings has been associated with increased satisfaction with care.<sup>6</sup>

In conducting a family meeting for a patient who is critically ill approaching end-of-life there are several important considerations. It is necessary to address both family and

patient needs. Potential areas of miscommunication or conflicting goals should also be addressed. When meeting with families, the clinician should be mindful of the amount of time spent sharing information, as compared to families being allowed to express concerns and hopes. A demonstrable decrease in stress symptoms and an increase in family satisfaction has been shown to be directly proportional to the amount of time a family is able to speak during family meetings, as compared to time spent in which the clinician is directing communications.<sup>4,7</sup>

For critically ill and dying patients, current recommendations on addressing redirection of care encourage the family to focus on what the patient would want. However, the issue of what a patient would want does not sufficiently ground the family in the reality of the situation. For example, a family may say that their loved one would want further therapy (i.e., hemodialysis) that may not be an option. Instead, experts suggest eliciting from the family what the patient would think of their current situation, or how they would respond given their situation.<sup>8</sup> This helps to focus a family's attention and thought on the reality of their loved one's illness.

**Table 1.** Suggestions for Family Meeting discussions – As referenced, this table is adapted from several references as suggestions for possible verbiage during end-of-life and difficult conversations.

Word Choice for Family Discussions	
Commonly Used Phrases	Suggestions for Rephrasing
Withdrawing care	Redirecting focus of care
Do Not Resuscitate	Allow natural death
What do you think we should do next? OR: What do you want to do?	What would your [loved one] think if they were sitting here?
What would [loved one] want?	You've told me (or, you can tell me) about what [loved one] would think so I can help you best respect their values
Your [loved one] is very sick. This is what's happening...	What is your understanding about what's happening with your loved one? OR: What do you think is going on with your loved one?
I'm not sure what's going to happen	I wish I could tell you that [loved one] will improve.
General Principles for Family Meetings	
<ol style="list-style-type: none"> <li>1. Use 'wish' statements when conveying concern and helping family come to terms with unrealistic goals.</li> <li>2. Approach family meetings with mentality of "Hope for the best, prepare for the worst."</li> <li>3. Try to foreshadow possible outcomes and give the family an idea of what clinicians are looking for in their loved one's course.</li> <li>4. Normalize common reactions.</li> <li>5. Frequently pause to assess family understanding and reactions</li> <li>6. Focus discussion around what family believes the patient's goals are</li> </ol>	

Attention to word choice extends to descriptions of medical interventions and changing the focus of a patient's care. Careful attention to how messages are conveyed can help to support families and their decision-making during a stressful time, while minimizing conflict with the medical team due to lack of understanding (Table 1).

While successful communication with families should be the goal of all ICU clinicians, there are often occasions in which the clinicians' perspective of patient care conflicts with family hopes or goals. In these situations, an ethics consultation, if available, has been shown to be helpful on multiple levels. One particular study demonstrated reduced hospital stay and life-sustaining treatments without a change in patient mortality. Perhaps more significantly, this study also demonstrated that the majority of physicians, nurses, and surrogates found the consultation to be helpful in resolving conflict as well as distress.<sup>9</sup>

**FAMILY SUPPORT & REDUCING DISTRESS**

In addition to communication, the ability of family members to be present at the bedside is crucial. The 2017 SCCM guidelines recommend that families be allowed at the bedside on an open and flexible basis, including at bedside rounds and even during resuscitation if the family so chooses.<sup>2</sup> One study of families who witnessed CPR demonstrated reduced anxiety and depression symptoms than in those who were unable to witness CPR being performed on their loved ones.<sup>10</sup> In keeping with these guidelines, the Rhode Island Hospital and Miriam Hospital Medical Intensive Care Units allow patients' families to have unrestricted visitation with their loved ones.

Among pediatric and neonatal populations, family involvement in care has been consistently demonstrated to improve parent comfort and reduce distress. However, assessments of family needs without a concomitant change in provider approach has been associated with increased distress, indicating the need for providers to actively respond to family needs instead of merely elucidating them.<sup>11</sup> Additionally, narrative writing is becoming an increasingly recognized tool for emotional support during times of stress. Among both pediatric and adult populations, there is some data to suggest that the use of regular journaling may be a useful tool for families while dealing with the stress of ICU admission.<sup>12</sup> Data thus far seems to indicate a potential impact on both family satisfaction and stress scale measurements but limited utility amongst patients themselves for prevention of PTSD.<sup>13,14</sup>

There is a growing body of literature focused on mitigating the high prevalence of delirium in patients during and after being hospitalized in the intensive care unit, as well as PTSD following ICU/hospital discharge.<sup>2,15</sup> In addition to the impact on patients, recent studies have looked at the likelihood of anxiety, depression, and PTSD symptoms

amongst family members after a patient's ICU stay, regardless of the patient's ultimate outcome.<sup>15,16</sup> There is some data that families of patients who are chronically ill, as well as patients who remain unresponsive on mechanical ventilation after 10 days, are at higher risk of developing PTSD.<sup>15</sup> Recent work has shown flexible visitation hours in the ICU does not significantly impact patient outcomes, but have a positive impact on anxiety and depression symptoms in family members.<sup>16</sup>

A key tenant of distress reduction focuses on sharing information in a way that is meaningful to families. A communication facilitator may be a helpful way of ensuring that families understand their loved ones' care and clinicians' concerns.<sup>6</sup> Programs which focus on sharing information about the ICU and the individual patient's illness, and also follow-up with families after leaving the ICU or after discharge, can also help to smooth the transition and reduce family trauma.<sup>2</sup>

While there are ways to reduce distress while an individual is in the ICU, many recent studies have focused on interventions after a patient is discharged. For patients who survive to hospital discharge, post-ICU specific rehabilitation and follow-up clinic may help to alleviate their distress and likelihood of describing post-traumatic symptoms. There is some data to suggest that these clinics may also be helpful for families.<sup>17</sup> In addition, support groups may be beneficial as a means of coping and processing. In an age of increased accessibility and frequent smartphone use, the use of mindfulness programs via self-directed application use may offer an interesting new approach for healthy coping on an individual basis.<sup>18</sup>

The care team in the ICU can help to reduce family distress through careful communication that follows families after patients leave the intensive care unit. Efforts to support patients' families, particularly if there is a traumatic outcome, after their ICU stay may be beneficial in reducing longer term distress as well.

**PALLIATIVE CARE**

Palliative care is an often-overlooked component to responsible and patient-centered care at the end-of-life in an ICU. Current data regarding palliative care involvement has demonstrated unclear benefit of palliative care consultations in ICU patients.<sup>19</sup> However, the integration of palliative principles can significantly lessen distress of both patients and families in the ICU.<sup>2,20</sup>

Within the ICU, individual physicians may have varying levels of comfort with palliative-based care. A specific palliative care consult may not be necessary for individual cases in which symptoms are easily managed, but this should be

determined on a case-by-case basis. One recent review distinguishes between two main models for the integration of palliative care in the ICU.<sup>20</sup> In the first model, described as the 'consultative model,' the focus is primarily on engaging palliative care consultants for help with symptom management, family and patient-centered care, and clear communication with the team. This may be particularly helpful with issues such as withdrawal of care and transitioning out of the ICU for patients who are at the end of life. Current SCCM guidelines recommend the early consideration of palliative care as a potential means of decreasing cost of care and length of ICU stay, although this recommendation is based on low quality evidence.<sup>2</sup>

The second model, advocated by many critical care societies as a core competency for ICU physicians, is an 'integrative model'.<sup>20</sup> With this approach, palliative care is a focus, rather than a consulting service. Many societies advocate for, and provide for, professional training of ICU providers in basic tenets of palliative care, and there is a small but growing subpopulation of critical care physicians who receive additional training in palliative care.

