## **Evidence-Based Practice** of Critical Care

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# Dedication

To John Paul Pryor, MD, 1966-2008 Friend and colleague, contributor to this volume, whose deeply felt obligation to serve the innocent victims of violence cost him his life, for showing us all how to be better human beings

> To my family: Chris, who makes everything possible Cate, Nicki and Beth, who make it all worthwhile (and make their parents proud) Linus, who makes it fun—most of the time Clifford S. Deutschman, MD

To Diane, Conor and David and my parents, Dympna and Maurice Neligan—for all of their support and wisdom. Patrick J. Neligan, MD

# How Does One Evaluate and Monitor Respiratory Function in the Intensive Care Unit?

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The purpose of evaluating and monitoring pulmonary function in the intensive care unit (ICU) is to assess the severity of pulmonary disease, its progression, and the patient's response to therapy, most often mechanical ventilation. Unfortunately, pulmonary physiologic variables in ventilated patients have questionable prognostic value, and it is unclear how they should be used in daily clinical practice. These factors likely explain the limited clinical use of pulmonary function monitoring beyond the strictly essential variables (i.e., blood gases and ventilator volumes and pressures). However, research on pulmonary pathophysiology and, particularly, on respiratory mechanics has provided the rationale for outcome studies on ventilatory management and is responsible for the development of lung-protective mechanical ventilation strategies. This chapter attempts to highlight how pulmonary function monitoring allows the application of pathophysiologic knowledge to the management of each ventilated patient, implementing protective ventilatory strategies with the ultimate goal of improving outcomes.

#### **BASIC RESPIRATORY MECHANICS**

The respiratory system requires the generation of pressure for its inflation, as a result of its resistive and elastic properties. Resistance is mainly caused by the airways, with a small contribution by tissue resistance, stress relaxation, and gas maldistribution.<sup>1</sup> The elasticity of the respiratory system is expressed either as *elastance* (change in pressure divided by change in volume) or by its reciprocal, *compliance*, which is more commonly used at the bedside. Several techniques are available to measure respiratory mechanics, but the most practical one is the rapid airway occlusion technique.<sup>2</sup> It estimates the elastic recoil pressure of the alveoli by measuring the inspiratory plateau airway pressure (Pplat). To use this technique, muscle paralysis is not required if respiratory muscle activity is negligible during the occlusion.

An important respiratory mechanics variable is intrinsic positive end-expiratory pressure (PEEPi). This is commonly measured using end-expiratory airway occlusion. PEEPi has important cardiopulmonary effects. These include decreased cardiac output, alveolar overdistention, increased work of breathing, and patient-ventilator asynchrony. If neglected, PEEPi leads to underestimation of compliance.

The respiratory system is composed of two compartments in series: the lung and the chest wall. The chest wall includes the abdomen because abdominal pathology can affect respiratory mechanics. The measurement of esophageal pressure, in addition to airway pressure, is necessary to define the relative contribution of each of these two compartments to respiratory mechanics and particularly to compliance.<sup>3</sup> It must be remembered that esophageal pressure measurement can have significant inaccuracies, particularly in the supine position.<sup>4</sup>

#### MONITORING ALVEOLAR STRAIN

Considerable research has highlighted the pathophysiologic mechanisms underlying acute respiratory failure and particularly the acute respiratory distress syndrome (ARDS). From the mechanical point of view, ARDS is characterized by a decrease of lung volumes and compliance.<sup>3</sup> Computed tomography (CT) studies of patients with ARDS suggested that this pattern is not caused by increased rigidity of the parenchyma but rather by a decrease in the number of alveolar units that are available for ventilation.<sup>5</sup> This reflects a combination of atelectasis and intra-alveolar deposition of edema fluid. If this ARDS model, the so-called baby lung,<sup>6</sup> is valid, any given tidal volume (TV) will be distributed among a smaller number of alveoli than would be the case in normal lung (Fig. 1-1). Therefore, each alveolus will distend more than normal during inspiration.<sup>7</sup> If TV is not decreased proportionally to the reduction of viable parenchyma, strain on the alveolar walls will increase.<sup>8</sup> Excessive alveolar strain has been shown to cause ventilator-induced lung injury (VILI) in animals<sup>9,10</sup> subjected to mechanical injury, inflammation, or both.<sup>11</sup> So far, improved survival from the use of lower TV ventilation as opposed to higher TV<sup>12–14</sup> has been demonstrated in three randomized controlled clinical trials. These findings suggest that limiting alveolar strain improves outcome.

Alveolar strain can be defined as the ratio between TV and the end-expiratory lung volume (EELV).<sup>6</sup> However,



**Figure 1-1.** Visual illustration of the "baby lung" model. A decrease in the number of ventilated alveolar units results in a proportionally increased strain of the remaining units going from end-expiration (*dashed line*) to end-inspiration (*continuous line*), if the inspired tidal volume is not decreased. Increased alveolar strain is reflected by an increase in inspiratory plateau pressure (Pplat).

it is not known at what level alveolar strain in humans becomes harmful. Safety limits have been extrapolated from animal studies. Additionally, EELV can be measured only by techniques that currently are not widely available at the bedside. Thus, bedside monitoring of alveolar strain is mostly accomplished by measuring Pplat. This variable increases in direct proportion to the reduction in ventilated lung tissue. It is recommended that PEEP and TV be adjusted to keep Pplat below 30 to  $35 \text{ cm H}_2\text{O}.^{15}$ This value was chosen because it is the pressure that inflates healthy alveoli to a volume close to vital capacity. The assumption is that any pressures below these values are inherently safe. It must be remembered that there is little evidence to support this proposal.<sup>16</sup> Alveolar overdistention is possible even when the patient is ventilated with a small TV and at a Pplat lower than 35 cm  $H_2O$ .<sup>17</sup> Further, retrospective data analyses<sup>16</sup> and observational studies<sup>18,19</sup> suggest that patients may be harmed by high TV ventilation even when Pplat is lower than 30 cm H<sub>2</sub>O and in the absence of ARDS. Thus, although alveolar strain should be monitored through Pplat, the safe limits of this variable, if any exist, are still uncertain. The measurement of Pplat has other limitations. For example, Pplat is significantly and unpredictably affected by the elasticity of the chest wall, as documented by esophageal pressure and transpulmonary pressures.<sup>20</sup> High Pplat in patients with decreased chest wall compliance may lead to overestimation of alveolar strain unless esophageal pressure is also measured.

#### MONITORING ALVEOLAR RECRUITMENT

An important goal of mechanical ventilation is the recruitment of atelectatic alveoli. This should decrease intrapulmonary shunt and improve oxygenation. Alveolar recruitment is defined as an increase in intrapulmonary gas gained by increasing the number of ventilated alveolar units. It is to be distinguished from the further inflation of previously open alveoli. Recruitment occurs mainly at elevated airway pressures because a significant amount of energy is required to reestablish a normal alveolar air-fluid interface.<sup>21</sup> Contrary to a common misconception, the application of PEEP does not recruit alveoli but rather serves to prevent recurrent alveolar collapse.<sup>7,22</sup> Suboptimal levels of PEEP lead to alveolar instability<sup>23</sup> that is associated with VILI in animal models.<sup>24</sup> Awareness of VILI induced by lack of alveolar recruitment has prompted clinical trials aimed at demonstrating that a ventilatory strategy incorporating both low VT and high PEEP has a positive outcome effect.<sup>13,14,25</sup> The results of these studies have been discordant, and a clear recommendation on the use of PEEP in ARDS cannot yet be made. However, those studies that attempted to document alveolar recruitment and to choose PEEP accordingly showed a favorable outcome with higher PEEP.<sup>13,14</sup> Therefore, research into instruments that evaluate recruitment and guide ventilator settings using better functional parameters continues.

#### Gas Exchange

Measurement of gas exchange is the most practical and most frequently used tool to evaluate alveolar recruitment in acute respiratory failure. Pao2 has been shown to correlate with lung volumes at different levels of PEEP<sup>26,27</sup>; however, reopening of alveolar units may not translate into gas exchange if the same units do not receive adequate perfusion. This was suggested by recent studies in animals and humans, in which improvements in the Pao<sub>2</sub>/Fio<sub>2</sub> ratio had a poor predictive value for recruitment as quantified using chest CT.<sup>28,29</sup> Further, elevated PEEP can alter oxygenation through mechanisms that do not involve alveolar recruitment. Examples include redistribution of pulmonary blood flow or decreased cardiac output.<sup>30</sup> Thus, oxygenation changes may not accurately estimate mechanical recruitment of alveoli. This is an exceedingly relevant problem when the goal of ventilatory management is optimization of alveolar stability rather than maintenance of adequate arterial oxygenation.

Different variables besides  $Pao_2$  are used to monitor the level of oxygenation. These include the  $Pao_2/Fio_2$  ratio, alveolar-arterial oxygen gradient, venous admixture, and shunt fraction. These variables are limited by the fact that their values are affected by  $Fio_2$  in a way that depends on intrapulmonary shunt and ventilation-perfusion maldistribution.<sup>31,32</sup> Thus,  $Fio_2$  should be kept constant when assessing alveolar recruitment in a patient.

In animal models, alveolar recruitment and overdistention caused by PEEP have significant effects on alveolar dead space and Paco<sub>2</sub>. High PEEP decreases the perfusion of ventilated alveoli and increases Paco<sub>2</sub>, whereas moderate PEEP improves the distribution of ventilation and perfusion and reduces alveolar dead space.<sup>33</sup> For this reason, measurement of Paco<sub>2</sub> and dead space could be used to monitor recruitment of alveoli and detect their overdistention. In an animal study, the point of optimal alveolar recruitment and minimal overdistention was associated with improved Paco<sub>2</sub>.<sup>34</sup> However, the clinical use of dead space to titrate PEEP is underinvestigated.

#### **Computed Tomography**

Chest CT has provided important insight into the pathophysiology of ARDS.<sup>6</sup> By measuring tissue density, CT quantifies the ratio between air and water in each unit of volume analyzed (voxel) and allows assessment of alveolar recruitment by determining decreases in lung density induced by PEEP or by other interventions.<sup>35</sup> Visual inspection of different CT images is helpful but is affected by intraobserver and interobserver variability. However, quantitative analysis of CT densities distribution allows the partitioning of the lung among compartments with different degrees of aeration. Consequently, alveolar recruitment can be quantified as the weight or volume of lung tissue that shifts from nonaerated to better aerated compartments.<sup>35,36</sup> Additionally, hyperinflation can be detected as a compartment with abnormally low density.<sup>37</sup> In a recent study using CT in ARDS patients, the weight of lung tissue that reopened after a recruitment maneuver predicted response to PEEP<sup>28</sup> (Fig. 1-2). In this same study, neither gas exchange nor respiratory mechanics could identify recruitment with accuracy similar to CT.

CT has limitations. With conventional CT analysis, only a few slices of lung are analyzed, creating problems with image registration when intrathoracic contents shift. More information can be obtained with the use of whole-lung CT analysis.<sup>38</sup> This technique allows identification of lower lobar atelectasis as an important feature of ARDS.<sup>39</sup> It also must be remembered that CT only measures an average density within each voxel and cannot distinguish among the reopening of collapsed alveolar units, the inflation of previously open ones, and the redistribution of edema fluid.<sup>40</sup> Using metal markers, the presence of atelectasis and its recruitment could not be radiologically detected in animals injured with oleic acid.<sup>41,42</sup> This brings into question the validity of CT findings in this model.

In summary, chest CT likely provides a valid tool to evaluate and quantify alveolar recruitment and could be used to guide PEEP selection in ARDS. However, the greatest obstacle to this use of chest CT is the need to transport unstable patients out of the ICU. The advent of portable CT scanners could obviate to this limitation in the future.



**Figure 1-2.** Computed tomography (CT) of the chest at low (5 cm  $H_2O$ ) and high (45 cm  $H_2O$ ) airway pressure in two patients with ARDS. **A**, Shifting of lung regions from poor to normal aeration suggests a significant potential for alveolar recruitment in this patient, who might benefit from increased levels of positive end-expiratory pressure (PEEP). **B**, High airway pressure only results in overdistention of previously aerated lung without achieving recruitment of poorly aerated lung tissue, suggesting that this patient may possibly not respond to high PEEP. (*From Gattinoni L, Caironi P, Cressoni M, et al. Lung recruitment in patients with the acute respiratory distress syndrome*. N Engl J Med. 2006;354: 1775-1786.)

#### Volume-Pressure Curve

Volume-pressure (VP) curves are obtained by stepwise inflations and deflations of the lungs, plotting the delivered volume over the measured elastic recoil pressures. If esophageal pressure is measured, the VP relationship can be partitioned into pulmonary and chest wall components. Compliance is calculated from the slope of the curve. The classic technique for obtaining a VP curve requires inflation through a super-syringe and has the disadvantage of requiring disconnection from the ventilator, although the technique is safe in most patients.<sup>43</sup> Alternative techniques using a ventilator have been described. These include slow ventilator inflation<sup>44</sup> or the performance of multiple airway interruptions at varying TVs.<sup>27,45</sup> The different techniques used to record a VP curve deliver equivalent results.<sup>46,47</sup> VP curves typically are obtained during deep sedation and muscle paralysis. However, reliable data can be obtained while avoiding paralysis.<sup>48</sup>

In normal lungs, the inflation limb of the VP curve is mostly linear and is approximated by the deflation limb (Fig. 1-3). In a surfactant-deficient lung, alveoli are initially collapsed and require elevated pressures to reopen, but once recruited, their inflation becomes easier. Therefore, the inflation limb has a lower inflection point (LIP) at a pressure that should correspond to alveolar recruitment. The compliance of the linear portion of the curve above the LIP is thought to express the elastic properties of the recruited alveoli.<sup>5</sup> Deflation of a surfactantdeficient lung requires less energy and pressures than inflation, causing a significant amount of hysteresis.

This interpretation of the VP curve morphology was extrapolated from surfactant deficiency to patients with ARDS, whose VP curves often show a similar morphology.<sup>49</sup> An LIP on the inflation limb is thought to indicate the pressure required for alveolar recruitment,<sup>50</sup> as suggested by chest CT in ARDS patients.<sup>5</sup> Additionally, an upper inflection point (UIP) often can be identified at high volume and is likely related to alveolar overdistention.<sup>51</sup>



**Figure 1-3.** Schematic representation of volume-pressure (V-P) curves in a healthy individual (*dashed line*) and a surfactant-deficient individual (*continuous line*). The *shaded areas* represent hysteresis, which is increased in surfactant deficiency. *Thick arrows* indicate direction of inflation or deflation. LI, lower inflection point; UI, upper inflection point.

Thus, it was postulated that the LIP could be used to define the minimal level of PEEP and the UIP to identify the maximal tolerable Pplat, with the dual goal of maximizing alveolar recruitment and minimizing alveolar strain.<sup>37,51</sup> The validity of this approach was supported by studies that showed improved survival<sup>13,14</sup> and decreased cytokine levels<sup>52</sup> in ARDS patients ventilated with PEEP set above the LIP and with low TV, compared with a lower PEEP and higher TV strategy. However, these results may not support the routine use of VP curves to set PEEP. The studies can be criticized for not recognizing a distinction between the effects of PEEP and of TV selection. Additionally, there are perplexities about the interpretation of the VP curve in patients with ARDS. Although it is well recognized that the presence of an LIP identifies patients with high recruitment potential,<sup>36</sup> the value of the LIP may not correspond to the PEEP required to optimize recruit-ment.<sup>26</sup> In fact, CT studies in animals<sup>53</sup> and humans<sup>22,47</sup> have shown that recruitment occurs at pressures that are significantly higher than the LIP and are spread over a broad range. Additionally, studies showed that the VP curves do not predict pulmonary volume during steadystate mechanical ventilation,<sup>47,54</sup> suggesting a time dependence for alveolar recruitment that cannot be discerned from the VP curve.

Reanalysis of the physiology underlying the concept of the VP curve suggests that the morphology of the deflation limb may carry more information than initially recognized. Specifically, the deflation limb may reflect expiratory alveolar collapse.<sup>55</sup> In fact, in animal models, the deflation curve closely predicts the response of lung volumes to varying PEEP levels.<sup>56</sup> Additionally, compliance measurements obtained during a descending PEEP trial were able to identify the point of alveolar derecruitment as confirmed by CT.34 According to this approach, analysis of deflation VP curves or performance of descending PEEP trials may indicate the level of PEEP needed to preserve alveolar recruitment.<sup>57</sup> However, a descending PEEP trial in ARDS patients could not identify a clear-cut point of alveolar derecruitment, suggesting that alveolar collapse is a continuous phenomenon that occurs throughout a wide distribution of airway pressures.<sup>26</sup>

Other important characteristics of VP curves should be mentioned. The VP relationship and compliance values are not static but change as a result of previous conditions of alveolar recruitment<sup>58</sup> and also increase after the performance of a vital capacity maneuver.<sup>56</sup> Therefore, it is important to standardize the ventilator history before performing a VP curve measurement. Impairments of chest wall mechanics, as in the case of abdominal hypertension, may cause the appearance of an LIP in the absence of alveolar recruitment.<sup>59</sup> Although manual analysis of the VP curve has acceptable interobserver and intraobserver variability in the estimation of the LIP and UIP,<sup>60</sup> computerized analysis and model fitting are increasingly used to interpret the VP relationship.<sup>61</sup>

In summary, the VP curve may be used to identify which patients have recruitment potential and thus may benefit from a higher level of PEEP. However, further research is needed before this tool can be used to identify the amount of PEEP needed to optimize recruitment and improve outcomes.

#### Static Compliance

Static compliance is probably the respiratory mechanics variable that is most commonly measured at the bedside. It typically is obtained by the rapid occlusion technique. The measurement of esophageal pressure has identified decreased chest wall compliance as a significant contributor to respiratory mechanics impairment, at least in certain populations of patients.<sup>62</sup> In ARDS, static lung compliance is decreased proportionally to the reduction of EELV, likely due to a smaller number of ventilated alveoli.<sup>3</sup> If this assumption is valid, static compliance values should reflect alveolar recruitment. In fact, the increase in compliance after a recruitment maneuver is proportional to recruited lung volume if PEEP is maintained constant.<sup>29</sup> Early studies suggested that static compliance could be used to define the optimal setting of PEEP.<sup>63</sup> However, the interrelation between static compliance and recruitment is less straightforward when PEEP is not constant. Studies in which mechanics and lung volumes were measured together did not always detect a correlation between compliance and recruitment at different levels of PEEP.<sup>47,64</sup> Compliance may actually remain constant as PEEP is increased, even in the presence of significant alveolar recruitment.<sup>26,47,65</sup> This effect may be due to the fact that PEEP recruitment may occur simultaneously with overdistention of previously open alveoli. Thus, the measured value of compliance could be an expression of the balance between these two phenomena. In summary, static compliance directly reflects alveolar recruitment when PEEP is stable. When PEEP is raised, a lack of increase in the value of compliance should not rule out the presence of alveolar recruitment, whereas its decrease should warn that alveolar overdistention may be occurring.