Most successful integrations of intensive and palliative care ultimately rely on both consultative and integrative models for palliative care. Clinicians who are competent and comfortable with principles of palliative care are well-positioned to effectively and empathetically communicate with families of critically ill patients as well as guide dying individuals and their families through difficult symptoms that arise. These clinicians may also be better able to recognize opportunities for further palliative care assistance through consultation, which can work synergistically with the primary team's efforts towards palliation.

**CONCLUSION**

A hospitalization in an intensive care unit, particularly at the end-of-life, carries with it a high burden of patient symptoms, family distress, and difficult decisions that can manifest for many family members in the form of PTSD and depressive symptoms. These symptoms can continue months after the individual is discharged from the ICU. Three main principles for limiting distress and providing the highest quality care for those at the end of life can help guide ICU care. A focus on supporting families, limiting distress as much as possible, and appropriately directing efforts towards palliative care are crucial considerations for critically ill patients and their loved ones. Following these principles, providers can help to mitigate some of the difficulty and trauma of a stressful time and help people to feel supported and listened to during their time in the ICU.

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# Lung Ultrasound for Diagnosing Patients with Severe Dyspnea and Acute Hypoxic Respiratory Failure

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## ABSTRACT

Acute hypoxic respiratory failure can be caused by severe pneumonia, cardiogenic pulmonary edema (CPE), and acute respiratory distress syndrome (ARDS). Differentiating between these causes in critically ill patients can be challenging. Lung ultrasound (LUS) evaluation of acute respiratory failure has been developed and adopted only recently. LUS offers promise as a valuable clinical tool for the diagnosis and treatment of patients with severe dyspnea and acute hypoxic respiratory failure.

**KEYWORDS:** lung ultrasound, point-of-care ultrasound, pneumonia, cardiogenic pulmonary edema (CPE), acute respiratory distress syndrome (ARDS)

## INTRODUCTION

Acute respiratory failure is a common problem encountered on a daily basis caring for critically ill patients. While diagnostic imaging is commonly obtained in order to reach a diagnosis in a timely manner in the critically ill patient, some of the imaging techniques, including computed tomography (CT) and routine chest radiography (CXR), have significant drawbacks. These drawbacks include cost, radiation exposure, and the need for transportation across the hospital.

The increasing availability of point-of-care ultrasound equipment as well as technical expertise has opened a door into new areas of bedside diagnostics. Although lung ultrasound (LUS) is unlikely to replace commonly used imaging modalities, it has become a valuable tool in the care of the critically ill patients. LUS performed by the physician taking care of the patient allows for the direct correlation of imaging findings to the clinical presentation.

LUS has been shown to significantly reduce the number of chest radiographs and CT scans obtained in the ICU.<sup>1</sup> In addition, lung ultrasound has been shown to maintain diagnostic accuracy in differentiating various causes of acute respiratory failure, including pneumothorax, lung consolidation, and alveolar-interstitial syndrome.<sup>2</sup>

## BASIC LUNG ULTRASOUND

Air is a strong ultrasound beam reflector. Lung ultrasound depends on artifacts in the detection of different lung pathologies. The high frequency linear transducer (5–12 MHz) can be used to detect the pleural line and the lung parenchyma immediately below the pleural line. The low frequency microconvex or convex transducers (2–5 MHz) can be used to visualize the pleural line as well as deeper lung parenchyma. Current techniques for performing complete lung scanning using standard point-of-care ultrasound machines and transducers can be learned quickly and specific methods and protocols are well described in the literature.<sup>1</sup> Which transducer is best for lung ultrasound is currently controversial.<sup>3</sup>

## NORMAL LUNG ULTRASOUND FINDINGS

Normal LUS findings include the Bat sign, lung sliding, A-lines, and B-lines.

The Bat sign occurs when, as the probe is placed longitudinally, the pleural line can be visualized as a horizontal hyperechoic line between the two adjacent ribs (Figures 1 and 2).

A-lines are horizontal single or multiple hyperechoic lines that are parallel to the pleural line and perpendicular to the

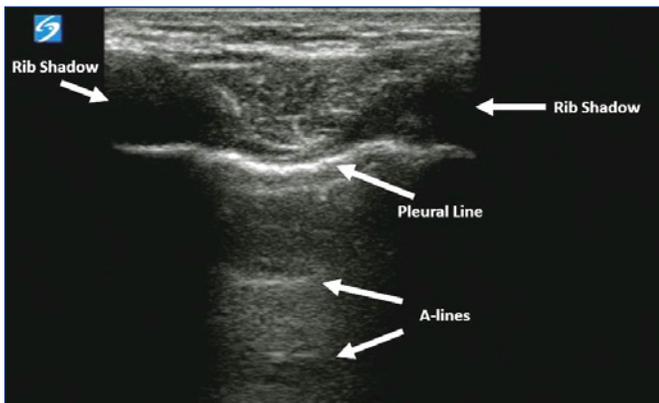
**Figure 1.** The pleural line is visualized as a horizontal hyperechoic line at the top of the image. This is the area where lung sliding can be seen on real-time imaging.



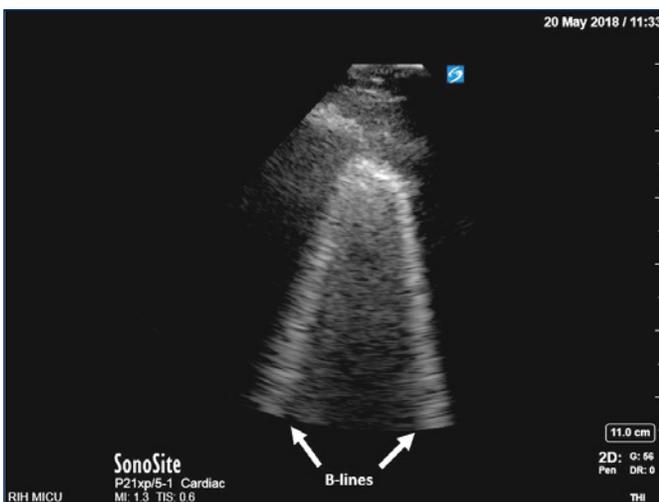
ultrasound beam. These lines represent repetitive reverberation artifacts of the pleura. Visualizing A-line confirms the presence of air, which can be alveolar or pleural in location (Figure 2).

Lung sliding is the movement of the parietal pleura against the visceral pleura. The absence of lung sliding can be the result of pleural separation from pneumothorax, or pleural adhesions due to lung pleurodesis or fibrotic lung disease, as well as non-vented lung from right main stem intubation or collapse.

**Figure 2.** "Bat sign" and A-lines: The bat sign is formed by the pleural line between the two adjacent ribs with hypoechoic areas below the ribs due to rib-shadow artifact. A-lines, seen below the pleural line, are horizontal single or multiple hyperechoic lines that are parallel to the pleural line and perpendicular to the ultrasound beam. These lines represent repetitive reverberation artifacts of the pleura. They are a normal finding in healthy lung.



**Figure 3.** B-lines: Vertical hyperechoic lines that originate from the interface of the pleura extend down to the bottom of the screen. B-lines represent a filling process of the interlobular septa, and can be seen in acute cardiogenic pulmonary edema (CPE), acute respiratory distress syndrome (ARDS), pneumonia and pulmonary fibrosis.



B-Lines are vertical hyperechoic lines that originate from the interface of the pleura, extend down to the bottom of the screen and move with lung sliding while effacing A-lines. Although the presence of two or less B-lines in a single view can be normal, they can also represent a pathologic process including a filling process of the interlobular septa, often seen in acute cardiogenic pulmonary edema, acute respiratory distress syndrome (ARDS), pneumonia and pulmonary fibrosis among others (Figure 3). These abnormal findings usually are represented by a higher number of B-lines in each ultrasound window view.