#### Lung Volume Measurements

If optimization of alveolar recruitment is the goal of mechanical ventilation, verification through direct measurement of lung volumes is reasonable. Recruitment or derecruitment can be identified as the change in EELV when PEEP is constant.<sup>66</sup> If PEEP is not constant, recruitment can be quantified as a change in the volumes present in the lungs at a fixed, predetermined alveolar pressure.<sup>26,27,47,56,64,66</sup> This measurement can be made by examining changes in exhaled volume and assuming that the functional residual capacity (FRC) remains constant.<sup>26</sup> However, the FRC is likely affected by the previous ventilatory history. Thus, a direct determination of EELV and FRC is more desirable to estimate alveolar recruitment. Helium dilution, nitrogen washout,<sup>67,68</sup> and chest CT have been used to quantify FRC, but the use of these tools in ventilated patients has been so far confined to research. Clinical monitors of FRC could become available in the future.

#### Stress Index

During the delivery of a TV with constant flow pattern, the airway pressure-time tracing should be linear. However, deviations from linearity, with convexities or concavities

of the pressure-time tracing, are often observed and are related to alveolar recruitment and overdistention within the TV. The degree and the direction of deviation from linearity can be expressed mathematically by a variable called the stress index. CT scans in animals confirm that the value of the stress index is 1 in the absence of both recruitment and overdistention.<sup>69</sup> In animals, a stress index near 1 minimized pulmonary inflammatory cytokine production,<sup>70</sup> suggesting that using this index to target mechanical ventilation settings may minimize VILI. In a recent study, the stress index detected alveolar overdistention in ARDS patients ventilated according to a lung-protective strategy.<sup>71</sup> Setting PEEP with the aim of optimizing the stress index resulted in decreased plasma cytokine levels. This suggests that the stress index could be a useful tool to monitor alveolar derecruitment and overdistention and that it could help optimize mechanical ventilation settings. The stress index has the advantage of being measured on a breath-to-breath basis by standard ventilator monitoring equipment. However, it requires constant flow inflation and minimal activity of the respiratory muscles during measurement, although muscle relaxation is not necessary.<sup>71</sup>

#### **INSPIRATORY RESISTANCE**

Resistance is relatively easy to monitor through the rapid airway occlusion technique.<sup>2</sup> However, the value of this technique is limited by the fact that it only measures the resistance at the end of inspiration and neglects the expiratory component. Because of the presence of turbulent flow in the airways, the values of resistance change with inspiratory flow, and measurements obtained at different times can be compared only if the same inspiratory pattern and flows are used. The contribution of artificial airways to total resistance should be accounted for when comparing values obtained from different patients.

Measuring inspiratory resistance helps in diagnosing the presence of obstructive disease and in monitoring the response to therapeutic agents such as bronchodilators.<sup>72</sup> Respiratory resistance is typically elevated in patients with asthma and chronic obstructive pulmonary disease in whom both the airways and the maldistributive components of resistance are higher than normal.<sup>73,74</sup> Although elevated inspiratory resistance is not the hallmark of ARDS, inspiratory resistance is increased in these patients.<sup>75</sup> This phenomenon can be due to increased airway hyperreactivity related to local inflammation and to time constant inequalities, but it can also be related to the loss of lung volume.<sup>3,75</sup>

#### PROGNOSTIC VALUE OF PULMONARY FUNCTION VARIABLES

Pulmonary function variables often are used clinically as indexes of severity and are thought to have prognostic value. Although this assumption is physiologically reasonable, its validity is largely undemonstrated. Functional variables such as the Pao<sub>2</sub>/Fio<sub>2</sub> ratio and static respiratory compliance were incorporated in the lung injury score (LIS) by Murray and colleagues.<sup>76</sup> However, the LIS was not confirmed to predict outcome of ARDS,<sup>77</sup> and when studied alone, neither the  $Pao_2/Fio_2$  ratio nor compliance was an independent predictor of mortality.<sup>78</sup> Interesting results from observational studies suggest that the efficiency of CO<sub>2</sub> elimination might better correlate with outcomes than oxygenation. In fact, alveolar dead space was an independent predictor of mortality in a group of ARDS patients, whereas oxygenation was not.<sup>79</sup>

Patients with late-stage ARDS have decreased compliance compared with the early-stage disease,<sup>80</sup> likely because of fibrosis and tissue remodeling. Early studies using VP curves suggest that respiratory mechanics may help detect the presence of fibrosis in late stages of ARDS.<sup>49</sup> The connection between low compliance and the extent of tissue remodeling and fibrosis is also suggested by a study in ARDS patients showing that compliance was related to markers of collagen turnover and surfactant degradation.<sup>81</sup>

Recent evidence suggests that chest CT may have a role in outcome prediction and in risk assessment. In contrast to oxygenation, the amount of recruitable lung tissue independently predicted mortality in a group of ARDS patients.<sup>28</sup> Further, there is a correlation among mortality, high alveolar recruitability, and a diffuse pattern of opacities on CT scan.<sup>82</sup> This correlation among CT appearance, recruitment, and outcome might reflect a relationship between alveolar recruitment and a significant amount of lung edema. In fact, the amount of pulmonary edema is probably associated with mortality.<sup>83,84</sup>

#### CONCLUSION

Despite abundant research on pulmonary pathophysiology, functional lung monitoring has questionable prognostic value and is of limited use in daily clinical practice. However, awareness of the outcome implications of mechanical ventilation has increased attention on measurements of lung function and particularly of respiratory mechanics. Bedside monitoring of static compliance and Pplat should be used routinely to detect the presence of alveolar overdistention and at least qualitatively assess the risk for VILI. Multiple techniques allow the detection of alveolar recruitment, although it is still unclear how to quantify the level of PEEP needed for each patient. Other techniques for the assessment of alveolar recruitment, such as CT scan and stress index, are available and likely will find more use in the future.

#### AUTHOR'S RECOMMENDATIONS

- Monitoring respiratory function is essential to identify patients' responses to ventilatory support and to limit iatrogenic injury from mechanical ventilation.
- The essential mechanical characteristics of the respiratory system are compliance, resistance, and intrinsic PEEP, all of which can be measured using standard ventilator monitors and simple bedside maneuvers. These variables allow detecting changes in respiratory status and responses to therapeutic maneuvers.

- Patients with acute respiratory failure are at risk for excessive alveolar strain. Monitoring and limitation of plateau alveolar pressures decrease alveolar strain, although they may not guarantee its complete avoidance.
- Esophageal pressure monitoring can help assess the extent of alveolar strain, particularly in patients with abnormal chest wall mechanics.
- PEEP is clinically titrated by measuring its effects on gas exchange and on hemodynamics. However, direct measurement of alveolar recruitment assumes a high priority if the goal of mechanical ventilation is to avoid alveolar instability. Quantitative CT analysis of the chest is probably the best tool to evaluate alveolar recruitment, although practical issues limit its use. Other tools, such as VP curves, are available at the bedside and are helpful in detecting the presence of recruitable lung tissue. However, their validity in the determination of the optimal PEEP level is still undetermined.
- The relevance of respiratory function variables in predicting outcomes is uncertain in acute respiratory failure.

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2

# What Are the Indications for Intubation in the Critically III Patient?

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The specific indications for endotracheal intubation are difficult to define. Although a seasoned practitioner could easily identify a patient who requires intubation, it is challenging to explain the exact parameters used for making such a decision. To date, there have been no significant studies evaluating the specific indications or guidelines for endotracheal intubation. These indications are increasingly more complicated in an era of advanced technology in oxygen delivery systems and noninvasive forms of ventilation.

Currently accepted indications can be divided into three basic groups: hypoxic respiratory failure, hypercarbic ventilatory failure (including cardiac arrest), and impaired consciousness and airway protection. These general indications are all based on accepted practice, with few or no data available to support specific guidelines. Perhaps Marino stated it best when he commented that, "...the indication for intubation and mechanical ventilation is thinking of it."<sup>1</sup>

This chapter briefly discusses the evaluation of patients with hypoxic respiratory failure and hypercarbic ventilatory failure leading to the decision for endotracheal intubation. Additionally, information is presented on assessing patients with impaired consciousness and inability to protect their airway as well as other secondary indications for endotracheal intubation.

#### HYPOXIC RESPIRATORY FAILURE

Acute hypoxic respiratory failure results from inadequate exchange of oxygen across the pulmonary alveolarcapillary membrane. This impairment leads to a decrease in arterial oxygen tension (hypoxemia) and insufficient delivery of oxygen to tissues and cells (hypoxia). In medical literature, this type of failure is often described as type I failure, that is, hypoxemia without hypercarbia.

Oxygen delivery is the product of arterial oxygen content and cardiac output. Therefore, hypoxia can also occur secondary to decreased cardiac output, anemia, or abnormal oxygen-hemoglobin binding affinity.

The diagnosis of hypoxemia requires obtaining an arterial blood gas and is commonly defined as a  $Pao_2$  of less than 60 mm Hg. Pulse oximetry is commonly used for assessing hypoxemia. However, this modality measures

the saturation of hemoglobin and not Pao2, reflecting oxygen dissolved in the blood or oxygen content, which includes both bound and unbound O2. Thus, a patient with severe anemia may have a normal Pao<sub>2</sub> but a low O<sub>2</sub> content. Low pulse oximetry values coincide with significant hypoxemia, but normal oxygen saturation does not exclude hypoxemia, especially in patients receiving a high FIO2. Normal PaO2 levels are 80 to 100 mm Hg in a healthy patient breathing room air and can exceed 500 mm Hg in a patient breathing 100% oxygen. Pulse oximetry values may remain normal until Pao2 decreases to less than 60 mm Hg. For this reason, the alveolararterial oxygen gradient should be evaluated in patients receiving a high FIO<sub>2</sub>. A widening alveolar-arterial oxygen gradient is a sign of worsening hypoxemia. Pulse oximetry may be unreliable in cases of severe anemia, carbon monoxide poisoning, methemoglobinemia, or peripheral vasoconstriction.

The symptoms and signs of hypoxia are nonspecific and are noted in Table 2-1. Tachypnea and dyspnea may or may not be present depending on the etiology of the hypoxia.

Many disease processes can lead to hypoxemia, and the most common causes of hypoxemia respiratory failure and their pathophysiologies are described in Table 2-2.

The initial treatment of all causes of hypoxemia is the same: ensure a patent airway and adequate ventilation, and provide supplemental oxygen. A Pao<sub>2</sub> value of 50 to 60 mm Hg or an arterial oxygen saturation of 88% to 90% is often suggested as a minimal accepted value, although specific patients (i.e., patients with myocardial ischemia and those in shock) may warrant other cutoff values for escalation of therapy. Except in patients with severe shunt, hypoxemia will improve with delivery of high FIO<sub>2</sub>. Initial treatment starts with low-flow nasal cannula and escalates to a 100% non-rebreather mask or high-flow O<sub>2</sub> therapy. If hypoxemia fails to reverse with supplemental oxygen and the patient has symptoms, noninvasive assisted ventilation with 100% O<sub>2</sub> may be attempted. Certain specific contraindications, described elsewhere, preclude this approach. If a patient is unable to maintain a minimal oxygen saturation while ventilating with 100% FIO2, endotracheal intubation and mechanical ventilation will be required to improve this value.

#### Table 2-1 Symptoms and Signs of Hypoxia

#### SYMPTOMS

Headache Irritability Confusion Exhaustion

#### SIGNS

Agitation Lethargy Somnolence Coma Central cyanosis Seizures

#### Table 2-2 Causes of Hypoxemic Respiratory Failure

#### INTRINSIC LUNG DISEASE

Atelectasis Pneumonia Lung consolidation Noncardiogenic pulmonary edema Transfusion-related acute lung injury (TRALI) ARDS

#### CARDIAC DISORDERS

Cardiogenic pulmonary edema

#### VASCULAR DISORDERS

Pulmonary embolism

TOXINS

Carbon monoxide

#### HYPERCARBIC VENTILATORY FAILURE

Acute ventilatory failure results from inadequate removal of gas from distal alveoli. This alveolar hypoventilation results in subsequent hypercarbia and respiratory acidosis. Mild ventilatory failure can exist alone or, when impairment is more severe, may be associated with hypoxemia. Ventilatory failure can result from a primary lung process or can occur secondary to disorders in the cardiac, neurologic, metabolic, or other systems. When associated with hypoxemia, this type of failure may be described in the literature as type II respiratory failure.

The diagnosis of hypercarbia is best made by obtaining an arterial blood gas. Hypercarbia is commonly defined as a Paco<sub>2</sub> of more than 45. Unlike pulse oximetry for detecting hypoxemia, bedside monitors for detecting hypercarbia are not routinely available. End-tidal CO<sub>2</sub> monitoring, now standard in intraoperative care, is not currently available at many institutions. This lack of bedside monitoring is particularly significant because the most common form of respiratory monitoring is normal pulse oximetry. Normal oxygen saturation can be found in the presence of significant hypoventilation, providing false confidence. It also is important to follow  $Paco_2$  values over time because changes in this parameter may provide information that is more important than the absolute value.

The signs and symptoms of hypercarbia depend on the patient's baseline Paco<sub>2</sub>, the absolute value of Paco<sub>2</sub>, and the rate of change. Chronic hypercapnia may be well tolerated. Eliciting a history of chronic CO<sub>2</sub> retention and performing careful serial evaluations of arterial pH are essential because hypercarbia with a near-normal pH is a sign of chronic compensation and often does not reflect an acute disorder. The symptoms and signs of hypercarbia, like those seen in patients suffering from hypoxia, are nonspecific and are noted in Table 2-3. These all may indicate respiratory fatigue and suggest that the patient soon may be unable to achieve the minute ventilation required to maintain normocarbia.

As stated previously, the etiology of hypercarbic ventilatory failure can be a primary lung process or result from a nonpulmonary process. For the purposes of this chapter, respiratory and cardiac arrest are included as ventilatory failure. The most common causes of ventilatory failure are listed in Table 2-4.

As in hypoxic respiratory failure, the initial treatment of hypercarbic ventilatory failure is to ensure a patent airway and provide supplemental oxygen to treat associated hypoxemia. However, although the treatment for all causes of hypoxemic respiratory failure is to increase the oxygen content in the blood, the approach to hypercarbic ventilatory failure depends on etiology. In cases in which ventilatory failure is not the primary disorder, support of ventilation may be indicated, but definitive therapy should be directed at the underlying cause. For example, a narcotic overdose is treated with reversal agents, whereas ventilatory failure secondary to cardiogenic shock can be treated with inotropic agents. Describing the specific treatments for all causes of ventilatory failure is beyond the scope of this chapter.

When specific medical therapies are not available or not successful in increasing ventilation, or when ventilatory failure is the primary problem, treatment is

#### Table 2-3 Symptoms and Signs of Hypercarbia

#### SYMPTOMS

Dyspnea Headache Confusion Exhaustion

#### SIGNS

Increased work of breathing Accessory respiratory muscle use Tachypnea Shallow or small tidal volume breathing Lethargy Somnolence Coma Flapping tremor Seizures Cardiovascular collapse

#### Table 2-4 Causes of Hypercarbic Ventilatory Failure

#### INTRINSIC LUNG DISEASES

Chronic obstructive pulmonary disease Asthma

#### ANATOMIC DISORDERS

Sleep apnea Airway obstruction

#### **NEUROLOGIC DISORDERS**

Brainstem or medullary stroke Opiate or sedative overdose Obesity-hypoventilation syndrome Myasthenia gravis, Guillain-Barré syndrome Critical illness myopathy or polyneuropathy

#### CARDIAC DISORDERS

Cardiac arrest Cardiogenic shock Heart failure

VASCULAR DISORDERS

Pulmonary embolism

#### METABOLIC DISORDERS

Hypomagnesemia Hypophosphatemia

concentrated on providing a means to increase minute ventilation. This most often is provided through noninvasive positive-pressure ventilation or endotracheal intubation and mechanical ventilation. Therapy is often initiated when hypercapnia is associated with worsening hypoxemia or when the patient experiences cardiac or neurologic failure secondary to effects of elevated CO<sub>2</sub>. The assisted ventilation provided from noninvasive positive-pressure therapy can provide additional time for treatment of underlying medical conditions (i.e., steroids, bronchodilators, diuretics, nitrates). This approach to chronic obstructive pulmonary disease (COPD) and congestive heart failure (CHF) exacerbations is well supported by evidence. The specific indications for noninvasive positive-pressure ventilation and a discussion of its use are provided in Chapter 4. Ventilatory failure despite optimal medical management and noninvasive ventilation is a clear indication for endotracheal intubation and mechanical ventilation.

In addition to instruments and tests available to detect worsening ventilatory failure, it is essential to evaluate the patient's clinical condition for signs of fatigue and impending respiratory collapse on a continuous basis. Clinical assessment, combined with medical experience, is the most important tool for identifying patients requiring early intubation. Signs of impending collapse often include worsening dyspnea, tachypnea, use of accessory breathing muscles, and low tidal volume ventilation. Planned endotracheal intubation in a controlled setting is always preferable to emergent airway management.

## IMPAIRED CONSCIOUSNESS AND AIRWAY PROTECTION

Impaired consciousness with inability to protect the airway is another often-described indication for endotracheal intubation. Neurologic indications for endotracheal intubation are important because intubation for impaired consciousness and presumed airway protection may account for 20% of patients intubated in the intensive care unit (ICU).<sup>2</sup> The trauma and neurologic literature often cites a Glasgow Coma Scale (GCS) value of 8 or less as a specific indicator for endotracheal intubation.<sup>3–5</sup> GCS criterion for intubation is not based on concerns for respiratory distress but rather on the concern for development of worsening consciousness, hypoventilation, and airway protection. This arises from a retrospective analysis of the National Traumatic Coma Data Bank that demonstrates a greater risk for aspiration and worse clinical outcome in comatose patients (GCS < 8) not endotracheally intubated.<sup>6</sup> Several subsequent studies support this conclusion.<sup>7</sup> Severe brain injury is associated with decreased respiratory drive and hypoventilation, and patients likewise often have decreased muscle tone. This may increase the risk for airway obstruction and a failure to clear secretions.<sup>8–10</sup> In addition, patients with traumatic brain injury and subarachnoid hemorrhage have been shown to be at increased risk for developing pulmonary edema. Indeed, as many as 30% of these patients may progress to severe acute lung injury or acute respiratory distress syndrome.<sup>11,12</sup>

Although intubation for a depressed level of consciousness has become the standard of care, no definitive controlled studies are available on the subject. Recent studies dispute the requirement for intubation based on neurologic status alone. Coplin and colleagues studied criteria used for extubation and found that neither level of consciousness nor the presence of a gag or cough reflex predicted success.<sup>13</sup> In this study, 80% of patients with a GCS value of 8 or less and 90% of patients with a GCS value of 4 or less were successfully extubated. This also was the case for 88% of patients with an absent or weak gag reflex and 82% of patients with an absent or weak cough. Additionally, studies have shown that the risk for ventilator-induced lung injury is increased in patients with traumatic brain injury and subarachnoid hemorrhage, and many of these patients develop ventilatorassociated pneumonia. This may lead to a prolonged hospital stay and increased mortality.<sup>14–17</sup> Endotracheal intubation and mechanical ventilation also are associated with increased ICU delirium.

At one time, therapeutic hyperventilation was considered an indication for endotracheal intubation and mechanical ventilation in patients with traumatic brain injury. Hyperventilation lowers intracranial pressure (ICP) by inducing cerebral vasoconstriction and decreasing cerebral blood volume. However, the decrease in blood flow also can lead to cerebral ischemia, especially because injured brain tissue is more susceptible to ischemic insult. Because of this risk and a lack of clear benefit, current guidelines recommend against prophylactic or prolonged use of hyperventilation.<sup>18–21</sup> Succinct, controlled hyperventilation still may be indicated in cases of acute neurologic deterioration secondary to herniation or sudden ICP elevation.<sup>21</sup>

Apart from cases of reduced consciousness, endotracheal intubation for airway protection also may be appropriate for patients with traumatic injury or swelling of the face, neck, or airway who are at risk for airway obstruction.

#### SECONDARY INDICATIONS

A few special considerations for endotracheal intubation warrant brief discussion:

- 1. Patients with significant aspiration of particulate matter may be candidates for brief endotracheal intubation to facilitate bronchoscopy and lavage.
- 2. Neurologically or traumatically injured patients may warrant deep sedation and intubation in order to perform necessary imaging tests or diagnostic and therapeutic procedures.
- 3. Patients with status epilepticus may require deep sedation or paralysis for treatment of seizures.

#### CONCLUSION

The goal of endotracheal intubation and mechanical ventilation is to provide the delivery of the oxygen and ventilation that is primary to a patient's survival. The decision to proceed with this invasive procedure requires an understanding of the pathologic and physiologic disorders that necessitate its use. Although much information is available on the study of respiratory pathology and physiology and on the delivery and modes of mechanical ventilation, little has been written about the specific indicators for endotracheal intubation. Because of the severity of a patient's clinical condition and difficulty with study design, strong evidence and randomized controlled studies are not available on the subject. Until better clinical trials are available, one must use available clinical information in combination with specific medical knowledge and experience in making this decision.

#### **AUTHORS' RECOMMENDATIONS**

- Indications for endotracheal intubation and mechanical ventilation are commonly divided into hypoxic respiratory failure, hypercarbic ventilatory failure, and impaired consciousness and airway protection.
- Indications are all based on accepted practice, with few or no data available to support specific guidelines.
- Clinical assessment, combined with medical experience, is the most important tool for identifying patients requiring intubation.
- Arterial blood gas and PacO<sub>2</sub> measurements are necessary to evaluate hypercarbic ventilatory failure because pulse oximetry values can remain near normal until ventilatory collapse.

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3

# How Should Exacerbations of COPD Be Managed in the Intensive Care Unit?

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#### COPD PREVALENCE

It is estimated that 80 million people worldwide and up to 10% of the U.S. population suffer from chronic obstructive pulmonary disease (COPD).<sup>1</sup> It is the fourth leading cause of death and chronic morbidity in the United States and accounted for 5% of total deaths worldwide in 2002.<sup>2</sup> COPD is the only leading cause of death that is rising, and it is predicted to be the third leading cause of mortality by 2030.<sup>3</sup>

Acute episodes of respiratory failure in patients with COPD are estimated to account for between 5% and 10% of acute emergency hospital admissions. Failure of firstline medical treatment is a common source of intensive care unit (ICU) referral, accounting for 2% to 3% of nonsurgical ICU admissions.<sup>4</sup> Data reported in 1996 on 1016 patients who were hospitalized for acute exacerbations, half of whom required intensive care, demonstrated an in-hospital mortality rate of 11% and 6-month and 1-year mortality rates of 33% and 43%, respectively. Those who survived the first hospitalization had a 50% rate of rehospitalization within 6 months after discharge.<sup>5</sup>

#### **RESPIRATORY FAILURE**

The pathophysiology of acute respiratory failure in COPD is incompletely understood but may be precipitated by any condition that increases the work of breathing or, less commonly, decreases the respiratory drive (Table 3-1). Respiratory failure may be predominantly hypoxic (type 1) or hypercapnic (type 2). The mechanism of hypercapnia in COPD is unclear, and it is no longer believed to reflect problems with respiratory drive, as suggested by the concept of "pink puffers/blue bloaters." Gas exchange abnormalities appear to result predominantly from ventilation-perfusion mismatch due to airflow limitation. Progressive respiratory failure reflects a combination of severe airflow obstruction, hyperinflation, and respiratory muscle fatigue. Regardless of the cause, hypercapnia and the need to assist ventilation identify patients with high initial mortality rates (up to 27%) and significant 12-month mortality rates (up to 40%).<sup>6-10</sup>

#### CLINICAL PRECIPITANTS OF RESPIRATORY FAILURE

Viral and bacterial infections account for between 50% and 70% of cases of acute respiratory failure in COPD.<sup>11,12</sup> Numerous viral and bacterial agents have been implicated, but rhinoviruses, respiratory syncytial virus, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae* are the frequent pathogens.<sup>12–15</sup> *Pseudomonas aeruginosa*, Enterobacteriaceae, and *Stenotrophomonas* species are also isolated, particularly from patients with severe COPD and those requiring mechanical ventilation.<sup>16</sup> The prevalence of atypical organisms, such as *Mycoplasma* and *Chlamydia* species, is less well defined.

Up to a further 10% of cases are caused by environmental pollution, including airway irritants such as smoke or fumes. In the remainder of cases, the cause is not always clear. Medical conditions can mimic or cause COPD exacerbations. Patients with COPD have higher rates of comorbid illnesses, in part reflecting exposure to cigarette smoke (Table 3-2). This is supported by results from the Towards a Revolution in COPD Health (TORCH) trial,<sup>17</sup> in which only 35% of deaths were adjudicated as due to pulmonary causes, with cardiovascular disease being the second major cause of death (27%) and cancer the third (21%).

Pulmonary embolism can be an occult cause of acute respiratory failure in COPD. Tillie-Leblond and colleagues, in a prospective cohort study, reported that 22% of patients with a severe COPD exacerbation *of unknown etiology* had coexisting pulmonary emboli.<sup>18</sup> Rutschmann and coworkers studied all patients presenting to the emergency room with COPD exacerbations and reported that the overall incidence of clinically unsuspected pulmonary embolism was 1.3%.<sup>19</sup>

#### MANAGEMENT OF COPD

Treatment guidelines for management of acute exacerbations of COPD requiring admission to the ICU are broadly similar to those principles employed in patients without respiratory failure, although significantly more attention

#### Table 3-1 Physiologic Factors Contributing to Respiratory Failure

Increased resistive load

- Widespread airflow obstruction (bronchospasm) Decreased respiratory system compliance
- High lung volume (hyperinflation)
- Dynamic hyperinflation (air trapping)
- Shortened expiratory time with prolonged expiration Reduced power of respiratory pump (fatigue)
  - Impaired mechanical efficiency
  - Effects of acidosis and hypoxemia

Impaired drive

- Sleep deprivation
- CO<sub>2</sub> narcosis

#### Table 3-2 Differential Diagnosis: Nonrespiratory Causes of Respiratory Failure in Patients with COPD

- Cardiovascular disease: myocardial ischemia, heart failure, pulmonary embolism
- Central nervous system depression: head trauma or injudicious use of sedatives, opioids, tranquilizers, or oxygen (O<sub>2</sub>)
- Endocrine and metabolic disorders: myxedema or metabolic alkalosis
- Thoracic abnormalities: chest trauma, pneumothorax, or thoracic or abdominal surgery

must be paid to safe and appropriate gas exchange. Addressing the issue of poor respiratory mechanics due to dynamic hyperinflation, loss of alveolar volume, and impaired ventilation is fundamental to COPD management. Clinically compensated chronic respiratory failure can rapidly become decompensated respiratory failure because of poor chest wall mechanics, suboptimal respiratory muscle function, malnutrition, obesity, and myopathy. Reducing the work of breathing using noninvasive positive-pressure ventilation (NIPPV) to improve oxygenation, rest muscles, and manage hyperinflation is key to the management of COPD.

Indications for referral to ICU include dyspnea that does not respond to emergency treatment, changes in mental status (confusion, drowsiness, or coma), persistent or worsening hypoxemia or severe or worsening hypercapnia, acidosis (pH < 7.2), and hemodynamic instability.<sup>3</sup>

#### Corticosteroids

For patients hospitalized with acute exacerbations of COPD, systemic corticosteroids administered for up to 2 weeks are clinically useful.<sup>20</sup> Treatment of an exacerbation of COPD with oral or parenteral corticosteroids significantly reduces treatment failure and the need for additional medical treatment. Steroids increase the rate of improvement in lung function and dyspnea over the first 72 hours.<sup>21</sup> They also reduce the length of hospital stay.<sup>22</sup>

The optimal dose and need for tapering, route of administration, and length of treatment are uncertain.

Intravenous corticosteroids should be given to patients who present with a severe exacerbation of COPD, in particular all those requiring ICU admission, and to patients who may have impaired absorption due to splanchnic hypoperfusion (e.g., patients in shock or congestive heart failure). Nevertheless, if tolerated, oral therapy is equally effective as intravenous administration in most patients.<sup>23</sup> Nebulized steroids are superior to placebo but not better than parenteral therapy.<sup>24</sup>

Among the widely known side effects of corticosteroids, hyperglycemia occurs in about 15%.<sup>28</sup> There appears to be no benefit to prolonged treatment with steroids beyond 2 weeks.<sup>25</sup>

#### **Bronchodilators**

Inhaled short-acting  $\beta$ -adrenergic agonists are the mainstay of therapy for an acute exacerbation of COPD because of their rapid onset of action and efficacy in producing bronchodilation.<sup>20</sup> Parenteral or subcutaneous injection of short-acting  $\beta$ -adrenergic agonists is reserved for situations in which inhaled administration is not possible. Parenteral use of these agents results in greater inotropic and chronotropic side effects, which may precipitate myocardial ischemia or arrhythmias and cannot be recommended for most patients.

Anticholinergic bronchodilators such as ipratropium are equally efficacious,<sup>26</sup> and it has been reported that combination therapy with inhaled  $\beta$ -adrenergic agonists provides better bronchodilation than either alone.<sup>27</sup> This has not, however, been replicated in all studies.<sup>28</sup>

Bronchodilators may be administered through a nebulizer or a metered-dose inhaler (MDI) with a spacer device. Neither method has been shown to be superior, although physicians tend to favor the nebulized route because of ease of administration.

The use of methylxanthines such as theophylline in the treatment of COPD remains controversial. A meta-analysis of four randomized controlled trials by Barr and colleagues failed to demonstrate the efficacy of theophylline in acute COPD.<sup>29</sup> Indeed, methylxanthines confer no additional benefit over and above conventional therapy with corticosteroids and bronchodilators, but are associated with significant side effects. These include nausea and vomiting, tremor, palpitations, and arrhythmias.

#### Antibiotics

The role of routine antimicrobials in acute exacerbations of COPD is also controversial. In patients with severe exacerbations requiring mechanical ventilation, antibiotic therapy is beneficial and has been shown to significantly decrease mortality (4% versus 22%), the need for additional courses of antibiotics, the duration of mechanical ventilation, and the duration of hospital stay.<sup>30</sup>

If administered, antimicrobials should be bacteriocidal  $\beta$ -lactamase–producing organisms. Although the choice is determined by local infectious and antimicrobial resistance patterns, amoxicillin and clavulanic acid, second-generation cephalosporins, or macrolides are all reasonable first-line agents. Three to 7 days of treatment is recommended.<sup>31</sup> Broad-spectrum antibiotics such as fluoroquinolones and

 $\beta$ -lactam with antipseudomonal activity should be used in patients at risk for resistant gram-negative infections such as *Pseudomonas* (i.e., recent hospitalization, previous colonization, previous severe exacerbation, or more than four exacerbations per year).

Although antibiotic treatment is recommended in patients with severe exacerbation of COPD, a bacterial source is not always present. Procalcitonin, a small protein that is normally undetectable in plasma, increases markedly in bacterial infections, but is not increased by inflammation because of autoimmunity or viral infection. Preliminary, single-center studies have provided encouraging evidence for the use of procalcitonin to predict the need for antibiotics in exacerbations.<sup>14</sup> Procalcitoninguided antibiotic treatment could be helpful in reducing antibiotic use in these patients without changing clinical success rates, although further large-scale studies of this and other inflammatory markers (such as C-reactive protein) are required.

#### Oxygen Therapy

Adequate oxygenation can be achieved in most patients with acute exacerbations of COPD. Ventilation-perfusion mismatch is usually improved by 24% to 28% oxygen. There appears to be a tendency to develop  $CO_2$  retention with high inspired oxygen tensions, although this depends on the mechanism and degree of injury. Oxygen therapy should never be withheld based on concern of the development of CO<sub>2</sub> narcosis. The mechanism of oxygeninduced hypercarbia is likely to reflect increased physiologic dead space and the Haldane effect rather than any effect on hypoxic drive for ventilation. Nevertheless, controlled oxygen therapy is recommended in the critical care environment, based on sequential blood gas analysis. Hence, fixed-dose devices, such as venture masks or highflow systems, are recommended, rather than variabledose devices, such as nasal cannulas.

#### Assisted Ventilation

Recognition of the need for assisted ventilation is often a clinical judgment made as the patient fails to improve on initial treatment. Studies have shown that pH and degree of hypercapnia are better predictors of need for mechanical ventilation than hypoxia.<sup>32</sup> NIPPV is indicated after initial treatment if the pH remains less than 7.32 and should be considered before intubation and invasive mechanical ventilation. There are a number of relative contraindications to NIPPV (Table 3-3), although judgment of a patient's suitability should be made by the bed-side clinician, and there are no absolute contraindications.

A number of randomized controlled trials have validated use of NIPPV in the setting of acute hypercapnic respiratory failure in COPD,<sup>33</sup> and indeed several studies have demonstrated the superiority of NIPPV over tracheal intubation and mechanical ventilation. NIPPV is associated with reduction in intubation rates, nosocomial complications,<sup>34</sup> and mortality.<sup>33,35,36</sup> NIPPV may shorten the stay in the ICU. In addition, use of NIPPV has certainly improved the care of many COPD patients and has allowed some patients to undergo a more intense level of treatment than perhaps may have been previously available to them.

#### Table 3-3 Contraindications to Noninvasive Ventilation

- · Respiratory arrest
- Impaired level of consciousness (Glasgow Coma Score < 8)
- Cardiovascular collapse requiring vasopressors
- Profound hypoxemia
- Vomiting or very high aspiration risk due to excessive secretions
- Uncooperative patient
- Extreme obesity (body mass index  $> 50 \text{ kg/m}^2$ )
- Recent facial or gastrointestinal surgery
- Burns

NIPPV fails in up to 20% to 30% of patients, some occurring late in the admission.<sup>35,37</sup> These failures can reflect patient intolerance, inadequate augmentation of tidal volume, and problems with ventilation triggering. The prognosis in the late failure cohort is poor.<sup>37</sup>

The response to treatment needs to be closely monitored. This is primarily done by monitoring arterial blood gases, respiratory rate, hemodynamics, and overall degree of respiratory distress. Those who respond to NIPPV within 1 to 4 hours are consistently shown to have better outcomes.<sup>38</sup> An initial reduction in respiratory rate is generally a good indicator of a positive response to NIPPV. Failure of NIPPV, contraindications, or imminent cardiorespiratory arrest should prompt endotracheal intubation and mechanical ventilation. Ideally, this should be performed in the controlled setting of the ICU because intubation can precipitate cardiovascular collapse.<sup>4</sup>

Although the optimal method of mechanical ventilation of the COPD patient is unknown (volume-targetedpressure variable, pressure-targeted-volume variable, and dual control modes all have their adherents), tremendous care must be taken to balance the treatment of hypoxemia, unloading of the respiratory muscles, and autopositive end-expiratory pressure (auto-PEEP). This usually involves relatively low levels of PEEP, low respiratory rates, and long expiratory times. If volume-controlled modes are used, careful titration of peak flow is required to balance patient-ventilator synchrony with high peak airway pressures and pressure cycling. Pressure-controlled and pressure-support modes are associated with reduced incidence of inspiratory dyssynchrony, but expiratory cycling must be carefully titrated (particularly in pressure support) to ensure adequate tidal ventilation and prevent worsening of hyperinflation. Expiratory dyssynchrony is problematic in pressure-targeted modes. Extreme care should be taken with the use of PEEP and the respiratory rate because dynamic hyperinflation may result from gas trapping (auto-PEEP) and lead to a significant drop in right ventricular preload and increased right ventricular afterload. The result may be significant hypotension and worsened ventilation-perfusion mismatch.<sup>3</sup>

The ventilation strategy should be targeted at normalization of blood gases for that particular patient. In other words, if the patient's normal  $Paco_2$  is 60 mm Hg, this should be the target level. If  $CO_2$  levels below this are achieved, significant metabolic alkalosis will occur, and this is counterproductive.

Weaning can pose problems in ventilated COPD patients, with 20% to 30% of those meeting the traditional extubation criteria ( $F_{10_2} < 0.4$  and tidal volume > 10 mL/kg) failing trial of weaning.<sup>4</sup> Expiratory flow limitation has been proposed as a predictor of successful extubation, but more data are required.<sup>40</sup> Scala and associates randomly assigned patients with COPD who were intubated for 48 hours to extubation and NIPPV or to continued invasive ventilation and conventional discontinuation after an unsuccessful initial spontaneous-breathing trial.<sup>35</sup> The study demonstrated improved outcomes as measured by the percentage of patients in whom assisted ventilation could be discontinued, the duration of assisted ventilation, the length of stay in the ICU, and the incidence of ventilator-associated pneumonia. Therefore, early extubation directly to NIPPV should be considered in patients with exacerbations of COPD.