**LUNG ULTRASOUND FEATURES OF PNEUMOTHORAX**

There are a variety of LUS findings associated with pneumothorax. The visualization of lung sliding accurately rules out pneumothorax at the site of the transducer, but its absence does not necessarily confirm it.<sup>4</sup> In addition, the point at which the two pleural linings detach from each other is called the "lung point." The identification of a lung point is a 100% specific for pneumothorax and 66% sensitive.<sup>4</sup> Finally, as B-line arise from the visceral pleura, the appearance of even a single B-line rules out pneumothorax at the site of the transducer.<sup>5</sup>

**ULTRASOUND FEATURES OF SEVERE PNEUMONIA AND PULMONARY EDEMA**

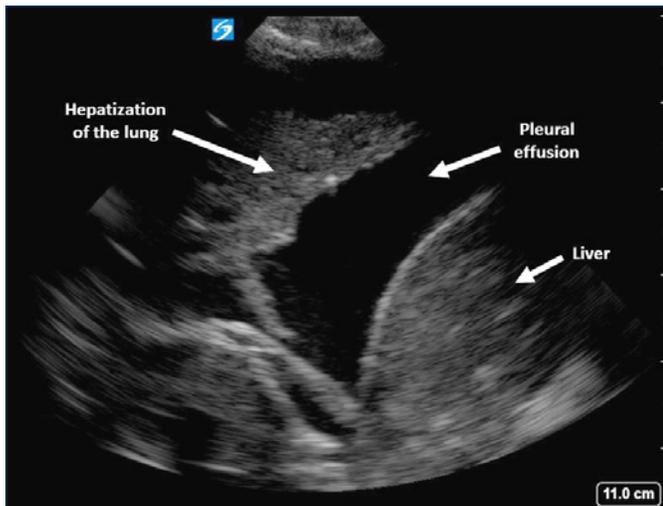
Lung ultrasound continues to grow as a tool for the evaluation of respiratory failure, including for the evaluation of common causes of dyspnea such as pneumonia and pulmonary edema. As discussed above, the normal lung findings include lung sliding, A-lines, and a small number of B-lines. When utilizing LUS to diagnose pneumonia and pulmonary edema, it is important to consider the etiologies for respiratory failure in these conditions.<sup>6</sup> Predominant findings found on LUS in patients with severe pneumonia and pulmonary edema include alveolar filling and interstitial or septal abnormalities.<sup>7</sup>

Findings in severe pneumonia on LUS include translobar alveolar consolidation (sonographic hepatization of the lung Figure 4), nontranslobar alveolar consolidation (shred or fractal sign), sonographic air bronchograms, alveolar-interstitial syndrome (AIS), and lung pulse.

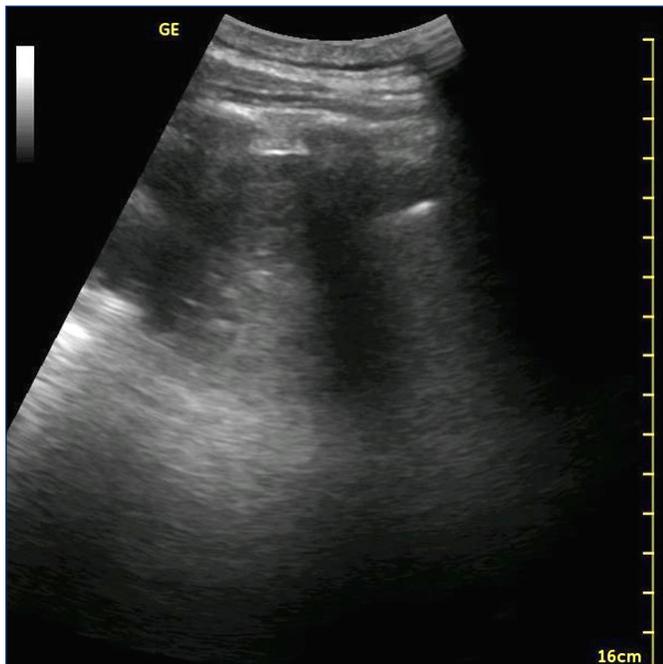
Translobar and nontranslobar pneumonia vary with the extent of disease. Translobar alveolar consolidation of the lung (sonographic hepatization of the lung) represents consolidation of an entire lobe or more (Figure 4). Nontranslobar alveolar consolidation (shred or fractal sign) represents less extensive pneumonia involving a localized area or sub-segment of a lobe of the lung (Figure 5). The differences in location and extent of consolidation result in unique ultrasound findings. With translobar pneumonia, sonographic

hepatization is apparent, which represents acoustic impedance to ultrasound waves due to alveolar filling from inflammatory exudates, which gives an appearance similar to that of the liver. The less extensive nontranslobar pneumonia has areas of alveolar filling adjacent to areas of normal aerated lung. The LUS findings of hypoechoogenic regions separated by an irregular line from normal lung findings result

**Figure 4.** Translobar alveolar consolidation of the lung with sonographic hepatization of the lung. The lung at the top of the screen is surrounded by a pleural effusion. At the bottom of the screen is the dome of the diaphragm and below that the liver. The appearance of the lung in this patient with lobar pneumonia appears similar to that of the liver.



**Figure 5.** Shred sign found in non-translobar pneumonia: In this image there is a relatively normal area of hypoechoogenic lung on the lower right and abnormal consolidated area on the lower left.



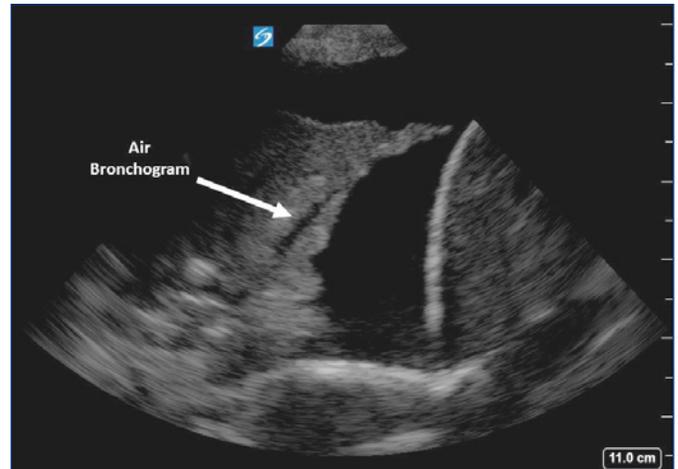
in the "shred" sign. The stark difference between hypoechoic and normal areas create a linear abnormality which can resemble a shredded piece of paper, which is why it is termed the shred sign.<sup>8</sup>

Other findings of pneumonia on ultrasound can be found in both trans and nontranslobar pneumonia. Sonographic air bronchograms appear similar to those seen on other radiographic techniques (Figure 6), including chest computed tomography scans. The air-filled bronchi become visible due to surrounding alveolar filling. Another finding which can be seen, especially in early pneumonia, is Alveolar Interstitial Syndrome (AIS), which is interstitial edema, represented by B lines (Figure 7).

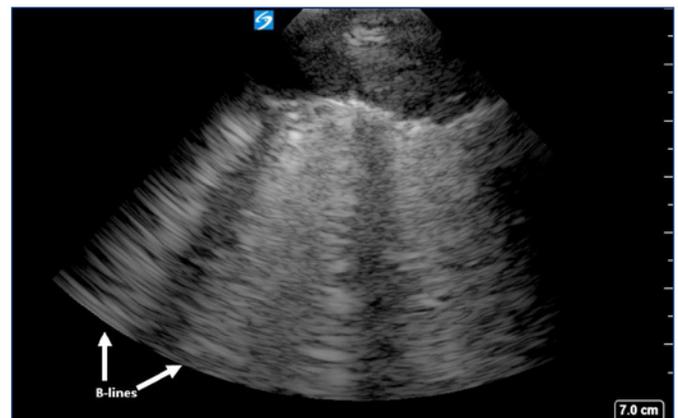
Combining the above findings with a history of infectious respiratory symptoms is suggestive of pneumonia. There are multiple studies that have shown LUS to be comparable or even more accurate than chest X-ray in diagnosing pneumonia when compared to computed tomography as the gold standard.<sup>9</sup>

The other major cause of respiratory failure which can be

**Figure 6.** Dense translobar consolidation with air-bronchogram with surrounding pleural effusion.



**Figure 7.** B-lines in a patient with pneumonia with alveolar-interstitial syndrome (AIS).



evaluated by LUS is left-sided heart failure with resultant pulmonary edema. Using the common LUS findings of A lines and B lines can help to differentiate pulmonary edema from normal aerated lung. Left-heart failure results in a combination of interstitial and septal edema, alveolar filling, and pleural effusions related to increased hydrostatic pressure.<sup>10</sup>

The LUS findings that are predominate in pulmonary edema are >2 B-lines in multiple lung fields. These B-lines are generally vertical, well defined, and extend from the pleural line with movement with lung sliding.<sup>11</sup>

### DIAGNOSING ETIOLOGIES OF SEVERE DYSPNEA WITH LUS

Acute dyspnea, especially in patients with comorbidities, is an extremely challenging clinical diagnosis to make, even for the experienced clinician. Multiple studies have found that chest radiograph, clinical examination, and the use of N-terminal pro-brain-type natriuretic peptide for differentiating between various etiologies of dyspnea are often quite inaccurate, with corresponding sensitivities of 50–60%. Treating patients for multiple possible causes (aka “triple therapy,” giving diuretics, antibiotics, and steroids) can be quite costly for the healthcare system as a whole and have significant negative side effects for individual patients.

Differentiating cardiogenic from non-cardiogenic pulmonary edema can be especially diagnostically challenging. Multiple studies have shown that brain-type natriuretic peptide (BNP), NT-proBNP, chest radiograph, and common physical examination findings are inaccurate for identifying and excluding patients with CPE, with sensitivities and specificities ranging from 50% to 60%.<sup>12</sup> In addition, meta-analyses show that BNP is inconclusive for ruling out acute CPE.<sup>13</sup>

LUS has been recently shown to be a very useful tool in helping to diagnose the etiology of dyspnea in non-critically ill patients. In one recent study of 152 patients admitted to a medical floor with a diagnosis of dyspnea, a definitive diagnosis was made by blinded reviewers of all available clinical evidence. Lung US and pro-BNP levels were obtained on admission and at 48 hours. The study found that Lung US findings (8 or more B-lines on LUS) was significantly better than utilizing BNP to diagnose CHF as the cause of dyspnea in patients admitted to the medical floor.<sup>14</sup> Another recent study in internal medicine patients examined 150 patients also admitted to the medical wards with acute dyspnea. Utilizing a blinded reviewer with access to the complete medical record as the “gold standard”, the study examined the predictive value of LUS findings compared to clinical exam and CXR findings alone to differentiate respiratory and cardiogenic etiologies for the patient’s dyspnea. The authors concluded that LUS greatly improved the accuracy of the clinical diagnosis of patients admitted to the general wards with acute dyspnea. The study also found that LUS diagnostic accuracy for the diagnosis of pneumonia was better than

chest X-ray.<sup>15</sup> A recent systematic review also found that lung ultrasound using B-lines had high sensitivity and specificity in the diagnosis of acute cardiogenic pulmonary edema.<sup>11</sup> Finally, a study in emergency department patients presenting with acute dyspnea found that LUS combined with point-of-care cardiac ultrasound was more sensitive for the diagnosis of heart failure; however, a standard evaluation without LUS was better in the diagnosis of COPD/asthma and PE.<sup>16</sup>

### DIFFERENTIATING SEVERE PNEUMONIA, CARDIOGENIC PULMONARY EDEMA, AND ARDS WITH LUS

Differentiating between severe pneumonia, CPE, and ARDS remains a diagnostic challenge in critically ill patients. LUS has been shown in many studies to have better predictive value than usual clinical practice in differentiating the causes of acute respiratory failure.<sup>11,14,15,17</sup>

Identification of pleural effusions on ultrasound can help differentiate CPE from ARDS. At the bedside, the use of ultrasound is more sensitive than chest radiograph for this identification.<sup>18</sup> The ultrasound finding of bilateral pleural effusions, especially if they are large, can be a rapid and effective diagnostic tool and in combination with interstitial syndrome can be suggestive of CPE from left-sided heart failure.

Specifically with regard to ARDS, the currently widely used Berlin definition requires 3 central criteria: “(1) Occurrence within 1 week of a known clinical insult or new or worsening respiratory symptoms; (2) bilateral opacities on chest imaging not fully explained by effusions, lobar/lung collapse, or nodules; and (3) respiratory failure not fully explained by cardiac failure or fluid overload, and need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present.” Imaging to fulfill the second criterion is traditionally by CT scan and/or chest radiograph.<sup>19,20</sup>

Specific findings on LUS, such as bilateral opacities not fully explained by effusions, lobar or lung collapse, or nodules, may suggest the diagnosis of ARDS.<sup>21</sup> Other findings suggestive of ARDS include multiple bilateral lung regions with 2 or more B lines or bilateral consolidations.

One study found significantly increased diagnostic accuracy for ARDS using LUS as the imaging modality compared with chest radiograph, when thoracic CT scan was used as the gold standard.<sup>22</sup> Another study that compared chest radiograph and LUS found they were both equally useful in the identification of ARDS using the Berlin definition, although LUS was more accurate in predicting mortality.<sup>23</sup>

### CONCLUSION

Diagnosing the cause of acute respiratory failure in a critically ill patient can often be quite challenging, even for skilled providers. LUS is rapidly being adopted as a complementary

modality to conventional thoracic imaging techniques for critically ill patients with dyspnea or acute hypoxic respiratory failure. LUS can help elucidate rapidly the etiologies of acute respiratory failure and severe dyspnea. There is growing evidence for the use of LUS to help differentiate cardiogenic pulmonary edema, ARDS, and pneumonia.

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# Extracorporeal Life Support in Adults with Acute Respiratory Failure: Current Evidence-Based Practices

ADEEL ABBASI, MD; CYNTHIA DEVERS; NEEL R. SODHA, MD; COREY E. VENTETUOLO, MD, MS

## ABSTRACT

There has been rapid adoption of extracorporeal life support (ECLS) in adult patients with severe acute respiratory failure. Extracorporeal membrane oxygenation (ECMO) is used to rescue patients with severe hypoxemic and hypercapnic respiratory failure refractory to optimal therapy and extracorporeal carbon dioxide removal (ECCO<sub>2</sub>R) supports hypercapnic respiratory failure and allows very low tidal volume ventilation to minimize the risk of ventilator-induced lung injury. Currently over 3,000 cases of ECLS (ECMO and ECCO<sub>2</sub>R) in adults with respiratory failure are reported annually to the Extracorporeal Life Support Organization registry. Advances in the care of patients with acute respiratory distress syndrome, technological innovations in extracorporeal circuitry, and insights from modern clinical trials of ECLS have led to favorable outcomes and a renewed interest in the use of this technology. Significant gaps in knowledge about best practices remain, however. This review will summarize indications for respiratory support in adults, current evidence available from clinical trials and our institution's experience with adult respiratory ECLS.