#### PROGNOSIS AND OUTCOMES

Despite reasonable survival to hospital discharge, the decision to admit a patient to the ICU in advanced cases is often difficult, and there are both national and international variations in practice. One has to take into account expected prognosis, comorbidities, and estimated quality of life after the acute event. Factors influencing the decision to ventilate include cultural attitudes toward disability, perceived impact of treatment, financial resources, local medical practice, and patient wishes.<sup>3</sup>

The short-term survival rate after invasive mechanical ventilation ranges from 63% to 86%, which is better than would be expected in unplanned medical admissions.<sup>8,41</sup> Survival after mechanical ventilation has been shown to be improved in the absence of a major precipitating cause for acute deterioration; perhaps because shorter periods of assisted ventilation are required, there are fewer iatrogenic complications.<sup>9</sup>

Identifying patients most likely to derive benefit from aggressive management remains problematic. Long-term survival rates are not as encouraging as survival to discharge figures. Rates of 52%, 42%, and 37% at 1, 2, and 3 years, respectively, were reported in one study from the United Kingdom,<sup>10</sup> and similar numbers have been reported from other centers. Factors associated with poor prognosis are low physiologic reserve, increasing severity of illness, and multiorgan dysfunction (Table 3-4).

 Table
 3-4
 Poor Prognostic Indicators Associated

 with Severe Exacerbation of COPD
 Image: Comparison of Copp

- · Increased age; presence of severe respiratory disease
- Increased length of stay in hospital before intensive care unit admission
- · Cardiopulmonary resuscitation within 24 hr before admission
- Requirement for intubation
- Severe hypoxemia (Pao<sub>2</sub>/Fio<sub>2</sub> ratio < 100)
- Hypercapnia
- Hypoalbuminemia
- Low body mass index (<20 kg/m<sup>2</sup>)
- Multiorgan failure

Although all these factors have been associated with increased in-hospital mortality,<sup>7</sup> there is currently no reliable or definitive method for identifying patients at high risk for inpatient or 6-month mortality. Therefore, these parameters should not influence decisions about instituting, continuing, or withdrawing life-sustaining treatment.

A study of 166 COPD patients requiring mechanical ventilation found that absence of comorbid condition more than halved the in-hospital mortality rate (28% versus 12%; adjusted relative risk, 16%; P < .05).<sup>41</sup> Adverse outcomes were associated with mechanical ventilation for more than 72 hours (37% versus 16%), no previous episodes of mechanical ventilation (33% versus 11%), and at least one failed extubation attempt (36% versus 11%). Further larger studies would be beneficial to decision making.

Although the information presented earlier can guide us in treatment decision making, patient preference also represents an essential component of our assessment. A prospective cohort study carried out in 92 ICUs and 3 respiratory high-dependency units in the United Kingdom examined outcomes in patients with COPD who were admitted to the ICU for decompensated type II respiratory failure, including survival and quality of life at 180 days.<sup>2</sup> Of the survivors, 73% considered their quality of life to be the same as or better than it had been in the stable period before they were admitted, and 96% would choose similar treatment again.

In conclusion, if NIPPV fails, a short course of mechanical ventilation is warranted in most cases. Early reevaluation is then recommended. Patient wishes play an important role in this decision, and advance directives based on discussion, ideally occurring during a medically stable period, regarding risks and complications of invasive ventilation are advocated.

#### **AUTHORS' RECOMMENDATIONS**

- Bronchodilators, including β<sub>2</sub>-adrenergic agonists and anticholinergics, remain the mainstay of therapy for patients with acute exacerbation of COPD.
- In most cases, a course of corticosteroids, not exceeding 14 days, is indicated.
- Theophylline is not currently supported by best evidence.
- Although the use of antibiotics is controversial, the development of respiratory failure of sufficient severity to warrant intensive care admission is an indication for antimicrobial therapy.
- Oxygen therapy should be titrated against blood gases, aiming at normalizing Pao<sub>2</sub>.
- Noninvasive ventilation is an effective intervention for severe hypercarbic respiratory failure. If NIPPV fails, mechanical ventilation should be considered.
- Ventilatory strategy in COPD should focus on delivering adequate flow to match patient demands while minimizing the development of auto-PEEP.
- During mechanical ventilation, Paco<sub>2</sub> should be targeted at the patient's normal range rather than "normal levels." Normalization of Paco<sub>2</sub> will result in significant metabolic alkalosis.

- The time on mechanical ventilation should be a short as possible; consideration should be given to extubation of the patient to NIPPV.
- Prognosis for patients admitted to the ICU with exacerbations of COPD is overall very good, and admission is warranted in most cases, dependent on patients wishes and advance directives.

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4

# What Is the Role of Noninvasive Ventilation in the Intensive Care Unit?

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Noninvasive ventilation (NIV) has assumed an important role in the intensive care unit (ICU), with increasing use during the past 10 years. It is now considered the ventilatory mode of first choice for such forms of acute respiratory failure as chronic obstructive pulmonary disease (COPD) exacerbations, acute cardiogenic pulmonary edema, and hypoxemic respiratory failure in immunocompromised patients and for facilitating extubation in patients with COPD who fail spontaneous breathing trials. Multiple randomized controlled trials have demonstrated that NIV improves outcomes in these forms of respiratory failure. Improved outcomes include avoidance of intubation and reduced morbidity and mortality compared to conventional therapy including intubation. Additionally, the role of NIV is expanding as more studies are completed in other forms of respiratory failure. There are encouraging results from trials evaluating NIV use in postoperative respiratory failure and preoxygenation of patients with hypoxemic respiratory failure before intubation in the ICU. The results are less clear in other forms of respiratory failure such as severe asthma, pneumonia, and acute lung injury (ALI)/acute respiratory disease syndrome (ARDS) and in postextubation respiratory failure in non-COPD patients.

## SELECTING PATIENTS FOR NONINVASIVE VENTILATION

The first question that should be addressed when selecting patients for NIV is whether the patient needs ventilatory support. Such patients usually have moderate to severe respiratory distress, signs of increased work of breathing such as tachypnea, increased use of accessory muscles, or abdominal paradox. Arterial blood gases should be obtained before starting NIV in order to assess the severity of the gas exchange derangement (particularly Paco<sub>2</sub>) and to establish a baseline for comparison after the first 1 to 2 hours. Acutely ill patients should be monitored initially in an ICU or stepdown unit to make sure the patient is improving and tolerating the mask. Trials have shown that the response at the 1- to 2-hour time point is highly predictive of subsequent outcome; patients improving at this point are likely to succeed, but those failing to respond are likely to fail. Risk factors for failure after 2 hours of NIV are listed in Table 4-1.<sup>1-3</sup>

## CONTRAINDICATIONS TO NONINVASIVE VENTILATION

When the need for ventilatory assistance is established, candidates for NIV should be screened for possible contraindications. NIV is contraindicated in patients with cardiopulmonary arrest because there is no time to place a mask and make adjustments. Any patient in shock requiring more than low doses of vasopressors is not a good candidate,<sup>4</sup> nor is the patient with a large acute myocardial infarction, uncontrolled arrhythmias or cardiac ischemia, or a large upper gastrointestinal bleed that is threatening the upper airway. Uncooperative and agitated patients and those with severe claustrophobia are unlikely to tolerate the mask. Patients with copious secretions, impaired swallowing, and frequent vomiting are at risk for aspiration and are poor candidates. Recent upper gastrointestinal surgery is also a relative contraindication because of the risk for abdominal distention and suture line rupture, although there have been some reports of successful use of NIV in these patients. Upper airway obstruction due to epiglottitis or angioedema is best treated with intubation to avoid progression to complete airway obstruction and the need for emergent cricothyrotomy, although upper airway obstruction due to glottic edema after extubation may respond well.<sup>5</sup> Impaired mental status is a relative contraindication, with one of the major concerns being the patient's inability to remove the mask in the event of vomiting. However, hypercapnic coma in patients with COPD exacerbations should not be considered a contraindication, and one trial has shown good outcomes with NIV use in these patients<sup>6</sup> (Table 4-2).

#### Table 4-1 Risk Factors for Failure of Noninvasive Ventilation

- pH < 7.25
- Relative risk > 35
- Acute Physiology and Chronic Health Evaluation II (APACHE II) score > 29
- Acute lung injury/acute respiratory distress syndrome
- Pneumonia
- Severe hypoxemia
- Shock
- Metabolic acidosis
- · Impaired mental status

#### Table 4-2 Contraindications to Noninvasive Ventilation

- Cardiopulmonary arrest, shock
- · Uncontrolled cardiac ischemia or arrhythmias
- Uncooperative or agitated
- Severe upper gastrointestinal hemorrhage
- Coma, nonhypercapnic
- High aspiration risk, vomiting
- Copious secretions
- Upper airway obstruction
- Severe bulbar dysfunction
- Recent esophageal or upper airway surgery
- Multiorgan dysfunction
- · Inability to fit mask due to craniofacial abnormalities

#### APPLICATIONS OF NONINVASIVE VENTILATION IN THE INTENSIVE CARE UNIT

NIV has been tried for many types of respiratory failure in the ICU. However, the evidence to support these applications varies depending on the diagnosis or circumstance. Table 4-3 lists the most common applications and the levels of evidence supporting them. In the following, we discuss the evidence supporting the various applications in more detail, starting with those supported by the strongest evidence.

#### **First-Line Therapy**

#### **COPD** Exacerbations

Multiple randomized trials and meta-analyses have shown decreased intubation and improved mortality rates with NIV use compared with standard medical therapy in patients with exacerbations of COPD.<sup>7–12</sup> Therefore, NIV should be considered the standard of care in patients with COPD exacerbations requiring ventilatory support in the absence of contraindications. The physiologic rationale in these patients is that NIV unloads the inspiratory muscles and increases tidal volume, decreases the dead space–to–tidal volume ratio, lowers respiratory rate, and improves alveolar ventilation.<sup>7</sup> The addition of positive end-expiratory pressure (PEEP) decreases the work of breathing by decreasing the inspiratory threshold load imposed by auto-PEEP that frequently is present in these patients.<sup>13</sup>

#### Acute Cardiogenic Pulmonary Edema

Multiple randomized trials and meta-analyses have shown that either continuous positive airway pressure (CPAP) alone or NIV lowers intubation rates and mortality when compared with conventional medical therapy in patients with cardiogenic pulmonary edema.<sup>14-24</sup> The benefit in these patients is mostly from the increase in intrathoracic pressure. This increases functional residual capacity (FRC), thereby recruiting flooded alveoli, improving gas exchange, and increasing lung compliance. It also reduces cardiac preload and afterload. This has salutary hemodynamic effects in most patients with cardiogenic pulmonary edema.<sup>25,26</sup> Longer-term use of CPAP in stable congestive heart failure (CHF) patients has improved left ventricular ejection fraction, decreased mitral regurgitation, and decreased atrial natriuretic peptide levels compared with controls.<sup>27</sup> Whether CPAP alone or NIV (i.e., pressure support plus PEEP) is the preferred modality is unclear. An early study showed an increased rate of myocardial infarctions with NIV,<sup>23</sup> but subsequent trials and meta-analyses have failed to replicate this and rather have demonstrated that both modalities similarly reduce the need for intubation and lower mortality rates.<sup>16,24</sup> Although CPAP has been suggested as the preferred initial modality because of its greater simplicity and lower expense, most centers use NIV initially because bilevel devices are readily available and unloading of the inspiratory muscles may be achieved more quickly. In unstable patients with pulmonary edema complicating ST elevation myocardial infarction, or in the presence of cardiogenic shock, early intubation is recommended.

#### Immunocompromised States

NIV decreases mortality compared with oxygen therapy alone in immunocompromised patients with hypoxemic respiratory failure. This includes patients with hematologic malignancies, patients who have had solid organ transplantation, or patients with HIV or AIDS.<sup>28,29</sup> The beneficial effects are attributed to the avoidance of infectious complications related to intubation. These patients are particularly vulnerable to intubation. These patients are particularly vulnerable to intubation-associated pneumonias and septic complications.<sup>30</sup> We would recommend instituting this therapy early when there is a window of opportunity to avoid the progression to overt respiratory failure and the need for intubation. Once intubated, mortality rates among the immunocompromised are very high.<sup>30</sup>

#### **Extubating Patients with COPD**

Studies have shown decreased duration of mechanical ventilation and improved mortality when intubated COPD patients who have failed spontaneous breathing trials are extubated and supported with NIV.<sup>31,32</sup> This should be done with extreme caution, however. Patients should be excellent candidates for NIV in every

Table 4-3 Indications for Noninvasive Ventilation Use

Strength of Recommendation*	Indication for Noninvasive Ventilation	Quality of Evidence <sup>†</sup>
Strong	COPD exacerbations Acute cardiogenic pulmonary edema	A A
	Immunocompromised states	А
	Facilitating extubation in COPD	А
Intermediate	Postoperative respiratory failure	В
	Preoxygenation in hypoxemic respiratory failure	В
	Facilitation of flexible bronchoscopy	В
	Palliation in DNR/DNI patients	В
	Postextubation respiratory failure	В
Weak	ALI/ARDS	С
	Neuromuscular disease	С
	Pneumonia	С
	Status asthmaticus	С

\*Strength of recommendation: strong, recommended therapy; intermediate, strongly consider in good candidates for noninvasive ventilation (NIV); weak, cautious trial can be performed in otherwise excellent candidate for NIV.

<sup>†</sup>Quality of evidence: A, multiple randomized controlled trials showing benefit with NIV; B, single randomized trial or nonrandomized trials showing benefit with NIV; C, conflicting evidence or evidence of harm with NIV.

ALI/ARDS, acute lung injury/acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; DNR/DNI, do not resuscitate/do not intubate.

other way—hemodynamically stable, cooperative with a good cough, with manageable secretions and ability to be ventilated with pressure support levels not exceeding 15 cm  $H_2O$ . Further, initial intubation should not have been difficult because of the potential for catastrophe should these patients require emergent reintubation. We have found early extubation to NIV to be useful in avoiding the need for tracheostomies in such patients.<sup>31</sup> However, if this approach fails and reintubation is necessary, we usually proceed to prompt placement of a tracheostomy.

#### Other Intensive Care Unit Applications

#### Preoxygenation before Intubation

NIV can be an effective way of preoxygenating critically ill patients with hypoxemic respiratory failure before intubation.<sup>33</sup> In one randomized trial,<sup>33</sup> patients preoxygenated with NIV had improved oxygen saturations during intubation and a decreased incidence of significant desaturations during intubation. Anecdotally, we have had good success using this technique in our ICU. The beneficial effect of NIV likely is due to an increase in FRC with increased oxygen stores.

#### Flexible Bronchoscopy

NIV has been used during flexible bronchoscopy to avoid intubation.<sup>34,35</sup> This technique may be especially useful in patients, such as immunocompromised patients, at high risk for infectious complications from airway invasion. The technique involves passing the bronchoscope through an adaptor attached to the NIV mask. In one trial, flexible bronchoscopy was performed in eight immunocompromised patients with hypoxemic respiratory failure. NIV improved oxygenation compared with oxygen supplementation alone, and none of the patients required intubation.<sup>35</sup> Because of the risk for respiratory deterioration during the procedure, clinicians should be prepared for possible emergent intubation. An alternative technique to consider in these patients is performing bronchoscopy through a supraglottic device, such as a laryngeal mask airway, but this technique requires deep sedation.

#### **Postoperative Respiratory Failure**

One randomized trial in lung resection patients with postoperative respiratory failure showed decreased intubation rates and mortality with NIV compared with standard therapy.<sup>36</sup> Another randomized trial found that prophylactic CPAP at 10 cm H<sub>2</sub>O for 12 to 24 hours after thoracoabdominal aortic surgery reduced pulmonary complications and decreased hospital length of stay compared with oxygen supplementation alone.<sup>37</sup> Twenty-four hours of CPAP use after upper abdominal surgery was also associated with fewer intubations, a decreased occurrence of pneumonia and septic complications, and shorter ICU lengths of stay than oxygen therapy alone.<sup>38</sup> Similar efficacy has been reported for post-gastric bypass patients.<sup>39</sup> One of the main reasons for the beneficial effect of CPAP or NIV in the postoperative setting is the avoidance of a sedation- or pain-associated reduction in the FRC and concomitant impairment of cough. These predispose to atelectasis, hypoxemia, pneumonia, and respiratory failure.

#### NEUROMUSCULAR DISEASE

Patients with neuromuscular disorders such as myopathies, muscular dystrophies, spinal muscular atrophy, scoliosis, and amyotrophic lateral sclerosis (ALS) are managed routinely with home NIV. This is supported by evidence from clinical trials showing improved quality of life with NIV use and, in some conditions, improved survival.<sup>40–43</sup> The role of NIV is for reversal of hypoventilation and stabilization of the upper airway and for treatment of obstructive sleep apnea, which commonly complicates these disorders. When these patients are admitted to the hospital, it is usually because of a respiratory infection. Aggressive management of secretion retention is paramount in avoiding respiratory catastrophe. Such patients should be managed only in an ICU where they can be monitored closely and frequently assisted
with coughing. They should receive around-the-clock NIV and help with coughing using manually assisted coughing combined with mechanical insufflation and exsufflation ("cough assist") as often as necessary.<sup>44</sup> There is a subset of rapidly progressive neuromuscular disorders, including myasthenic crisis and Guillain-Barré syndrome that involves "bulbar" muscles, impairing swallowing and the ability to mobilize secretions. These usually require preemptive intubation to avoid an unanticipated respiratory arrest.

#### PALLIATIVE CARE

NIV has a potential role in the treatment of patients with do-not-resuscitate/do-not-intubate (DNR/DNI) orders and end-of-life care. A study of NIV use in patients with heterogeneous respiratory failure and DNR/DNI status showed favorable outcomes in those with types of respiratory failure expected to do well with NIV, such as COPD and cardiogenic pulmonary edema.<sup>45</sup> NIV can also be used for palliation of dyspnea or to extend life for a few hours to permit settling of affairs but should be discontinued if the mask is poorly tolerated or if dyspnea is not improved.

# POSSIBLE ROLE IN THE INTENSIVE CARE UNIT

#### Asthma

Evidence regarding the use of NIV in severe asthma is lacking. One randomized trial in an Israeli emergency department of patients with acute asthma showed that NIV improved FEV<sub>1</sub> more rapidly and decreased the need for hospitalization compared with sham NIV.<sup>46</sup> The patients were not in respiratory failure, however, with all patients having normal arterial blood gases. A Cochrane review concluded that more trials are needed before NIV can be recommended in this setting.<sup>47</sup> NIV can be tried cautiously in asthma patients who fail to respond to initial bronchodilator therapy and have persistent increased work of breathing. This approach can be combined with heliox and continuous nebulization, although evidence is lacking to support this combination of therapies. Acute asthma patients treated with NIV must be watched closely, however, because they can deteriorate rapidly. Emergency intubation can be dangerous if delayed too long because these patients can have profound oxygen desaturations and can also progress to hemodynamic collapse from hyperinflation and increased intrathoracic pressure.