**KEYWORDS:** extracorporeal life support, extracorporeal membrane oxygenation, extracorporeal carbon dioxide removal, acute respiratory distress syndrome, low tidal volume ventilation

## INTRODUCTION

The first adult successfully supported with extracorporeal life support (ECLS) was a patient with acute respiratory failure in 1972.<sup>1</sup> Two consecutive negative trials failed to show a benefit of extracorporeal membrane oxygenation (ECMO) or extracorporeal carbon dioxide removal (ECCO<sub>2</sub>R) over mechanical ventilation in adults with severe respiratory failure, dampening enthusiasm for the use of ECLS in adults.<sup>2,3</sup> Widespread adoption of ECLS for acute respiratory failure in adults did not occur until the 2009 influenza A (H1N1) pandemic, which coincided with publication of the Conventional Ventilation or ECMO for Severe Adult Respiratory Failure (CESAR) trial.<sup>4</sup> Consequently ECLS (including ECMO and ECCO<sub>2</sub>R) has been rapidly integrated into the

management algorithm of adult patients with acute respiratory failure, most commonly acute respiratory distress syndrome (ARDS). Over 3,000 cases are reported annually to the Extracorporeal Life Support Organization (ELSO). Common respiratory indications for adults in cases reported to ELSO include ARDS, bacterial and viral pneumonia.

We will review common respiratory indications for ECLS and discuss three modern randomized trials that have compared ECLS to standard therapy in patients with severe ARDS: the CESAR trial, the ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial and the Xtravent trial. The Strategy of Ultra-Protective lung ventilation with Extracorporeal CO<sub>2</sub> Removal for New-Onset moderate to severe ARDS (SUPERNOVA) trial, a feasibility trial of ECCO<sub>2</sub>R support to achieve very low tidal volume ventilation (LTVV) for moderate ARDS will also be highlighted.<sup>4-7</sup> Finally, we will present our institution's experience using ECLS in the management of adult patients with acute respiratory failure.

## INDICATIONS

The goal of ECLS in acute respiratory failure is to permit lung rest while maintaining adequate gas exchange and oxygen delivery as a bridge to recovery or as a bridge to destination with transplantation. The use of ECLS to reduce the injurious effects of positive pressure mechanical ventilation is the greatest potential of this technology. A LTVV strategy that targets a tidal volume of 6 mL/kg of ideal body weight and plateau pressures < 30 cm H<sub>2</sub>O improves outcomes in ARDS.<sup>8</sup> However even higher plateau pressures (i.e., < 30 cm H<sub>2</sub>O) in patients with severe ARDS increases the risk of mortality, suggesting there may be no safe plateau pressure limit.<sup>9</sup> An aggressive strategy to protect the lungs on ECLS in which airway pressures and alveolar overdistention are minimized may therefore be beneficial.

The degree of respiratory support and configuration of ECLS used is determined by the severity of the patient's respiratory failure and the primary gas exchange abnormality. In patients with isolated respiratory failure that do not require concurrent hemodynamic support, veno-venous (VV-) ECMO is the most common configuration used. In VV-ECMO, blood is drained from a central vein, passed through a blood pump and oxygenator and then returned to a central vein. Lower flow ECCO<sub>2</sub>R (which requires smaller

cannulae with target flows of 10–20 mL/kg/min compared to flows of 60–80 mL/kg/min in ECMO) can be used to support adult patients with less severe respiratory failure including hypercapnic respiratory failure from airways exacerbations. ECCO<sub>2</sub>R can also be used to support very LTVV (< 6 mL/kg) strategies to maintain plateau pressures below 30 cm H<sub>2</sub>O in ARDS and to overcome permissive hypercapnia. In patients supported with ECCO<sub>2</sub>R, blood is drained via a central vein and passed through a blood pump and oxygenator before it is returned to the venous system; an arteriovenous (AV) configuration which drains blood from an artery and uses the patient's systemic blood pressure gradient without a blood pump may also be used.<sup>10</sup> Dual lumen cannulas, which offer single site cannulation to increase mobility, are available for both ECMO and ECCO<sub>2</sub>R.

The most common indication for respiratory support in adults reported to the ELSO registry remains ARDS. Respiratory support can be considered for all patients with a treatable underlying condition resulting in refractory hypoxemic or hypercapnic respiratory failure despite optimal care, massive air-leak syndromes, or as a bridge to transplantation.

In all four 'modern' trials of ECLS discussed here, patients on mechanical ventilation for 7 days or longer were excluded. While the ideal timing to consider ECLS after the initiation of mechanical ventilation remains unclear, prolonged mechanical ventilation is an independent predictor of in-hospital mortality.<sup>11</sup> The Respiratory ECMO Survival Prediction (RESP) Score is a validated risk assessment tool created to guide candidate evaluation for ECMO in adults with acute respiratory failure. In addition to younger age and the presence of single organ failure, patients supported with ECMO within 48 hours of initiation of mechanical ventilation had the most favorable outcomes while those supported after 7 days had a significantly higher mortality. Our institution's practice is to consider ECLS if a patient has not reached optimal ventilator targets after LTVV, early paralysis, and (in appropriate cases) a trial of proning and ideally within 48–72 hours of mechanical ventilation.<sup>8,12,13</sup>

### MODERN ECLS TRIALS

Early randomized trials of ECMO and ECCO<sub>2</sub>R for acute respiratory failure in adults with severe ARDS showed no benefit of ECLS.<sup>2,3</sup> These trials were problematic in their design, their execution, and limited by the available ECLS technology and prevailing clinical practices at the time. The last two decades have been marked by advances in extracorporeal technology including miniaturized, heparin-coated circuits, more durable solid hollow fiber oxygenators that are less prone to shear stress, and dual lumen cannulas. General medical care and ventilator strategies in patients with ARDS have also evolved. For these reasons, there has been a renewed interest in ECLS clinical trials.

### ECMO TRIALS

The first modern trial of ECLS for acute respiratory failure in adults with severe ARDS, the single-center CESAR trial, was similar in design to an earlier successful trial in neonates.<sup>4,14,15</sup> CESAR enrolled 180 adults with severe ARDS randomized to conventional mechanical ventilation versus transfer to a highly experienced ECMO center. Once transferred, subjects in the ECMO group were managed using a standardized ARDS protocol including lung protective LTVV, diuresis and prone positioning. If a subject did not improve within twelve hours they were cannulated for VV-ECMO. CESAR demonstrated that subjects in the ECMO group had a significantly higher composite of survival without severe disability at six months compared to the control group, 63% versus 47% respectively (RR 0.69, 95% CI 0.05–0.097, *p* = 0.03). Of note, only 75% of subjects transferred for ECMO actually received it. The major criticism of CESAR is that the management of subjects in the conventional mechanical ventilation arm was not standardized and those in the intervention arm who were transferred for ECMO were more likely to receive LTVV for longer periods of time.

The CESAR trial demonstrated that care at an ECMO-center including a standardized ARDS protocol may improve outcomes in ARDS. Experience from this pragmatic trial guided the design of the EOLIA trial. Published in 2018, EOLIA was the first international, multicenter randomized trial of ECLS for acute respiratory failure in adults with severe ARDS.<sup>5</sup> Adults with severe ARDS were randomized to VV-ECMO and very LTVV versus standardized LTVV. To account for the ethical quandary of potentially withholding a life-saving therapy within the control group, the study design permitted crossover to ECMO for patients in the control group with refractory hypoxemia. Unlike in the CESAR trial, subjects in both arms were treated with a standardized lung protective ARDS protocol including adjunctive therapies such as inhaled nitric oxide, prone positioning and recruitment maneuvers. The primary end point was 60-day mortality. After enrolling 249 subjects the trial was terminated early for statistical futility after the preplanned fourth interim analysis. While the ECMO group had a lower 60-day mortality compared to the control group (35% versus 46% respectively), this difference was not statistically significant (RR 0.76, 95% CI 0.55–1.04, *p* = 0.09). Given the high crossover rate (28%), the trial would not have achieved a statistically significant difference in the primary outcome between the two groups, defined *a priori* as an absolute reduction in mortality of 20% in favor of ECMO. It should be noted that at the time of crossover the 35 subjects in the control group were extremely ill. With rescue ECMO, 15 (43%) of these crossover subjects survived. Taking this into account, there was a significant reduction in the relative risk of treatment failure defined as death by 60 days in the ECMO group, crossover to ECMO or death in the control group (RR 0.62,

95% CI 0.47–0.82,  $p < 0.001$ ), a predefined key secondary end point. While EOLIA was a negative trial, it is difficult to draw definitive conclusions given these results. A post-hoc Bayesian analysis found it highly probable that ECMO reduced mortality in EOLIA.<sup>16</sup> Taken together, these results suggest that ECMO is effective but the size of the benefit and the risk/benefit ratio in individual candidates is yet to be defined.