#### Pneumonia

Acute pneumonia has long been considered a risk factor for NIV failure.<sup>3</sup> A trial evaluating NIV use in heterogeneous respiratory failure showed very poor outcome in the group of patients with pneumonia, with all such patients requiring intubation.<sup>48</sup> Another study evaluated NIV use in patients with hypoxemic respiratory failure and identified community-acquired pneumonia as a subcategory with a high NIV failure rate (50% intubation rate).<sup>3</sup> A randomized trial showed benefit of NIV in patients with severe community acquired pneumonia but only in the subgroup with underlying COPD.<sup>2</sup> These data suggest that NIV should not be used routinely in patients with severe pneumonia.

#### Acute Lung Injury and Acute Respiratory Distress Syndrome

Like pneumonia, the evidence does not support the routine use of NIV in patients with ALI/ARDS. In a trial by Antonelli, ARDS was identified as a risk factor for NIV failure in addition to a higher Simplified Acute Physiology (SAPS) II score (>35).<sup>3</sup> A recent trial evaluated NIV use in patients with ALI/ARDS and found a very high rate of failure (70%). Risk factors for NIV failure included shock (100% intubation rate), metabolic acidosis, and severe hypoxemia. These authors concluded that NIV should be used cautiously if at all if risk factors for failure are present.<sup>1</sup> A recent cohort study showed that some patients with ARDS may benefit from NIV. Used as first-line therapy for ARDS patients not yet intubated on admission to the ICU, NIV was able to prevent subsequent intubation in 54% of patients. A SAPS II score higher than 34 and lack of improvement in Po<sub>2</sub>/Fio<sub>2</sub> ratio to more than 175 after 1 hour of therapy were risk factors for NIV failure.49 This latest study suggests that some patients with ALI/ARDS may benefit from NIV, especially less severely ill patients without shock, metabolic acidosis, or severe hypoxemia. Close monitoring is essential, and if the PO<sub>2</sub>/FIO<sub>2</sub> ratio does not improve after 1 hour, intubation and mechanical ventilation should be initiated.

#### POSTEXTUBATION RESPIRATORY FAILURE

A large multicenter trial evaluated a heterogeneous group of patients with postextubation respiratory failure and randomized patients to treatment with NIV or standard therapy. Unexpectedly, the group that received NIV had an increased ICU mortality rate as well as a 10-hour longer delay before reintubation.<sup>50</sup> These results underscore the importance of proper patient selection in terms of the type of respiratory failure, with certain etiologies such as pneumonia and ALI/ARDS having poor outcomes. It is also clear that not delaying a needed intubation is essential. Postextubation respiratory failure can be treated with NIV if the patient is a good candidate without any contraindications and has a form of respiratory failure likely to respond to NIV, such as COPD or cardiogenic pulmonary edema. Again, closely evaluating the patient at the 1- to 2-hour point is critical to avoid delaying intubation.

#### CONCLUSION

The role of NIV in the ICU is gaining in importance as the evidence supporting its use in certain forms of acute respiratory failure accumulates. Some studies support the use of

NIV to preoxygenate patients with hypoxemic respiratory failure before intubation as well as to facilitate flexible bronchoscopy in certain patients at high risk for infectious or bleeding complications from endotracheal intubation. The results of NIV or CPAP use in postoperative respiratory failure are encouraging, and this application requires further study. Data to support use in other forms of respiratory failure, including severe pneumonia, status asthmaticus, ALI/ARDS, and hypoxemic respiratory failure after extubation, are weaker, but selected patients with these conditions can be tried on NIV as long as they are closely monitored and intubated promptly if they fail to improve. Recent surveys have shown that the use of NIV is increasing in critical care units throughout Europe<sup>51</sup> and presumably in the United States as well. Patients started on NIV should be monitored closely in an ICU or stepdown unit for mask tolerance and leaks, respiratory rate, use of accessory muscles, synchrony with the ventilator, and gas exchange. A careful assessment within 1 to 2 hours is important in determining the likelihood of success with NIV. This usually is sufficient to continue or demonstrate that intubation is required. Future studies should further define the role of NIV in the ICU and will likely expand the use of this important technology.

#### **AUTHORS' RECOMMENDATIONS**

- NIV has become an important part of the critical care ventilator armamentarium.
- Strong evidence supports the use of NIV for acute respiratory failure associated with COPD exacerbations, acute cardiogenic pulmonary edema, and immunocompromised states.
- Patients must be carefully selected for NIV, and NIV should be reserved for patients who require ventilatory assistance but have no contraindications.
- If patients are not improving within the first 1 or 2 hours of NIV, intubation should be performed without further delay.

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5

# How Should Acute Severe Asthma Be Managed in the Intensive Care Unit?

Edward Warren, E.R. McFadden, Jr.

Bronchial asthma is a common disorder. About 22.2 million people in the United States are affected.<sup>1</sup> Of these, about 55% experienced at least one attack in the previous year. This results in 1.8 million visits to the emergency department (ED) and 497,000 hospitalizations.<sup>1</sup> Given the sheer magnitude of the problem, one would think that evidence-based treatment algorithms for all acute phases of the illness would be readily available. Regrettably, this is not the case, and empirical approaches still abound. Nowhere is this more evident than in the intensive care unit (ICU), where robust data to support decision making and therapeutic approaches in key areas are surprisingly sparse.

Whenever possible, this chapter relies on conclusions drawn from randomized controlled trials (RCTs) to try to provide information. Meta-analyses, systematic reviews, and consensus statements from professional organizations are employed, with the caveat that such information can be viewed only as limited secondary evidence and not as the gold standard.<sup>2-4</sup>

#### TREATMENT OF ACUTE EPISODES IN THE EMERGENCY DEPARTMENT

The care of the acute asthmatic in the hospital almost always begins in the ED. It is here that proper evaluation and management may ward off the need for intubation and intensive care, and it is here that there is substantial evidence for determining optimal care. On the other hand, evidence for specific therapeutic approaches in the ICU is scarce. Should an episode of acute severe asthma occur in the ICU, however, it is logical to use evidence-based approaches that have been validated in the ED setting.

Asthma is a reversible disease, and most attacks are short-lived and clear with removal of the offending agent. Rapid reversal of acute airflow obstruction is best achieved by the inhalation of a short-acting  $\beta_2$ -adrenergic agonist (SABA) like albuterol and the early administration of systemic corticosteroids to those patients who fail to respond adequately.<sup>5</sup> Albuterol most often is given either as three doses of 2.5 mg every 20 minutes for 1 hour or two doses of 5 mg over 40 minutes. The optimal amount to terminate an attack appears to lie between 5 and 10 mg.<sup>6</sup> About 70% to 80% of patients quickly respond to

albuterol and can be discharged to home. About one third of patients achieve this with the first dose.<sup>6</sup>

A systematic review of 22 trials involving 1520 patients suggests there is no difference between administration of SABA by metered-dose inhaler (MDI) with a holding chamber or by jet nebulization.<sup>7</sup> Continuous administration may be more effective in terms of admission rates and pulmonary function, particularly in children with severe exacerbations, but the effect is small.<sup>8</sup> In adult patients, there is no benefit of intravenous administration of  $\beta_2$ -adrenergic agonists over inhaled administration.

The place of anticholinergic agents, like ipratropium bromide, is unclear. The major difficulty with this class of drugs is that, in contrast to the sympathomimetics, they have slow onset of action (30 to 60 minutes versus 15 seconds) and are only medium-potency bronchodilators (10% to 15% versus 25% to 50% increases in FEV<sub>1</sub>).<sup>9</sup> Data from meta-analyses and RCTs, however, suggest that when given in combination with albuterol, they may facilitate resolution and improve lung function.<sup>10,11</sup> Generally, the effect is small. To date, there have not been any prospective attempts to study the impact of ipratropium in patients resistant to SABA, and it is here that they would be of the greatest benefit.

The National Institutes of Health (NIH) consensus guidelines state that systemic glucocorticoids should be given to patients who have moderate or severe exacerbations and to those who are not completely responsive to initial SABA therapy.<sup>5</sup> Corticosteroids require liganddependent activation of receptors, gene expression, and ultimately new protein synthesis to decrease inflammation; thus, the benefits occur gradually over 6 to 12 hours.<sup>12</sup> In most cases, the attack has ended long before the impact of the drug is seen. In view of this, it is most prudent to reserve corticosteroids for those patients who are resistant or respond slowly to SABA. The appropriate dose of corticosteroids remains a matter of debate<sup>9,12</sup>; however, oral administration appears to have equivalent efficacy to intravenous methylprednisolone.<sup>13</sup> Inhaled corticosteroids in very high doses have been purported to reduce admission rates compared with placebo, but it remains unclear whether they can replace systemic glucocorticoids or should be employed in conjunction.<sup>9</sup> Like epinephrine, these agents are potent vasoconstrictors and likely produce their beneficial consequences through this mechanism.<sup>14</sup>

Methylxanthines are not recommended. A Cochrane review demonstrated no additional benefit to optimal SABA therapy and a higher frequency of palpitations, arrhythmias, and vomiting.<sup>15</sup>

#### TREATMENT OF ACUTE ATTACKS IN THE HOSPITAL

As noted earlier, between 20% and 30% of asthmatic patients in the ED have poor short-term responses to albuterol and require admission to the hospital.<sup>6</sup> Because these patients have already failed first-line treatment, they are particularly challenging. Here too, however, the natural history is one of resolution, albeit slower than in the ED. The usual therapeutic approach is to continue nebulized albuterol and glucocorticoids with frequent monitoring of the response. With protocol therapy, it generally takes about 36 to 48 hours for such patients to achieve discharge criteria.

It is critical that objective measures of airflow limitation such as  $FEV_1$  or peak expiratory flow rate (PEFR) and gas exchange be repetitively determined in hospitalized patients. Essential components also include clinical evaluations of the degree of respiratory distress and fatigue. Physicians' subjective estimates of the severity of illness often are grossly inaccurate and cannot be relied on." Ordinarily, monitoring of O<sub>2</sub> saturation by pulse oximetry (Spo<sub>2</sub>) is sufficient to assess ventilatory efficiency. Patients in whom measures of arterial blood gases are absolutely essential are those with a pretreatment Spo<sub>2</sub> saturation of less than 90%, anyone in whom saturation falls during observation, and those in whom PEFR does not improve to 40% to 45% of predicted or worsens after treatment.<sup>9</sup> Patients with hypercapnia or normocapnia and persistent respiratory or metabolic acidosis early in the course of their episode require follow-up assessments after receiving adequate doses of  $\beta_2$ -adrenergic agonists.<sup>9</sup> The presence of any of these elements requires continuous monitoring in an ICU environment that can provide immediate ventilatory support.

We are unaware of any prospective studies using rigorously standardized treatment that have determined the number of hospitalized patients who worsen on general medical units and require transfer to the ICU. In one large series involving a survey of 29,430 admissions for asthma in 215 hospitals, the ED was the source for 80% to 90% of ICU patients.<sup>16</sup> Only 5% to 10% of patients appear to have started out as routine admissions and been transferred.<sup>17</sup> In our experience, continuous monitoring on an every 2- to 4-hour basis over the first 24 to 36 hours after admission using standardized "care paths" has virtually eliminated the need for ICU transfers from the floor.

## TREATMENT OF ACUTE ASTHMA IN THE INTENSIVE CARE UNIT

Precise numbers on the need for ICU admissions for refractory asthma are unavailable. The range in the literature varies from 2% to 20%,<sup>16–35</sup> with several recent large

studies reporting a figure between 10% and 15%.<sup>16,18</sup> It is difficult to know how to interpret these numbers. Given that the criteria used to determine ICU admissions are rarely stated and that preadmission treatment often is not standardized, they cannot be used unequivocally as a surrogate for severity. Rather, they appear to be a reflection of caregiver comfort. For example, when we installed protocol therapies in the ED and established objective criteria for hospitalization, ICU admissions decreased 41%.<sup>36</sup> When a new group of physicians assumed responsibilities for the ED, admissions rose.

In general, the therapeutic approaches in the ICU are similar to those in the hospital and involve administering SABA, corticosteroids, and O<sub>2</sub> as well as frequent assessment of clinical status, pulmonary mechanics, and gas exchange. Here too, most patients respond well to therapy, but a small number worsen. Signs of impending respiratory failure include dyspnea sufficient to interfere with speech, changes in mental status, and new or increasing use of the accessory muscles of respiration.<sup>5,9</sup> The ultimate morbidity and mortality in the ICU are a function of how the patients are treated. All studies show that the more invasive the therapeutics approaches, the greater the incidence of complications and death. Intubation in particular increases the risk.<sup>16-35</sup> Consensus recommendations on asthma care<sup>5</sup> suggest that adjunct treatments such as intravenous magnesium sulfate and Heliox be considered to avoid the need for intubation. However, intubation should not be delayed if it is thought necessary.

Magnesium is an important cofactor in many enzymatic reactions, and hypomagnesemia and hypermagnesemia can promote contraction and relaxation of smooth muscle, respectively. Further, there is evidence that intravenous administration of magnesium can cause bronchodilation and may reduce the neutrophilic burst seen with the inflammatory response. For these reasons, magnesium sulfate has been proposed for the treatment of severe acute asthma. Unfortunately, evidence of efficacy is inconclusive. Meta-analyses and systematic reviews have not shown benefit in either admission rates or pulmonary function improvement, save possibly in those presenting with severe attacks (PEFR < 25% to 30% predicted) who fail to respond to initial treatments.<sup>5,9</sup> However, the effect is small (i.e., about 10% increase in  $\ensuremath{\text{FEV}}_1$  or 50 L/min increase in PEFR), with only a trend toward a reduction in hospitalization rates. Nonetheless, because this is the group in whom there is a pressing need for additional treatments, expert panels have suggested that magnesium sulfate merits a try if an hour of conventional therapy does not produce the desired results.<sup>5</sup> Ultimately, appropriately designed RCTs of sufficient size will be needed before firm conclusions can be drawn. The advantages and disadvantages of treatment with magnesium sulfate are detailed in references 5 and 9.

Heliox, a blend of helium and oxygen, has also been offered as a therapeutic option for patients with severe attacks. Because of its low density relative to air or oxygen alone, it reduces airway flow resistance and with it the resistive work of breathing. It does not appear to have any influence on the basic disease process in asthma. Hence, any beneficial effects are transitory and disappear when air or  $O_2$  is once again breathed. It is theorized that

Heliox use may forestall muscle fatigue until bronchodilators and steroids can take effect. Favorable and unfavorable meta-analyses and RCTs have appeared regarding the benefits of Heliox-driven albuterol nebulization. Thus, the issue remains controversial. As with magnesium sulfate, appropriately designed RCTs are needed. The pros and cons of Heliox use are reviewed in detail in references 5 and 9.

Leukotriene modifiers have also been proposed as adjunct treatments, but there is insufficient evidence to make recommendations regarding these agents in the management of refractory asthma.<sup>5</sup>

When all the aforementioned treatments fail, and the patient remains in severe respiratory distress, decisions must be made about whether to initiate ventilatory support. This can be accomplished by either noninvasive or invasive techniques.<sup>37–39</sup> Noninvasive face mask ventilation may offer short-term support for some subjects with hypercapnic respiratory failure who can cooperate with their care and are able to protect their airways, but its application is limited by poor patient acceptance. In contrast to acute respiratory failure due to chronic obstructive pulmonary disease (COPD), for which there is strong evidence for the benefits of this treatment,<sup>40</sup> the role of non-invasive ventilation in treating respiratory failure due to asthma remains unproved.<sup>5,9</sup>

In contrast, employing invasive ventilatory support can be life saving. About 30% of patients in published reports are believed to need intubation, but the range varies from 2% to 70%.<sup>16–35</sup> The reasons are unknown, and the criteria employed in making the decision are only provided in about 40% of the publications.<sup>16–35</sup> In most cases, the decision is based on clinical judgment. Consensus recommendations hold that patients with apnea or coma should be intubated immediately, but there are no other absolute indications.<sup>5</sup> The mere presence of CO<sub>2</sub> retention is not sufficient.<sup>37</sup> However, progressive hypercapnia, deterioration of mental status, exhaustion, and impending cardiopulmonary arrest strongly suggest the need for ventilatory support. All authorities agree that intubation should be considered before any of the aforementioned reasons develop and that it should be performed by a physician who has extensive experience with the procedure and airway management.

If possible, a large-bore ( $\geq 8 \text{ mm}$ ) endotracheal tube should be used, both to facilitate the suctioning of secretions and to decrease resistance to airflow. Adequate sedation is paramount to keep the patient relaxed and breathing in synchrony with the ventilator.<sup>37,38,41–47</sup> This can usually be achieved with benzodiazepines combined with opioids, or propofol.<sup>48–50</sup> Ketamine is an attractive agent because of its bronchodilating properties; however, its psychotropic and sympathomimetic actions are major limitations. Trials in nonintubated patients with severe exacerbations have not shown clinical benefit.<sup>5</sup> Studies of intubated patients are not available. If dyssynchrony with the ventilator persists, neuromuscular blockade may be necessary. Paralysis also eliminates expiratory effort that may result in airway collapse and dynamic hyperinflation. A variety of agents are available, but there are no comparative RCTs as to the relative effectiveness in asthma. These agents should be administered judiciously because they can be associated with a myopathy that is worsened by concomitant corticosteroids.<sup>44</sup> The risk increases with the duration of paralysis.<sup>44</sup>

After the patient is intubated and sedated, bronchodilators and corticosteroids must be continued until the attack clears. Factors related to the endotracheal tube, the ventilator circuit, the ventilatory pattern and settings, and the patient-ventilator interface may reduce aerosol deposition in the lower airway to as low as 5%, and higher doses must be used.<sup>45–48</sup> MDIs are the preferred route of administration.<sup>47,48</sup>

Intubation and mechanical ventilation are not without problems. Morbidity, cost, and mortality are all higher in patients so treated.<sup>16–35</sup> On average, the literature suggests that this therapy carries with it 1.3 complications per intubation, including hypotension, pneumothorax, pneumomediastinum, atelectasis, ventilator-assisted pneumonia, arrhythmias, sepsis, gastrointestinal bleeding, and cerebral hypoxia.<sup>17-38</sup> In the large multicenter study described earlier,<sup>16</sup> admission to the ICU prolonged hospitalization by 1 day, and intubation increased this time to 4.5 days at an additional cost of more than \$11,000. Asthma fatalities in the ICU vary widely but averaged 2.7% in one review.<sup>9</sup> In those intubated, the rate rises to 8.1%.9 Since this publication, several large studies reported mortality rates of 10% and 21%.<sup>16,18</sup> These figures are quite sobering given that death from acute exacerbations of asthma in general are reported in less than 0.5% of patients.<sup>9,49</sup>

A common, but often overlooked, complication associated with invasive ventilatory support is auto-positive end-expiratory pressure (auto-PEEP).<sup>37,38</sup> The problem derives from incomplete exhalation of a breath before the next inhalation begins. This results in progressive inflation of the lungs and compressive cardiopulmonary physiology.<sup>37,38,50</sup> Auto-PEEP rises directly with minute ventilation.<sup>50</sup> The lungs and chest walls become less elastic, and the inflation pressures and work of breathing rise. As this happens, venous return, blood pressure, and cardiac output fall. Even without auto-PEEP, the institution of positive-pressure ventilation in an already hyperinflated thorax can markedly worsen hemodynamics. This effect is amplified in the volume-depleted patient and by the vasodilatory effects of sedatives. In addition to the ventilator maneuvers, described later, fluid resuscitation should begin promptly.<sup>5</sup>

Recommended initial ventilator settings are as follows: a tidal volume of 8 mL/kg, a respiratory rate of 11 to 14, an inspiratory flow rate of 100 L/min, and a PEEP of zero.<sup>50,51</sup> Although high inspiratory flow rates increase peak airway pressures, there are no firm data suggesting that high peak pressures are associated with complications.<sup>52</sup> The ventilator should be adjusted to allow the maximal possible time for exhalation by combining small tidal volumes with slow respiratory rates and short inspiratory times. Although there is no clear level of static endinspiratory pressures (plateau pressures) predictive of complications, levels of 30 cm H<sub>2</sub>O or higher appear to correlate with hyperinflation and auto-PEEP.<sup>38,50–52</sup> The volume of gas at the end of inspiration above functional residual capacity (FRC; termed  $V_EI$ ) may be the best predictor of ventilator-induced hypotension and barotrauma in asthmatic patients. Values greater than 20 mL/kg are

associated with an increased rate of complications.<sup>51</sup> This is a more difficult measurement than plateau pressure, and most clinicians and respiratory therapists are unfamiliar with it.

Strategies to reduce auto-PEEP often result in hypoventilation.<sup>53</sup> The ensuing hypercapnia, termed *permissive hypercapnia*, is well tolerated as long as it develops slowly and the carbon dioxide tension remains at 90 mm Hg or less.<sup>53,54</sup> When necessary, the pH can be defended pharmacologically.<sup>54</sup> This approach is the current consensus recommendation of the NIH expert panel on asthma.<sup>5</sup> Permissive hypercapnia is not uniformly effective, and consultation with or comanagement by physicians who have expertise in ventilator management is appropriate to avoid risks.

#### CONCLUSION

Asthma is common, and severe exacerbations remain an enormous problem in terms of patient morbidity and resource use. Unfortunately, there is a dearth of evidence from which to base treatment decisions in the ICU. When data are lacking, it is reasonable to use evidence-based approaches that have been studied in the ED setting. Physicians have proved to be poor judges of the severity of an asthma attack, and it is essential to use objective criteria when triaging a patient to an unmonitored bed or an ICU bed. SABA and early administration of systemic corticosteroids are the mainstays of treatment. The added benefit of anticholinergic agents has not been adequately studied, and the effect is likely small. The roles of intravenous magnesium sulfate and Heliox are controversial; however, there is consensus for their use in trying to avoid the need for intubation. When ventilatory support is needed, noninvasive ventilation can be tried, although its efficacy has not been proved. Intubation and mechanical ventilation can be life saving but should be done with great care. In the setting of acute asthma, this therapy is associated with significant complications, including death. It is imperative that the physicians in the ICU pay close attention to the patient's physiology and the ventilatorpatient interactions.

#### AUTHORS' RECOMMENDATIONS

- Evidence-based treatment guidelines for the ICU management of acute asthma are lacking.
- Decisions about admission to the ICU should be based on objective, physiologic criteria.
- SABA and systemic steroids are the mainstay of treatment.
- Intravenous magnesium and Heliox can be used as adjunctive therapy.
- When needed, initiation of invasive ventilatory support should not be delayed.
- Complications from positive-pressure ventilation are common in asthmatic patients and contribute significantly to the hospital mortality of these patients.
- Understanding the physiologic effects of the ventilator-patient interaction is paramount.

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# How Should Pulmonary Embolism Be Diagnosed and Treated?

Jacob Gutsche, Jiri Horak

Pulmonary embolism (PE) represents the extreme end of a spectrum of disease characterized by the deposition and embolization of venous clot. Collectively, these disorders are referred to as venous thromboembolism (VTE). Patients with PE typically develop some degree of ventilation-perfusion mismatch and increased pulmonary arterial pressures. This can lead to hypoxemia and right heart strain or failure. Because of the high potential for associated mortality, the diagnosis of PE should be considered by the intensivist confronted with acute pulmonary or cardiovascular failure.

#### EPIDEMIOLOGY AND NATURAL HISTORY

The prevalence of PE among hospitalized patients in the United States, according to data collected between 1979 and 1999, was 0.4%. The incidence in the United States is estimated at 600,000 cases per year.<sup>1</sup> In reality, these numbers may be misleading because the clinical presentation of PE is nonspecific. The acute case fatality rate for PE ranges between 7% and 11%.

Most often, PE arises from deep venous thrombosis (DVT). In about 70% of patients with PE, DVT can be found in the lower limbs.<sup>2,3</sup> The initial studies on the natural history of VTE were carried out in the setting of orthopedic surgery during the 1960s. A landmark report showed that VTE started during surgery with DVT of the calf or more proximal venous system in about 30% of patients. DVT resolved spontaneously after a few days in about one third of cases and did not extend in about 40%. However, in 25%, it developed into proximal DVT and PE.<sup>4</sup> Major risk factors for the development of VTE are listed in Table 6-1.

PE typically occurs 3 to 7 days after the onset of DVT. PE presents with shock or hypotension in 5% to 10% of cases. In up to 50% of cases, shock is not present, but there are signs of right ventricular dysfunction or injury. This is associated with a poorer prognosis.<sup>5,6</sup>

PE is difficult to diagnose because of the nonspecific clinical presentation or complete lack of symptoms. Among patients with proximal DVT who have lung scans, about 50% will have associated, usually clinically asymptomatic, PE.<sup>7</sup>

#### PATHOPHYSIOLOGY

The initial clinical consequences of acute PE are primarily hemodynamic. They become apparent when more than 30% to 50% of the pulmonary arterial bed is occluded by thromboemboli.<sup>8</sup> Large or multiple emboli can acutely increase pulmonary vascular resistance. The resultant increased afterload cannot be overcome by the right ventricle (RV) because a non-preconditioned, thin-walled RV cannot generate mean pulmonary pressures that exceed 40 mm Hg.<sup>8</sup> Underfilling of the left ventricle (LV) decreases blood pressure and coronary blood flow. The combination of increased RV myocardial workload and decreased RV coronary perfusion gradient (decreased systemic diastolic pressure - increased intraventricular pressure) contributes to RV ischemia. This ischemia worsens RV dysfunction and may initiate a vicious circle that ultimately may result in pulseless electrical activity (PEA) and sudden cardiac death.

In up to one third of patients, right-to-left shunt through a patent foramen ovale may lead to severe hypoxemia and an increased risk for systemic embolization.<sup>10</sup>

#### DIAGNOSIS

Evaluating the likelihood of PE in an individual patient based on the clinical presentation is the first and the most important step to select an appropriate diagnostic strategy and interpret diagnostic test results.

#### **CLINICAL PRESENTATION**

Suspicion of PE should accompany clinical symptoms such as dyspnea, chest pain, and syncope. These are present in more than 90% of patients with PE.<sup>11,12</sup> The likelihood of PE increases with the number of risk factors present. However, in about 30% of cases, PE occurs in the absence of any risk factors. Individual clinical signs and symptoms are not very helpful because they are neither sensitive nor specific.

Other symptoms include cough and blood-tinged sputum. Signs include fever, tachycardia, tachypnea,

#### Table 6-1 Major Risk Factors for Venous Thromboembolism

- Spinal cord injury
- Major general surgery
- Major trauma
- · Major orthopedic surgery
- Pelvis, hip, and long bones fracture
- Malignancy
- Myocardial infarction
- Congestive heart or respiratory failure

Modified from: Anderson FA Jr, Spencer FA. Risk factors for venous thromboembolism. Circulation. 2003;107(Suppl 1):9-16.

cyanosis, and coarse breath sounds. Auscultation may yield a new fourth heart sound or accentuation of the pulmonic component of the second heart sound. Electrocardiography may reveal evidence of right heart strain, tachycardia, or atrial fibrillation.

The chest radiograph is usually abnormal, with the most frequently encountered findings (plate-like atelectasis, pleural effusion, or elevation of a hemidiaphragm) being nonspecific.<sup>13</sup> However, the chest radiograph is useful in excluding other causes of dyspnea and chest pain.

PE is generally associated with hypoxemia. However, up to 20% of patients with PE have a normal arterial oxygen pressure (Pao<sub>2</sub>) and a normal alveolar-arterial oxygen gradient.<sup>14</sup> Electrocardiographic signs of RV strain, such as inversion of T waves in leads V1 to V4, a QR pattern in lead V1, the classic S1Q3T3 type, and incomplete or complete right bundle-branch block, may be helpful, particularly when of new onset.<sup>15,16</sup> Electrocardiographic changes are generally associated with the more severe forms of PE, and lack of electrocardiographic changes does not exclude PE.

Based on clinical presentation or lack of it, PE can be divided into three groups: hemodynamically unstable, hemodynamically stable and symptomatic, and asymptomatic.

#### Hemodynamically Unstable Group

This group includes patients presenting with shock or severe hypotension associated with RV dysfunction and injury. These patients require rapid, specific diagnosis and therapy because of the high mortality risk (short-term mortality > 15%).<sup>17,18</sup>

Any intensive care unit (ICU) patient who is at risk for PE and is hemodynamically unstable should be evaluated for acute right heart failure and thrombus in the right heart or main pulmonary artery. Acute heart failure is not specific for PE, and other etiologies must be considered. The main therapeutic goal is to rapidly restore flow through the pulmonary circulation.

## Hemodynamically Stable, Symptomatic Group

This group of patients can be divided into intermediateand low-risk subgroups. Intermediate-risk PE is diagnosed when the patient has either RV dysfunction or myocardial injury. Indicators of RV dysfunction include (1) elevated right heart pressures and RV dilation, (2) hypokinesis, or (3) pressure overload on echocardiography. Elevation of cardiac troponin T or I indicates RV injury. Initial therapy is aimed at the prevention of further pulmonary thromboembolism.

#### Asymptomatic, Silent Group with Incidental Finding

Mild, untreated PEs carry a lower immediate mortality than recurrent PEs. Because of the intrinsic fibrinolytic activity of the lung, small PEs usually resolve spontaneously. Withholding anticoagulation treatment in nonmassive PE is an acceptable strategy for patients who have indeterminate ventilation perfusion study, negative serial lower extremity venous examination results, adequate cardiopulmonary reserve, and relative or absolute contraindications to anticoagulation treatment.<sup>19</sup> The rationale for this approach is based on synthesis of the results of several studies. The optimal management of patients with asymptomatic PE has not been studied prospectively.

#### **DIAGNOSTIC TOOLS**

Because chest radiography is neither sensitive nor specific, the literature describes two modalities used in the diagnosis of PE: perfusion lung scans and computed tomography (CT) pulmonary angiography. The ease and speed of acquiring a CT scan make it the most widely used diagnostic tool for patients with suspected PE.

Perfusion lung scans ( $\dot{V}/\dot{Q}$  scans) have been used to detect the presence of perfusion defects within the patients' pulmonary circulation. The patient is injected with radionucleotide agents, followed by sequential scans. The major advantage of perfusion lung scans is the avoidance of nephrotoxic radiographic contrast. In the PIOPED study, 755 patients underwent V/Q scans and selective pulmonary angiography within 24 hours of the symptoms that suggested PE.<sup>20</sup> Thirty-three percent<sup>20</sup> of the patients had angiographic evidence of PE. Almost all patients with PE (98%) had abnormal  $\dot{V}/\dot{Q}$  scan findings. Thus,  $\dot{V}/\dot{Q}$ scans are highly sensitive for acute PE. However, although PE was documented by angiography in 88%, only 41% of the patients with PE had a high-probability scan. Most patients with PE (57%) had an intermediateprobability or low-probability scan. Thus, specificity was low. In postoperative patients with significant atelectasis, consolidation, or PE, the negative predictive value is low.

High-resolution multidetector computed tomography (MDCT) has replaced the  $\dot{V}/\dot{Q}$  scan as the study of choice in many hospitals for PE evaluation. CT scanning is widely available, can be performed rapidly, and provides clear anatomic and pathologic lung images (so that the clinician often obtains a diagnosis despite a negative angiographic examination) and the ability to concurrently evaluate potential embolic sources in the legs or pelvis. The results of studies that have evaluated CT pulmonary angiography have shown sensitivities up to 90% with single-detector CT scans.<sup>21</sup> With developing technology,

in particular the availability of multidetector units, the accuracy of these scans is improving. Four-slice MDCT scans have an increased sensitivity for subsegmental PE. In two studies of about 100 patients, sensitivities for the detection of PE with four-slice CT angiography have been reported to be 96%<sup>22</sup> and 100%,<sup>23</sup> with respective specificities of 98% and 89%. The combination of arterial phase and venous phase CT angiography appears more sensitive (90%) and specific (96%) than arterial phase alone.<sup>24</sup> For nonoperative patients, the combination of a negative CT pulmonary angiogram and negative D-dimers effectively excludes PE.<sup>25,26</sup> However, D-dimers are neither sensitive nor specific in the perioperative period. Postoperative patients with high clinical suspicion of PE and a negative MDCT scan should undergo lower extremity ultrasonography.<sup>27</sup>

#### TREATMENT

Without treatment, mortality from hemodynamically unstable PE approaches 30%.<sup>28</sup> In treated patients, the overall mortality decreases to 15%.<sup>29</sup> The treatment of PE in the postoperative patient is complicated by the inherent potential for bleeding with therapeutic anticoagulation and thrombolytics.

For acute PE, the options for treatment include therapeutic anticoagulation, inferior vena cava (IVC) filter placement to prevent continued embolization from the lower extremities, clot thrombolysis, and surgical embolectomy. Hemodynamically stable patients diagnosed with PE should receive therapeutic anticoagulation with intravenous unfractionated heparin or subcutaneous low-molecular-weight heparin (LMWH). Meta-analyses have shown that LMWH treatment, when adjusted to body weight, is at least as effective and safe as doseadjusted unfractionated heparin.<sup>30</sup> However, in postoperative and critically ill patients and in patients in whom epidural catheters have been placed, the shorter half-life and reversibility of intravenous unfractionated heparin provides a safety buffer over LMWH. Therefore, despite the absence of randomized prospective trials, when there is a risk for clinically significant bleeding, unfractionated heparin may be safer. Treatment should be commenced before confirmation of the diagnosis if there is clinical suspicion of PE.<sup>31</sup> As described previously, heparin should be adjusted to goal activated partial thromboplastin time (aPTT) and anti-factor Xa levels checked if the patient is requiring large doses of unfractionated heparin without achieving therapeutic aPTT.

Patients who cannot be anticoagulated (such as those with intracranial bleeding) commonly have an IVC filter placed as soon as possible to prevent further embolization. Again, although this approach is logical, there are no randomized prospective trials to substantiate its adoption.

Following the success of thrombolytics in the management of acute myocardial infarction, thrombolysis been proposed as therapy for massive PE. Thrombolytic agents available for use in the United States include tissue plasminogen activator (tPA), streptokinase, and urokinase. These agents all convert plasminogen to plasmin, which in turn breaks down fibrin and promotes clot lysis. The International Cooperative Pulmonary Embolism Registry (ICOPER) reported on 108 patients with massive PE.<sup>32</sup> Thrombolysis did not improve 90-day outcomes in the 33 patients treated. This is consistent with an earlier systematic review that failed to demonstrate outcome improvement between thrombolysis and intravenous heparin.<sup>33</sup> In the absence of supportive data, and with evidence of increased risk for intracranial hemorrhage and bleeding from the wound site, thrombolysis cannot be recommended for postoperative patients who have undergone major abdominal or pelvic surgery.

Pulmonary embolectomy has been performed in patients who have massive PE, are hemodynamically unstable despite heparin and fluid resuscitation, and are not candidates for thrombolysis. Patients with life-threatening PEs may be placed on extracorporeal membrane oxygenation for stabilization and taken to the operating room for open thrombus extraction. No prospective clinical trials have evaluated outcomes from embolectomy. All available data consist of case reports and case series. The largest series of pulmonary embolectomies at one institution was reported by Meyer and colleagues Paris in 1991.<sup>34</sup> During a 20-year period from 1968 to 1988, 96 of 3000 patients (3%) with confirmed PE underwent pulmonary embolectomy under cardiopulmonary bypass. The overall hospital mortality rate was 37.5%. Preoperative cardiac arrest and preoperative shock were associated with an increased mortality: the mortality rate in patients in shock was 42%, as compared with 17% in those without shock. In general, embolectomy is considered a therapy of last resort and should not be considered for most patients with PE.

#### ACUTE RIGHT VENTRICULAR DYSFUNCTION MANAGEMENT

RV systolic function is determined by contractility, afterload, preload, rhythm, synchrony of ventricular contraction, and ventricular interdependence in the setting of acute pressure and volume overload. Acute dilation of the RV shifts the interventricular septum toward the left, alters LV geometry, and function and contributes to low cardiac output state.

Volume loading should be performed carefully. The absence of hemodynamic improvement with an initial fluid challenge suggests ventricular interdependence physiology. Logic would mandate cessation of fluid administration. Bedside echocardiography may be indicated in this case. Aggressive treatment of arrhythmias, atrioventricular dyssynchrony, and high-degree atrioventricular block in acutely dilated RV is required to prevent further decompensation.

Every effort should be made to avoid hypotension, which may lead to a vicious cycle of RV subendocardial ischemia and further hypotension. This may require the use of multiple vasogenic amine or phosphodiesterase inhibitor infusions. There are no data to support the use of any one medication or specific combinations. The RV is much more sensitive to increased afterload than the LV. This may make pulmonary vascular dilators useful and may limit the value of agents that constrict.