### ECCO<sub>2</sub>R TRIALS

Xtravent is the first modern trial of ECCO<sub>2</sub>R for acute respiratory failure in adults with ARDS. In this multicenter trial, 79 adult patients with ARDS were randomized to pumpless ECCO<sub>2</sub>R and very LTVV (3 mL/kg) versus standardized LTVV (6 mL/kg).<sup>6</sup> Patients with significant hemodynamic instability were excluded. The results of this trial published in 2013 revealed that very LTVV with ECCO<sub>2</sub>R was feasible and safe. The ECCO<sub>2</sub>R group had higher 28- and 60-day ventilator-free days (the primary end point) compared to the control group but the difference was not clinically nor statistically significant,  $10.0 \pm 8$  days versus  $9.3 \pm 9$  days ( $p = 0.78$ ) at 28 days and  $33.2 \pm 20$  days versus  $29.2 \pm 21$  days ( $p = 0.469$ ) at 60 days respectively. While Xtravent is a negative study, subjects in this trial were not as ill as those in the CESAR and EOLIA trials and the overall mortality was only 16.5%. In a post-hoc analysis of sicker patients ( $\text{PaO}_2/\text{FiO}_2 \leq 150$ ), subjects in the ECCO<sub>2</sub>R group had a significantly higher number of ventilator-free days at 60-days ( $40.9 \pm 12.8$  versus  $28.2 \pm 16.4$ ,  $p = 0.03$ ).

The recently published SUPERNOVA trial is the largest international, multicenter feasibility and safety trial to date of ECCO<sub>2</sub>R and very LTVV (4 mL/kg and plateau pressures  $\leq 25$  cm H<sub>2</sub>O) for acute respiratory failure in adults with moderate ARDS. SUPERNOVA enrolled 95 patients with moderate ARDS expected to require mechanical ventilation for more than 24 hours into this single-arm trial. In the first 24 hours, sedation and paralysis was used to maintain LTVV. After initiation of ECCO<sub>2</sub>R, the tidal volume was lowered incrementally from 6 mL/kg to 4 mL/kg, while titrating the positive end-expiratory pressure to maintain target plateau pressures of 23–25 cm H<sub>2</sub>O. The primary outcome, very LTVV without a rise in  $\text{PaCO}_2 > 20\%$  above baseline and an arterial  $\text{pH} > 7.30$  at 8 hours, was achieved in 78% subjects while 82% achieved these goals at 24 hours. Subjects were supported on ECCO<sub>2</sub>R for a mean of 5 days (range of 3–8 days) with an in-hospital survival of 62%. Adverse events occurred in 39% of subjects with two serious adverse events attributed to ECCO<sub>2</sub>R. Like the Xtravent trial, this trial showed that

ECCO<sub>2</sub>R and very LTVV for acute respiratory failure in adults with moderate ARDS is feasible. The randomized portion of the SUPERNOVA trial will help determine if a strategy to protect the lungs from ventilator-induced lung injury using ECCO<sub>2</sub>R and very LTVV is beneficial over conventional LTVV in ARDS. A similar randomized trial, the ongoing pRotective vEntilation with veno-venous lung assist in respiratory failure (REST) trial will also address this question by randomizing adults with moderate ARDS ( $\text{PaO}_2/\text{FiO}_2 < 150$  mm Hg) to ECCO<sub>2</sub>R and very LTVV (3 mL/kg or less and a plateau pressure  $\leq 25$  cm H<sub>2</sub>O) versus LTVV alone.<sup>17</sup> The primary outcome of the REST trial is mortality at 90-days following randomization (NCT02654327).

### LOCAL EXPERIENCE

The Lifespan ECLS program was started in 2010 with the first adult patient supported for acute respiratory failure the same year. It has been recognized as a Gold Center of Excellence by ELSO since 2015 and is the only ECLS center in Southern New England. Mirroring a global trend, acute respiratory failure is no longer the most common indication for ECLS in adults in our region. To date, 162 patients have been treated with ECLS, including 107 adults, of whom 57 were supported for acute respiratory failure. The overall survival to discharge or transfer in this subset of patients was 66%, while 75% of patients survived ECLS, comparable to similar-sized ECMO-centers. Rhode Island Hospital is one of the U.S. sites of the international, multicenter VENT-AVOID trial, the first randomized trial of ECCO<sub>2</sub>R in chronic obstructive pulmonary disease (COPD), which compares ventilator free days at day 60 in patients with severe COPD exacerbations randomized to ECCO<sub>2</sub>R versus standard of care (NCT03255057).

### SUMMARY

ECLS has been widely adopted to rescue adult patients with refractory respiratory failure and support patients with respiratory failure to minimize ventilator-induced lung injury. Two modern randomized trials suggest a possible benefit of rescue ECMO in adults with severe ARDS, while the role of ECCO<sub>2</sub>R and very LTVV in patients with moderate ARDS remains unclear based on current evidence.<sup>4,6</sup> While significant questions remain regarding patient selection, optimal care strategies, and cost effectiveness, this potentially life-saving therapy is best deployed by centers who are expert in its use.

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# High-Risk Pulmonary Embolism: Current Evidence-Based Practices

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## ABSTRACT

Acute pulmonary embolism (PE) causes significant morbidity and mortality, particularly for patients with subsequent right ventricular (RV) dysfunction. Once diagnosed, risk stratification is imperative for therapeutic decision making and centers on evaluation of RV function. Treatment includes supportive care, systemic anticoagulation, and consideration of reperfusion therapy. In addition to systemic anticoagulation, patients with high-risk PE should receive reperfusion therapy, typically with systemic thrombolysis. The role of reperfusion therapies, which include catheter-based interventions, systemic thrombolysis, and surgical embolectomy, are controversial in the management of intermediate risk PE. Catheter directed thrombolysis (CDT) can be considered in certain intermediate risk patients although prospective, comparative data for its use are lacking. Surgical or catheter embolectomy are viable treatment options for high-risk patients in whom reperfusion therapy is warranted but who have absolute contraindications to thrombolysis. Further research is needed to better elucidate which patients with PE would most benefit from advanced reperfusion therapies.