Inhaled pulmonary vasodilators, inhaled nitric oxide, inhaled prostacyclin, iloprost, and inhaled milrinone may help to decrease pulmonary vascular resistance and improve RV function.

Echocardiography is helpful in the diagnosis and management of acute RV dysfunction. In patients in lowflow states, the absence of echocardiographic evidence of pressure-overloaded RV most likely eliminates PE as a cause. Conversely, severe hypokinesis of the RV mid free wall, with preserved contraction of the apical segment (McConnell sign), may be specific for PE.<sup>35</sup>

RV dilation with tricuspid regurgitation and septal shift suggest volume-pressure overload, and further volume loading should be avoided.

#### **AUTHORS' RECOMMENDATIONS**

- VTE is a common problem in ICU. PE is the extreme end of the disease.
- PE arises most often from lower extremity DVT.
- PE signs and symptoms are neither sensitive nor specific. Therefore, PE should be considered in any ICU patient with acute pulmonary or cardiovascular dysfunction.
- The diagnostic strategy and initial management is based on hemodynamic stability. The main therapeutic goal for the hemodynamically unstable patient is restoration of flow through the pulmonary artery. Hypotension should be aggressively treated with careful volume loading and vasopressors.
- Perfusion lung scanning and CT pulmonary angiography are the modalities most often used to diagnose PE.
- Anticoagulation should be initiated immediately in any patient with a confirmed PE or a high clinical suspicion and low bleeding risk.
- The use of thrombolysis in ICU patients remains controversial.

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7

# What Is the Optimal Approach to Weaning and Liberation from Mechanical Ventilation?

Alistair Nichol, Ville Pettila, David James Cooper

Liberation from mechanical ventilation is a central component in the care of the critically ill patient. Weaning is the progressive reduction in the amount of support delivered by a mechanical ventilator. However, the term *weaning* is frequently used to cover the transition from intubation and full mechanical support through to a spontaneous breathing patient with a protected airway.<sup>1</sup> This chapter focuses on the clinical assessment of readiness to wean, the technique for conducting a spontaneous breathing trial, and the assessment of readiness of extubation. In addition, we review the evidence supporting various ventilator strategies in the difficult-to-wean patient.

A recent classification system divides intensive care patients into simple to wean, difficult to wean, or prolonged wean.<sup>2,3</sup> Simple-to-wean patients are extubated on the first attempt, make up most of the patients in the intensive care unit (ICU) (about 69%) and have a low mortality rate (about 5%).<sup>4,5</sup> The remaining cohort of either difficult-to-wean patients (requiring up to three attempts or up to 7 days from the onset of weaning) and prolonged-wean patients (more than three attempts or greater than 7 days from the onset of weaning) require greater effort to successfully liberate from mechanical ventilation. These difficult-to-wean and prolonged-wean patients have an associated higher mortality rate (about 25%).<sup>4,5</sup>

Longer duration of mechanical ventilation is associated with increased mortality<sup>6</sup> and costs (mechanical ventilation costs more than \$2000/day<sup>7</sup>), and it has been estimated that the 6% of patients who require prolonged mechanical ventilation consume 37% of ICU resources.<sup>8</sup> In part, this is because more severely ill patients usually require longer periods of mechanical ventilation. Overall, 40% to 50% of the time spent on mechanical ventilation occurs after the weaning process has started.<sup>4,6,9</sup>

Expert consensus<sup>2</sup> has proposed that the weaning process be considered in six steps:

- Treatment of acute respiratory failure
- Clinical judgment that weaning may be possible
- Assessment of the readiness to wean
- A spontaneous breathing trial
- Extubation
- Possible reintubation

Most critically ill patients require a period of rest after intubation, but these steps emphasize that consideration of the weaning process should begin *very soon after intubation* and also allow clinicians to examine the weaning process in a number of discrete logical sequential steps and develop contingency plans if patients fail to make sufficient progress. In addition, this framework allows failure of weaning to be considered as either failure of a spontaneous breathing trial or the need for reintubation and ventilation, or else death, within 48 hours of extubation.<sup>2</sup>

Current research has targeted a number of these steps and identified key areas by which clinicians may optimize liberation from mechanical ventilation.

# CLINICAL SUSPICION THAT WEANING MAY BE POSSIBLE

Because of the significant morbidity and mortality associated with prolonged mechanical ventilation, it is generally accepted that all ventilated ICU patients should be assessed for their readiness to wean at least on a daily basis. The importance of this readiness to wean assessment has been highlighted by a number of trials, which have demonstrated that weaning can be achieved in most patients after the first formal assessment of readiness to wean,<sup>10,11</sup> and by the finding that nearly 50% of unexpected self-extubations during the weaning process did not require reintubation.<sup>12</sup>

#### ASSESSMENT OF READINESS TO WEAN

The clinical assessment of readiness to wean is a two-step process based on (1) assessment of predictors of weaning and (2) successful completion of a spontaneous breathing trial. It is self-evident that both these steps are dependent on sensible clinicians minimizing sedation before assessment and weaning trials and choosing short-acting sedation infusions that can be optimized for nocturnal rest yet reduced rapidly before daytime breathing trials.<sup>13,14</sup> The concept of nocturnal rest, in conjunction with daytime respiratory muscle training, is important for those patients whose weaning is more difficult and prolonged.

#### Predictors of Successful Weaning

The initial screening evaluation of readiness to wean is composed of a clinical examination and an assessment of a number of objective criteria (respiratory, cardiovascular, and neurologic) that aim to predict successful weaning<sup>4,5,9-11,15,16</sup> (Table 7-1). Individually, these predictors are neither highly sensitive nor specific, but together with the clinical examination, they allow the clinician to identify patients who will clearly *not* be suitable for weaning and who may suffer detrimental effects from an unnecessary spontaneous breathing trial. All other patients should undergo a spontaneous breathing trial. This is an important point because many patients who meet some but not all of the criteria for weaning will still successfully wean, clinicians frequently underestimate the ability of patients to wean, and failure of a spontaneous breathing trial in most patients is less injurious than failure to wean.

#### Table 7-1 Clinical and Objective Measures of Readiness to Wean

Clinical assessment	Resolution of acute process requiring intubation and ventilation Patient awake and cooperative Chest wall pain controlled Adequate cough Absence of excessive tracheobronchial secretions Absence of Nasal flaring Suprasternal and intercostal recession Paradoxical movement of the rib cage or abdomen
Objective measures	Respiratory stability: oxygenation $SaO_2 > 90\%$ on $FiO_2 \le 0.4$ $PaO_2 \ge 50-60 \text{ mm Hg on } FiO_2 \le 0.5$ Alveolar-arterial $PO_2$ gradient < 350 mm Hg $(FiO_2 1.0)$ $PaO_2(FiO_2 > 150)$
	Respiratory stability: function Respiratory rate $\leq 35$ breaths/min <sup>-1</sup> Maximal inspiratory pressure $\leq -20$ to $-25$ cm H <sub>2</sub> 0 Tidal volume > 5 mL/kg <sup>-1</sup> Minute ventilation < 10 L/min <sup>-1</sup> No significant respiratory acidosis Respiratory rate/tidal volume < 105 breaths/ min <sup>-1</sup> /L <sup>-1*</sup> CROP index > 13 mL/breaths/min <sup>-1</sup> † Integrative index of Jabour < 4/min <sup>-1</sup> ‡ Cardiovascular stability Heart rate < 140 beats/min <sup>-1</sup> Systolic BP > 90 and < 160 mm Hg Minimal inotropic/vasopressor support Neurologic function

<sup>\*</sup>The respiratory rate/tidal volume ratio is also known as the rapid shallow breathing index.

#### Individual Limitations of the Readiness-to-Wean Predictors

Independent prediction criteria for successful weaning are neither sensitive nor specific. They are summarized here:

- A *minute ventilation* of less than 10 L/min is associated with a positive predictive value of only 50% and a negative predictive value of 40%.<sup>17</sup>
- The *maximal inspiratory pressure* (MIP), a measure of respiratory muscle strength, was initially suggested to be a good indicator of weaning success.<sup>18</sup> These findings have not been replicated in subsequent trials.
- Static compliance (i.e., tidal volume/ (plateau pressure - positive end expiratory pressure [PEEP]) has a low positive predictive value (60%) and negative predictive value (53%).<sup>17</sup>
- Occlusion pressure (P0.1), the airway pressure 0.1 second after the initiation of a spontaneous breath, is a measure of respiratory drive. The results from studies determining the utility of this index have been conflicting to date.<sup>19-21</sup>
- The rapid shallow breathing index (RSBI; respiratory rate/ tidal volume ratio) measured over 1 minute in the spontaneously breathing patient has demonstrated a high sensitivity (97%) and a moderate specificity (65%) for predicting patients who will subsequently successfully pass a spontaneous breathing trial compared with the other predictors.<sup>17</sup> RSBI remains controversial. For example, Tanios and colleagues reported that its use prolonged weaning time and did not reduce the incidence of extubation failure or tracheostomy.<sup>22</sup> However, this trial was small, and there was a high likelihood of selection bias and crossover in the non-RSBI utilization arm. Results from a more recent randomized controlled trial (RCT) suggest that the predictive value of RSBI may be improved using automatic tube compensation.<sup>23</sup>

In summary, individual mechanical criteria should not be considered reliable indicators to predict successful weaning. However, when used in combination with careful clinical examination, it is likely that these indices do predict the likelihood of *failure* to wean.

A variety of compiled prediction tools have been proposed that aim to improve the sensitivity and specificity of prediction over individual criteria. However, these predictors (see Table 7-1) are more complex and are more commonly used in clinical trials than in routine clinical practice.

- A compliance, respiratory rate, arterial oxygenation, and maximal inspiratory pressure (CROP) index (see Table 7-1) greater than 13 mL/breath/min has prospectively determined positive predictive value of 71% and a negative predictive value of 70% to predict weaning success.<sup>17</sup>
- A *Jabour pressure-time product* (see Table 7-1) of less than 4/min has been shown in a retrospective study to have a positive predictive value of 96% and a negative predictive value of 95%.<sup>24</sup>

Future research is required to identify simple predictors that are sufficiently sensitive and specific to predict successful weaning. In the absence of such measures, the clinician should have a low threshold for conducting a daily spontaneous breathing trial.

<sup>&</sup>lt;sup>†</sup>CROP index = [compliance (dynamic) × maximal inspiratory pressure × (arterial partial pressure of oxygen/alveolar partial pressure of oxygen)]/ respiratory rate.

<sup>&</sup>lt;sup>\*</sup>Integrative index of Jabour = pressure time product × (minute ventilation to bring the Paco<sub>2</sub> to 40 mm Hg/tidal volume during spontaneous breathing)

#### Spontaneous Breathing Trial

The initiation of the weaning process is defined as the commencement of the first spontaneous breathing trial. A number of techniques can be used to conduct a spontaneous breathing trial, including the T-tube or T-piece, pressure support ventilation (PSV), and automatic tube compensation (ATC), all of which may be used with or without continuous positive airway pressure (CPAP). Failure of a spontaneous breathing trial is defined as the development of respiratory (function or oxygenation), cardiovascular, or neurologic instability and is determined by clinical assessment and objective testing during the trial (Table 7-2).<sup>2,10,11,17,25,26</sup> There appears to be little predictive advantage to increasing the duration of the spontaneous breathing trial assessment to longer than 20 to 30 minutes.<sup>5,27</sup> Prospective studies have demonstrated that most patients successfully pass their first spontaneous breathing trials and more than 60% of patients successfully wean<sup>5,10,11,15,23,28,29</sup> (Table 7-3). Interestingly, trials to date have not demonstrated that any one of these techniques is superior in its ability to predict weaning success (see Table 7-3). However, clinicians still need to be aware of the relative advantages and disadvantages of each technique.

#### T-Tube or T-Piece

This well-established method involves attaching the end of the endotracheal tube to a short piece of tubing that acts

### Table 7-2 Clinical and Objective Determinantsof Failure of a Spontaneous Breathing Trial

Clinical assessment	Agitation and anxiety Reduced level of consciousness Significant sweating Cyanosis Evidence of increased respiratory muscle effort Increased accessory muscle use Facial signs of distress Dyspnea
Objective measures	Respiratory stability: oxygenation $PaO_2 \le 50-60 \text{ mm } Hg \text{ on } FiO_2 \ge 0.5 \text{ or } SaO_2$ < 90% Respiratory stability: function $Paco_2 > 50 \text{ mm } Hg \text{ or an increase in } Paco_2$ > 8  mm  Hg $pH < 7.32 \text{ or a decrease of } pH \ge 0.07 \text{ pH units}$ Respiratory rate/tidal volume > 105  breaths/ $min^{-1}/L^{-1*}$ $Respiratory rate > 35 \text{ breaths/min}^{-1} \text{ or increase}$ $\ge 50\%$ Cardiovascular stability $Heart rate > 140 \text{ beats/min}^{-1} \text{ (or increase}$ $\ge 20\%)$ $Systolic BP > 180 \text{ mm } Hg \text{ (or increase} \ge 20\%)$ Systolic BP < 90  mm  Hg Significant cardiac arrhythmias Neurologic function
	Reduced level of consciousness

\*The respiratory rate/tidal volume ratio is also known as the rapid shallow breathing index.

as a reservoir and a connection to the humidified fresh gas flow. There were initial concerns that the increased resistance to airflow and the increased work of breathing induced by the endotracheal tube resulted in a work load in excess of that required when the tube was removed. However, these studies did not account for the airway inflammation and edema that frequently accompanies extubation and results in little difference between the pre-extubation and postextubation work load.<sup>30,31</sup> The Tpiece may be modified with a PEEP valve to maintain functional residual capacity during the trial.

#### Pressure Support Ventilation

PSV is patient triggered, pressure targeted, and flow cycled. It is usually combined with PEEP. At low levels (5 to 7 cm  $H_2O_1$ , depending on tube diameter and length), pressure support is dissipated within the endotracheal tube, and there is no additional flow in the trachea. Consequently, pressure support is widely used during spontaneous breathing trials. There are theoretical concerns that the use of PSV may not mimic the true postextubation work load and about the difficulty of predicting the level of PSV necessary to completely compensate for the resistive load.<sup>32</sup> However, studies using low levels of PSV during spontaneous breathing trials have found no difference in predicting ultimate weaning success.<sup>9,28,29,33</sup> The advantage of this approach over the T-piece is safety: the patient is not disconnected from the ventilator, and tidal volumes and respiratory rate are measured. If the patient becomes apneic, the ventilator generates controlled backup breaths.

#### Automatic Tube Compensation

ATC is an automatic method by which the ventilator compensates for the degree of resistance provided by the endotracheal tube and is increasingly found on modern ventilators. With ATC, tube resistance is measured dynamically, and inspiratory flow is adjusted in response. This accounts for not only the diameter and length of tube but also the presence of inspissated secretions and kinks. ATC is as effective as PSV or T-piece weaning.<sup>23,29</sup> There are no published data that this modality confers additional benefit over PSV.

#### **Continuous Positive Airway Pressure**

CPAP is combined with T-pieces, PSV, and ATC in many ICUs as part of the spontaneous breathing trial. Proponents of CPAP argue that it increases functional residual capacity, maintains small airway patency, may be beneficial for left ventricular dysfunction, and has minimal harmful effects.<sup>34</sup> There are few data to support or refute this viewpoint.

#### Suitability for Extubation

Extubation is the final stage in successful liberation of a patient from the mechanical ventilator. However, it would be unwise to extubate any patient before assessing the ability of that patient to protect and maintain a patent airway. This clinical assessment involves testing for adequate level of consciousness, cough strength, frequency of secretions, and airway patency. The likelihood of

Table 7-3 Success of Spontaneous Breathing Trial and Success in Weaning from Mechanical Ventilation					
Author	Year	Number	Passed Initial SBT	Extubated at 48 hr (from all extubated)	Method
TRIALS DESCRIBING SUCCESS RATE OF INITIAL SBT AND EXTUBATION					
Brochard	1994	456	347 (76%)	330 (95%)	T-piece
Esteban	1995	546	416 (76%)	358 (86%)	T-piece
Vallverdu	1998	217	148 (68%)	125 (84%)	T-piece
Esteban	1999	526	416 (79%)	346 (82%)	T-piece
TRIALS DESCRIBING SUCCESS RATE OF INITIAL SBT AND EXTUBATION USING DIFFERING TECHNIQUES					
Esteban Subgroup Subgroup	1997	484 236 246	397 (82%) 205 (86%) 192 (78%)	323 (81%) 167 (81%) 156 (81%)	PSV/T-piece PSV 7 cm H <sub>2</sub> O T-piece
Farias Subgroup Subgroup	2001	257 125 132	201 (78%) 99 (79%) 102 (77%)	173 (86%) 79 (80%) 89 (87%)	PSV/T-piece PSV 10 cm H <sub>2</sub> O T-piece
Haberthur Subgroup Subgroup Subgroup	2002	90 30 30 30	78 (87%) 29 (96%) 23 (77%) 24 (80%)	63 (79%) 25 (86%) 18 (78%) 19 (79%)	ATC/PSV/T-piece* ATC PSV 5 cm H <sub>2</sub> O T-piece
Cohen Subgroup Subgroup	2009	190 87 93	161 (85%) 81 (93%) 80 (86%)	139 (86%) 71 (88%) 68 (86%)	ATC/PSV ATC PSV

\*Some patients initially randomized to the T-piece/PSV groups who failed an SBT were subsequently extubated after an ATC trial. ATC, automatic tube compression; PSV, pressure support ventilation, SBT, spontaneous breathing trial.

undergoing a successful extubation is significantly higher if the Glasgow Coma Scale score is 8 or higher, as opposed to less than 8.<sup>35</sup> Although there are a number of objective measures of cough strength (e.g., card moistening<sup>36</sup> and spirometry<sup>37</sup>), most clinicians subjectively determine the presence of a moderate to strong cough before extubation. In addition, it is important to quantify secretions because the likelihood of weaning success decreases with increased secretions and frequent suctioning intervals.<sup>16,36</sup>

The most common test for airway patency is determination of a cuff leak. This test is commonly used to identify patients at high risk for postextubation stridor or obstruction.<sup>38,39</sup> The cuff leak test is neither sensitive nor specific, although physicians report the presence of a leak to be reassuring. Intravenous steroid therapy, to reduce laryngeal edema, should be considered in all patients after prolonged intubation.<sup>40</sup>

# VENTILATOR MANAGEMENT OF THE DIFFICULT-TO-WEAN PATIENT

The difficult-to-wean patient has already failed at least one spontaneous breathing trial or has required reintubation within 48 hours of extubation. The failure of a spontaneous breathing trial may be accompanied by a significantly increased inspiratory effort,<sup>25</sup> which may strain the respiratory muscles.<sup>41</sup> Current evidence suggests that this extra burden does not cause long-lasting (low-frequency) fatigue,

but it is uncertain whether this may induce short-lasting (high-frequency) fatigue.<sup>25</sup> Therefore, after the failure of either a spontaneous breathing trial or trial of extubation, the clinician must determine the presence of exacerbating factors that reduced the success of weaning<sup>2,42</sup> (Table 7-4) and provide ventilatory management to balance the need for adequate ventilator support (minimizing respiratory fatigue) against the need to minimize support (increase patient respiratory autonomy) to improve the chances of subsequent successful weaning.