**KEYWORDS:** pulmonary embolism, catheter-directed thrombolysis, systemic thrombolysis

## INTRODUCTION

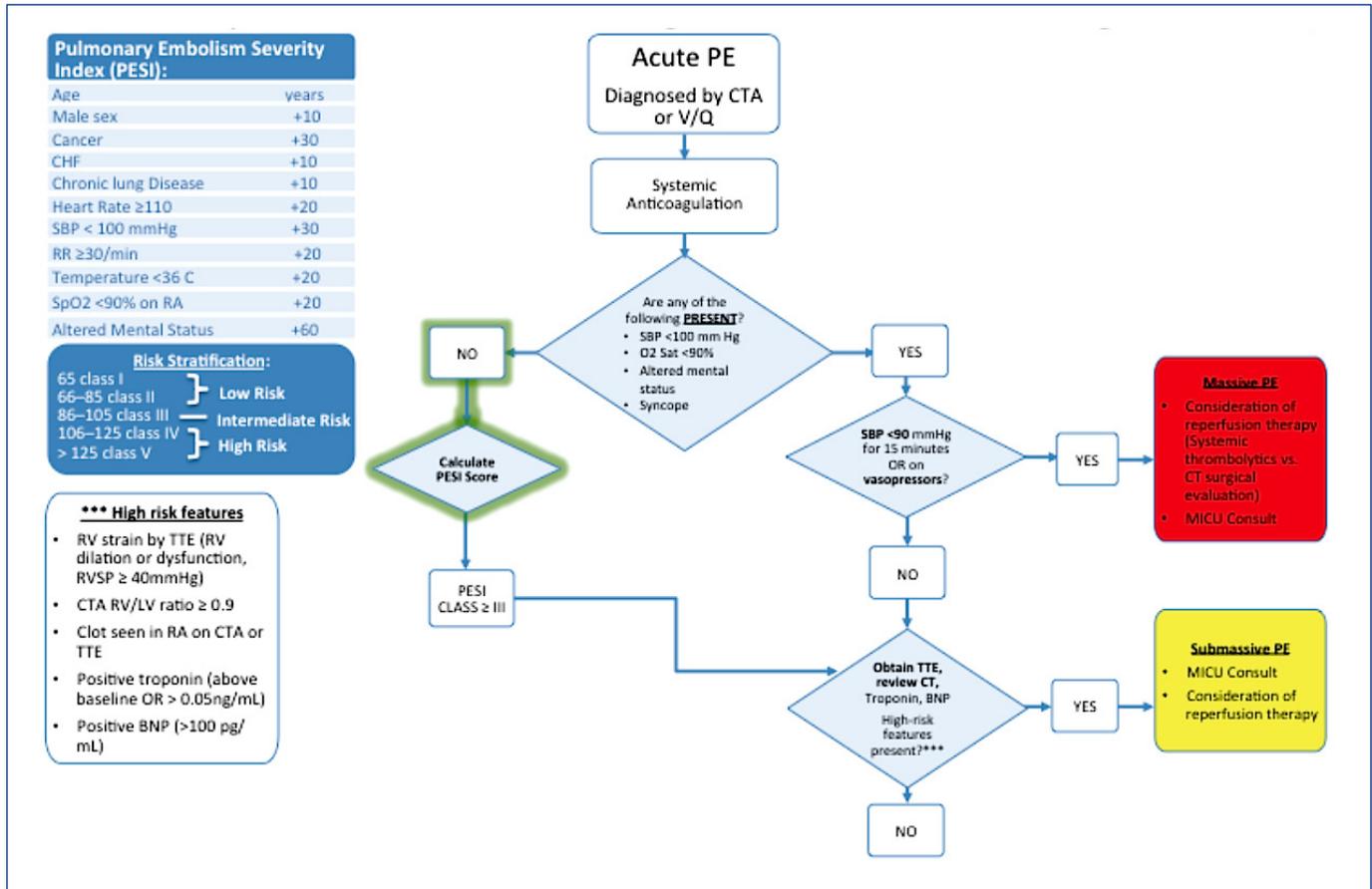
Pulmonary embolism (PE) is both common and a significant cause of morbidity and mortality worldwide. There are an estimated 900,000 cases of venous thromboembolism (VTE) every year in the United States. Although mortality from acute PE is reported to be as high as 100,000 per year, this is likely to be an underestimate, given that approximately 25% of patients with PE present with sudden death.<sup>1,2</sup> There is also a 10–30% mortality rate within one month of acute PE diagnosis.<sup>1</sup> Acute PE is a common indication for intensive care unit (ICU) admission and is associated with high short-term mortality.<sup>3</sup> As such, an understanding of diagnosis, risk stratification, and treatment of acute PE is paramount for critical care physicians.

## DIAGNOSIS AND RISK STRATIFICATION

The diagnosis of acute PE can be challenging, and diagnostic algorithms have been proposed.<sup>4,5</sup> According to all current diagnostic algorithms, contrast-enhanced chest computed tomography angiography (CTA) is the preferred imaging modality for diagnosis of acute PE. Once acute PE is diagnosed, risk stratification is essential to guide treatment decisions. In general, risk stratification for acute PE incorporates several factors, including clinical appearance, vital signs, validated PE risk scores, and right ventricular (RV) function assessed by imaging modalities and cardiac biomarkers. **Figure 1** demonstrates a risk stratification algorithm used by the Pulmonary Embolism Response Team at Rhode Island Hospital. The initial step in risk stratification is to assess for shock or hemodynamic instability, defined as a systolic blood pressure less than 90mmHg for more than 15 minutes or a need for vasopressors. Acute PE that causes hemodynamic instability is referred to as massive PE or high-risk PE, and warrants immediate consideration of reperfusion therapies. In acute PE patients who present without shock or hemodynamic instability, multimodal risk stratification is used to identify patients at low and intermediate risk.

The Pulmonary Embolism Severity Index (PESI) and simplified PESI (sPESI) are validated clinical scores used to predict 30-day mortality in acute PE.<sup>6,7</sup> Patients with PESI class III-VI or sPESI  $\geq 1$  (see **Figure 1**), or who have signs of RV dysfunction on CTA or echocardiography, or elevated cardiac biomarkers (Brain natriuretic peptide or BNP and troponin above the normal lab values) have intermediate risk, or sub-massive PE. These patients can be sub-classified into intermediate-low and intermediate-high risk, the latter defined by the presence of RV dysfunction by both imaging and biomarkers.<sup>4</sup> Patients with PESI class I-II or sPESI=0 are classified as low risk, indicating a low likelihood of mortality, and are unlikely to be encountered in the ICU setting. In addition to informing treatment decisions, risk stratification can be helpful in assessing the need for ICU level of care. In our practice, patients with high or intermediate-high risk PE are routinely admitted to the medical ICU for initial evaluation, although clinical gestalt is used in conjunction with risk scores and risk stratification algorithms when making these decisions.

**Figure 1.** Adaptation of the risk stratification algorithm for acute pulmonary embolism used by the Pulmonary Embolism Response Team at Rhode Island Hospital.



PE: pulmonary embolism; CTA: chest computed tomography angiography; V/Q: Ventilation Perfusion Scan; CHF: congestive heart failure; SBP: systemic blood pressure; RR: respiratory rate; SpO2: peripheral oxygen saturation, TTE: transthoracic echocardiogram, RV: right ventricle; LV: left ventricle; BNP: brain natriuretic peptide.

**TREATMENT OF ACUTE PULMONARY EMBOLISM**

Once the diagnosis of acute PE is made, treatment focuses on supportive care, systemic anticoagulation, and consideration of reperfusion therapy. Unless there are contraindications, systemic anticoagulation should be started after the diagnosis of acute PE is established. For higher risk patients, intravenous unfractionated heparin is typically the preferred agent as its pharmacokinetics allow the ability to stop if thrombolysis or interventional procedures are indicated. In addition to anticoagulation, hemodynamic and respiratory support should be provided. Clinicians should be extremely cautious with intravenous volume expansion as this may worsen right ventricular function and precipitate rapid clinical decompensation. Pulmonary Embolism Response Teams (PERT) are multi-disciplinary teams that can be activated similarly to teams for acute myocardial infarction or acute stroke. These can be constituted by a wide variety of specialists, including pulmonologists, cardiologists, intensivists, radiologists, hematologists, pharmacists, emergency medicine physicians, and cardiac and vascular surgeons. PERT

can be activated for intermediate or high risk PE, or in any case where there is uncertainty about diagnosis or optimal treatment strategy.<sup>5</sup>

**SYSTEMIC THROMBOLYSIS**

Systemic thrombolysis is well established for the management of high risk or massive PE. Thrombolytics reduce pulmonary artery resistance and pressure, and in hemodynamically unstable patients decrease mortality.<sup>8</sup> Guidelines routinely recommend systemic thrombolysis for patients with massive PE without contraindications to thrombolytics.<sup>4</sup> The use of systemic thrombolytics for intermediate-risk PE remains controversial.<sup>4,9</sup> This question was addressed in the Pulmonary Embolism Thrombolysis (PEITHO) trial, a multicenter, randomized, double-blind, placebo-controlled trial that is the largest trial to examine systemic thrombolytics in intermediate-risk PE.<sup>10</sup> In this study, 1006 acute PE patients (symptoms less than 15 days) were randomized to receive either unfractionated heparin alone or in conjunction

with tenecteplase. PE was confirmed by VQ scan, CTA, or pulmonary angiogram, and right ventricular dysfunction confirmed by echocardiogram or CTA and elevated troponin. At seven days, the tenecteplase group had a significant decrease in a composite endpoint of all-cause mortality and hemodynamic decompensation (2.6% vs 5.6%;  $p=0.02$ ), although there was no difference in mortality. The incidence of extracranial bleeding (6.3% vs 1.2%,  $p<0.001$ ) and stroke (2.4% vs 0.2%,  $p=0.003$ ) were higher in patients that received tenecteplase compared to heparin alone, suggesting an unfavorable risk-benefit ratio for the use of systemic thrombolytics for hemodynamically stable PE with RV dysfunction. Subsequent meta-analyses have shown that systemic thrombolysis reduces overall mortality but is associated with a higher risk of fatal or intracranial hemorrhage.<sup>11,12</sup> Reduced dose thrombolytics have been studied in small trials, but this is also not recommended for routine use in intermediate-risk PE. In the PEITHO study, 23 patients in the heparin alone group required open-label thrombolysis after randomization. Only 2 of these patients died, suggesting, as is our current clinical practice, a role for close observation of patients with intermediate-risk PE, and consideration of the use of rescue systemic thrombolysis if clinical deterioration subsequently occurs.<sup>10</sup> Further study is needed in this particular area as sample size is a limiting factor.

### CATHETER-BASED INTERVENTIONS

Several catheter-based interventions are currently available for the treatment of acute PE. These broadly fit into two categories: catheter directed thrombolysis (CDT) and catheter embolectomy. The two are currently proposed for use in intermediate-high risk patients who are at risk for clinical deterioration based on vital signs, severity of RV dysfunction, tissue perfusion, and/or gas exchange, and who have absolute or relative contraindications to or failed response to systemic thrombolysis.<sup>5</sup> CDT uses imaging guidance to place an infusion catheter to the site of the clot in order to locally deliver low-dose thrombolytics over the course of several hours. The thrombolytic dose is significantly lower than what is administered systemically. Depending on the specific device used, this can be accompanied by low-power, high-frequency ultrasound, which is referred to as ultrasound-assisted catheter-directed thrombolysis (UACDT). There is only one prospective, randomized trial comparing CDT to anticoagulation alone for the management of acute PE.<sup>13</sup> The ULTIMA trial randomized 59 patients with acute main or lower lobe PE and a transthoracic echocardiogram RV/LV ratio  $>1.0$  to receive either unfractionated heparin alone or with a UACDT regimen of 10 to 20mg recombinant tissue plasminogen activator (tPA) over 15 hours. Compared to the heparin alone group, the UACDT group had a greater decrease in mean RV/LV ratio from baseline to 24 hours, although at 90 days there was no difference in RV/LV

ratio improvement. Another retrospective, comparative study found no difference in echocardiographic RV/LV ratio at 30 days between patients who received CDT compared to anticoagulation alone.<sup>14</sup> Although these and other non-comparative studies<sup>15, 16</sup> have shown that CDT improves RV function and PA pressures in the short term, it remains unclear if CDT confers any meaningful long-term benefit. The only patient that died in the ULTIMA study was in the heparin-alone group. Pooled mortality estimates from studies for CDT are similar to the mortality estimates of the anticoagulation groups of the larger studies of systemic thrombolysis in intermediate risk PE.<sup>10,11,17</sup> While these may represent slightly different patient populations, it seems unlikely that CDT carries a mortality benefit. The rate of bleeding complications for UACDT are likely less than that of systemic thrombolysis, but more than that of systemic anticoagulation alone.<sup>16,17,18</sup> It is our opinion that prospective, randomized trials with more meaningful or validated clinical outcomes are necessary before CDT can be used routinely for intermediate-risk PE. In our clinical practice, CDT is considered on a case-by-case basis and is reserved for patients with high likelihood of clinical decompensation. It is possible that improvement in risk stratification of intermediate risk PE might allow for better identification of those patients at higher risk of decompensation who might benefit from early intervention with CDT.

Catheter embolectomy is feasible with devices currently on the market in the United States. All have a similar mechanism of action, and work by introducing a catheter to the site of clot for retrieval by aspiration. In the FLARE study, 104 acute PE patients with elevated RV/LV ratio on CT were treated with catheter embolectomy using the FlowTrieve System (Inari Medical, Irvine, California) in addition to systemic anticoagulation. This resulted in a significant reduction of RV/LV ratio, but only a modest decrease in PA pressure. Adverse event rate was 3.8% with no reported cases of intracerebral hemorrhage and only one case of adverse bleeding.<sup>19</sup> This is currently the only embolectomy device that is FDA-approved for treatment of acute PE, although trials remain ongoing for several other catheter embolectomy systems. While catheter embolectomy offers the possibility of clot removal without exposure to thrombolytics, there are no trials comparing this to anticoagulation alone or to CDT. Similar to CDT, it remains to be seen if catheter embolectomy results in outcomes that are more clinically meaningful than an acute reduction in RV/LV ratio. The utility of CDT and catheter embolectomy systems as an effective treatment modality for acute PE depends largely on equipment availability at centers as well as requisite expertise of providers and staff. Its use remains an option in patients with contraindications to systemic thrombolysis or failure of thrombolysis, when surgical embolectomy is unavailable or infeasible, if the institution has the requisite capabilities. In our opinion, catheter-based interventions

can be considered on a patient case-by-case basis so long as local technical capabilities allow and the decision should be made after a multi-disciplinary or PERT discussion.

### SURGICAL EMBOLLECTOMY

Current indications for surgical embolectomy include high-risk and intermediate-risk PE with an absolute contraindication to thrombolysis, failed thrombolysis, or hemodynamic collapse that may result in death prior to full effect of systemic thrombolysis.<sup>5</sup> Pre-surgical systemic thrombolysis is not an absolute contraindication to surgical embolectomy. Presently, no randomized trials exist comparing systemic thrombolytics to surgical embolectomy, although both are associated with improvement in RV function and PA systolic pressure.<sup>20</sup> Compared to systemic thrombolytics, surgical embolectomy is associated with a decreased risk of major bleeding,<sup>21</sup> however, mortality from surgical embolectomy is estimated to be 4–11%.<sup>22</sup> This modality should be used as reperfusion therapy in higher-risk patients who warrant reperfusion therapy but have an absolute contraindication to systemic thrombolysis. Surgical embolectomy is frequently considered in acute PE patients with presence of right heart thrombi<sup>23</sup>, although optimal treatment for acute PE with “clot in transit” remains uncertain.

### CONCLUSION

The management of high- and intermediate-risk PE is an evolving area that requires appropriate risk stratification, monitoring, and supportive care after acute PE diagnosis is made. Hemodynamically unstable patients should receive systemic thrombolysis unless there is a clear contraindication. The use of catheter-based interventions and surgical embolectomy should be reserved for patients with an absolute contraindication to systemic thrombolysis. There are currently insufficient data to recommend the use of CDT for acute intermediate-risk PE. As such, prospective, comparative randomized, clinical trials for CDT in acute PE are necessary in order to elucidate the possible role of this treatment modality in this subpopulation.

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