The clinician should conduct a careful physical examination and review the patient's diagnostic tests to uncover and treat any reversible contributory factors (see Table 7-4). In the absence of any obvious remedial conditions or while such conditions are being treated, the most appropriate modality of ventilation must be chosen with which to manage these difficult-to-wean patients. The most widely used modes of ventilation are (volume) assist-control ventilation (ACV), synchronized intermittent mechanical ventilation (SIMV—volume control), and PSV.

#### **Assist Control Ventilation**

ACV is the most widely used mode of ventilation worldwide and is frequently described by the moniker *CMV* (controlled or conventional mechanical ventilation). It is widely believed to rest the diaphragm during respiratory

### Table 7-4 Assessment of Factors That Reduce the Success of Weaning

Respiratory	Increased restrictive load: bronchospasm, tube kinking, tube obstruction Increased chest wall elastic load: pleural effusion, pneumothorax, abdominal distention Increase lung elastic load: infection, edema, hyperinflation
Cardiovascular	Cardiac dysfunction, either long-standing or secondary to increased load
Neuromuscular	Depressed central drive: metabolic alkalosis, sedatives analgesics Neural transmission: spinal cord injury, Guillain-Barré syndrome, myasthenia gravis, phrenic nerve injury Peripheral dysfunction: critical illness neuropathy and myopathy
Neurophysiologic	Delirium Depression Anxiety
Metabolic	Hypophosphatemia Hypomagnesemia Hypokalemia Hyperglycemia Steroid use—controversial
Nutrition	Obesity Malnutrition Overfeeding
Anemia	Hemoglobin: 70-100 g/dL

failure and after a spontaneous breathing trial. Conversely, short periods of ACV may induce diaphragm dysfunction and injury.<sup>43</sup>

## Synchronized Intermittent Mechanical Ventilation

The use of SIMV as a weaning tool involves a progressive reduction of the mechanical ventilator respiratory rate in steps of 1 to 3 breaths/min; 30 to 60 minutes later, the patient is assessed for signs of failure to adapt to the increased patient load (similar to failure of breathing trial criteria; see Table 7-2). Accumulating data support the contention that SIMV is a poor weaning mode.

SIMV may actually contribute to respiratory muscle fatigue or prevent recovery from fatigue<sup>11</sup> secondary to an increased work of breathing due to ventilator factors (increased effort to activate the SIMV demand valve, inspiratory, and expiratory dyssyncrony<sup>44,45</sup>) or patient factors (inability of respiratory center to coordinate with the intermittent nature of the support<sup>41</sup>).

Brochard and colleagues randomized 457 patients to SIMV or PSV.<sup>10</sup> They demonstrated that SIMV (with Tpiece spontaneous breathing trials) resulted in slightly longer duration of mechanical ventilation (9.9  $\pm$  8.2 days) compared with PSV (9.7  $\pm$  3.7 days). This trial also found that SIMV had higher rates of weaning failure (SIMV, 42%; PSV, 23%; T-piece, 43%). A second RCT of 546 patients reported that an SIMV-based weaning strategy resulted in longer duration of mechanical ventilation (5 days) compared with a PSV-based strategy (4 days) and T-piece ventilation (3 days).<sup>11</sup>

#### Pressure Support Ventilation

PSV allows the patient to determine the depth, length, flow, and rate of breathing.<sup>46</sup> PSV as a weaning tool involves the gradual reduction of pressure support by 2 to 4 cm H<sub>2</sub>O once or twice a day as tolerated. This method results in a progressive reduction in ventilatory support over hours to days. Two large RCTs have demonstrated that PSV is superior to SIMV in reducing the duration of mechanical ventilation in difficult-to-wean patients.<sup>10,11</sup> Although one of these trials demonstrated that PSV weaning was more efficient than T-piece weaning,<sup>10</sup> the other trial demonstrated T-piece trials to be superior.<sup>11</sup> However, these potentially contradictory results may be accounted for by differences in the trial weaning protocols. Interestingly, one small prospective RCT has recently suggested that PSV weaning is superior to T-piece weaning in patients with chronic obstructive pulmonary disease (COPD).47

#### **T-Piece Trials**

This method is the oldest ventilator weaning technique and involves sequentially increasing the amount of time the patient spends on the T-piece.<sup>10,11</sup> A single daily trial is as efficient and effective as multiple short trials and is less labor intensive.<sup>11</sup>

#### Noninvasive Ventilation

The increasing clinical use and familiarity with noninvasive ventilation (NIV) in the critical care setting makes it an attractive tool in the difficult-to-wean patient. The potential advantages of NIV are to avoid the complications of intubation and sedation and to reduce the total time of invasive mechanical ventilation. The use of NIV in weaning can be separated into preventing extubation failure in selected patients, providing a rescue therapy for postextubation respiratory distress, and permitting early extubation in patients who fail to meet standard extubation criteria.

#### Preventing Extubation Failure in Selected Patients (Prophylactic Therapy)

Prophylactic NIV has the potential to prevent hypoxia, hypercapnia, and atelectasis and to reduce the work of breathing, thereby reducing the rate of respiratory complications. RCTs have demonstrated that in high-risk postoperative patients (vascular, abdominal, and thora-coabdominal surgery), NIV results in trends toward improved oxygenation, reduced infection rate, reduced reintubation rate, and reduced hospital stay and mortal-ity.<sup>48-50</sup> A meta-analysis by Agarwal and colleagues (n = 259) suggested that prophylactic NIV in carefully selected patients is associated with a reduced reintubation rate (relative risk [RR], 0.46; 95% confidence interval [CI], 0.25 to 0.84) and intensive care unit mortality (RR,

0.26; 95% CI, 0.1 to 0.66), but not the hospital mortality rate.<sup>51</sup> These results suggest that the application of prophylactic NIV may be beneficial in carefully selected high-risk patients.

#### Rescue Therapy to Avoid Reintubation for Postextubation Respiratory Distress (Rescue Therapy)

A recent meta-analysis of two RCTs that compared NIV with the standard medical therapy in patients (n = 302) with postextubation respiratory failure did not demonstrate a reduction in the reintubation rate (RR, 1.03; 95% CI, 0.84 to 1.25) or ICU mortality rate (RR, 1.14; 95% CI, 0.43 to 3.0) in the NIV group.<sup>51</sup> Therefore, current evidence suggests that NIV should not be used for patients with postextubation respiratory failure. These patients should be reintubated expeditiously.

#### Permitting Early Extubation in Patients Who Fail to Meet Standard Extubation Criteria (Facilitation Therapy)

Interest has emerged in using NIV in highly selected patients to facilitate earlier removal of the endotracheal tube while still allowing a progressive stepwise reduction of ventilator support. This strategy involves extubating the patient who has failed a spontaneous breathing trial directly on to NIV (PSV + CPAP) compared with standard therapy (invasive mechanical ventilation). Clearly, this approach can only be successful in patients who have good airway protection, a strong cough, and minimal secretions, so they are likely to be conscious alert patients who have slowly resolving lung injury but who retain good respiratory neuromuscular function. In practice, these patients frequently have COPD. Four RCTs have suggested that this approach may reduce the duration of mechanical ventilation, ICU stay, and the rate of infection.<sup>52-55</sup> Two meta-analyses that included these studies demonstrated a consistent positive effect on overall mortality.56,57 Since the time of these publications, another small RCT of 65 patients with COPD demonstrated that NIV reduces the incidence of pneumonia associated with mechanical ventilation and the need for tracheotomy in patients who fail initial weaning attempts.<sup>58</sup> These studies suggest that NIV used to facilitate weaning in mechanically ventilated patients, with predominantly COPD, is associated with promising evidence of clinical benefit.57 The utility of this approach in hypoxic respiratory failure, trauma, and surgical patients has yet to be determined.

#### ROLE OF TRACHEOSTOMY IN WEANING

The insertion of a tracheostomy is an important tool in the difficult-to-wean patient. Tracheostomy is usually far less irritating to the patient than an endotracheal tube, and the decreased sedation requirements usually enable weaning strategies that would otherwise not be possible. Tracheostomy also provides a more secure airway,<sup>59</sup> reduced work of breathing,<sup>60,61</sup> and a reduced rate of ventilator-associated pneumonia.<sup>59</sup> Studies have not determined whether early or late tracheostomy is superior.<sup>62</sup>

## CONSIDERATION OF WEANING PROTOCOLS

A number of studies have reported that either lack of attention to screening for the ability to progress or the unnecessary delay in progression through the weaning steps is associated with increased morbidity and mortality<sup>4,16,63</sup> and that weaning protocols have resulted in reduced ventilator-associated pneumonia, self-extubation rates, tracheostomy rates, and cost.<sup>4,9</sup> Although it could be suggested that strict weaning protocols should be implemented in all ICUs, there are conflicting data.<sup>64</sup>

#### **AUTHORS' RECOMMENDATIONS**

- Sedation reduction and use of short-acting titratable sedative infusions is essential to enable early appropriate clinical assessments. Assessment of readiness to wean and reductions in sedative infusions should be considered early and frequently in critically ill patients receiving mechanical ventilation.
- After the acute insult has resolved, clinicians should have a low threshold for conducting a spontaneous breathing trial in all critically ill patients.
- The spontaneous breathing trial should last more than 30 minutes and may employ a T-piece or T-tube, PSV ( $\leq 10$  cm H<sub>2</sub>O), or ATC, with or without CPA ( $\leq 5$  cm H<sub>2</sub>O).
- Current data support PSV as being the simplest and most effective method.
- If the patient can protect the airway, extubate; if not, consider an artificial airway early to facilitate liberation from mechanical ventilation.
- If the patient fails a spontaneous breathing test, the clinician should (1) address all contributory causes of failure to wean, (2) not perform or repeat a spontaneous breathing trial for 24 hours, (3) support the patient with a non fatiguing mode of ventilation (most commonly PSV), (4) consider NIV if appropriate, and (5) consider tracheostomy.
- Weaning protocols may be cautiously considered in ICUs; however, these are not a replacement for expert clinical opinion.

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8

# Is Oxygen Toxic?

Craig Dunlop, Pauline Whyte

Supplementary oxygen is the most frequently used therapeutic intervention in clinical medicine. Oxygen is administered to treat hypoxia in acute and chronic respiratory failure, often in high inspired concentrations. It is given to perioperative patients; there is emerging evidence that this therapy may reduce the incidence of surgical site infections. Hyperbaric oxygen therapy, in which oxygen is administered in a high pressure chamber, is used to treat decompression illness and carbon monoxide poisoning, enhance wound healing, and kill anaerobic bacteria. Since the late 19<sup>th</sup> century, the toxic effects of hyperbaric oxygen have been known. Since the 1960s, it has been believed that high concentrations of normobaric oxygen may be toxic, in particular to lung tissue.<sup>1</sup> This chapter aims to unravel the published data on oxygen toxicity, from both the normobaric and hyperbaric literature. These data are of varying quality, often conflicting in their conclusions and rarely involving critically ill patients. Finally, we conclude with the question: Is oxygen beneficial?

#### FORMATION OF REACTIVE OXYGEN SPECIES

Oxygen is a highly reactive element, a property that leads to its toxic potential. The oxygen molecule, an electron acceptor, is nontoxic, and normal mitochondrial function reduces most molecular oxygen to water through the sequential donation of four electrons. Less than 5% of oxygen molecules at mitochondrial level convert to reactive oxygen species (ROS)<sup>2</sup> and are responsible for oxidative damage. The term reactive oxygen species encompasses both free radicals and chemicals that take part in radical-type reactions (gain or loss of electrons); they do not contain unpaired electrons and are not true radicals in themselves. The most common ROS include the superoxide anion  $(O_2^-)$ , hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), hydroxyl radicals (OH<sup>-</sup>), singlet oxygen (O<sup>-</sup>), hypochlorous acid (HOCl), and ozone (O<sub>3</sub>). Cellular sources of ROS include the mitochondrial electron transport chain, oxidant enzymes such as xanthine oxidase, phagocytic cells through NADPH oxidase, cyclooxygenase during arachidonic acid metabolism, cellular auto-oxidation of Fe<sup>2+</sup> and epinephrine, and metabolic enzymes such as the cytochrome P-450 family and the nitric oxide synthetases when inadequate substrate is available.<sup>3</sup>

#### MECHANISM OF INJURY

ROS cause injury to lipids, proteins, and nucleic acids. Lipid peroxidation results in disruption of the cell membrane with consequent interruption of cellular signaling. Oxidative protein damage alters the conformation of receptors, enzymes, and signal pathways, with the obvious potential for altered function. Oxidative injury by ROS may result in DNA strand breaks, with abnormal replication and transcription. Thus, oxidative stress may produce a wide spectrum of injury, ranging from modulation of gene expression to altered cell growth and necrosis.

#### DEFENSES AGAINST REACTIVE OXYGEN SPECIES

Because ROS are produced as byproducts of normal metabolism, defense mechanisms exist to limit damage. Accumulation of ROS is usually prevented by cellular enzymes such as superoxide dismutase, catalase, and components of the glutathione redox cycle, including glutathione peroxidase and glutathione reductase. Nonenzyme antioxidants, including vitamins C and E,  $\beta$ -carotene, and uric acid, also reduce ROS to less harmful molecules (Fig. 8-1).

Actively dividing cells are potentially at increased risk for oxidative damage due to exposure of rapidly replicating DNA. Effective protection in this setting may be achieved by cells entering a transient growth-arrested state.<sup>4</sup>

Damage repair systems also exist and may occur either by direct mechanisms or indirectly by removal and subsequent replacement of injured molecules.

#### MANIFESTATIONS OF OXYGEN TOXICITY

Much of the early work on oxygen toxicity was done by Donald, who exposed a number of Royal Navy divers to high oxygen pressures, both in wet and dry conditions.<sup>5</sup> He demonstrated marked variation in individual susceptibility between divers and marked variation in individual susceptibility from day to day.

Oxidative stress occurring as a result of ROS production is thought to be an ongoing process at physiologic levels of oxygen. When the balance between ROS and scavenging systems is altered, free radicals may contribute to the normal aging process,<sup>6</sup> development of cancers,<sup>7</sup> heart failure,<sup>8</sup> and diabetic vascular and cerebrovascular disease.<sup>9</sup>

The effects of oxidative stress are potentially increased during normobaric administration of high oxygen concentrations and are accentuated further in hyperbaric conditions.<sup>1</sup> Formation of ROS is increased with administration OH

$O_2 \pm O_2^- \pm H_2O_2$	±
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Superoxide Catalyse N Dismutase	Myeloperoxidase
Glutathione	Vit. E
Peroxidase	Vit. A

Figure 8-1. Formation of reactive oxygen species.

of higher partial pressures or concentrations of oxygen, and when scavenging systems are overwhelmed, this may potentially lead to tissue injury.

In summary, high levels of oxygen the at cellular level results in the formation of ROS. ROS cause lipid peroxidation, oxidative injury to nucleic acid chains, and oxidative protein damage.

#### NORMOBARIC OXYGEN ADMINISTRATION

#### Pulmonary Toxicity

Hyperoxia has been shown to be toxic in a variety of animal models; there are few published data that demonstrate similar effects in humans. Hence, pulmonary toxicity in critical care, although widely believed to occur, remains controversial. Lorrain Smith first noted congestion and consolidation of the lungs in mice and larks after inhalation of high oxygen partial pressure at various levels in 1899.<sup>10</sup> Most of the information on the physiologic effects in humans has been obtained from healthy volunteers, with few clear data available on those with known lung disease.<sup>11–13</sup> Of all the cells in the human body, those of the tracheobronchial tree and lung parenchyma are exposed to the highest oxygen tensions, whereas the oxygen cascade affords those elsewhere a degree of protection. Effects range from atelectasis to diffuse alveolar damage (DAD) indistinguishable from the acute respiratory distress syndrome (ARDS).

A fraction of oxygen (Fio<sub>2</sub>) less than 0.5 at atmospheric pressure is commonly accepted to be tolerated indefinitely, although the evidence for this is not clear. Barach, experimenting with rabbits, concluded that 60% oxygen does not cause pulmonary damage, even after prolonged exposure varying from 1 to 2 months.<sup>14</sup> More recently, Aoki and colleagues similarly concluded that long-term 40% oxygen exposure did not produce significant lung injury in guinea pigs.<sup>15</sup> However, even at low delivered oxygen concentrations, increased levels of inflammatory mediators have been detected in expired gas in humans, suggesting the potential for damage to occur.<sup>16</sup> In a small study of 25 patients, Register and associates concluded that administration of 50% oxygen compared with 30% may contribute to postextubation pulmonary dysfunction.<sup>17</sup>

Above an  $Fio_2$  of 0.6, there is an initial asymptomatic decrease in vital capacity, with washout of alveolar nitrogen by elevated oxygen concentrations resulting in alveolar atelectasis and production of a right-to-left shunt.<sup>18</sup>

The classic features of oxygen toxicity are the morphologic changes seen in response to hyperoxia and their subsequent clinical consequences. Most human studies are in healthy volunteers, with small sample sizes and uncertain relevance to clinical practice. For example, a small study of six healthy volunteers suggested that retrosternal discomfort was the earliest presenting symptom of tracheobronchitis.<sup>19</sup> Other features include pleuritic chest pain, cough, and dyspnea. Spirometry demonstrated a decrease in vital capacity. Features develop at an early stage, with inflammatory change visible on bronchoscopic examination after 6 hours of breathing oxygen at greater than 90%.<sup>20</sup> Resolution of symptoms usually occurs over a number of days.

The clinical progression of DAD mirrors that of ARDS. An initial exudative phase is characterized by increasing dyspnea, bilateral crackles, frothy and bloody sputum, and widespread infiltrates on chest radiograph. This may progress to a fibrotic phase. Although some studies have attempted to define the impact of oxygen toxicity on acute lung injury in a critical care setting, the large number of confounding variables mean that answers remain unclear. Other factors include ventilator-associated pneumonia, ventilatorrelated barotrauma and volutrauma (ventilator-induced lung injury [VILI]), and the underlying disease processes.

Elliot and colleagues attempted to define predictors for lung function in survivors of ARDS and found the duration of administration FIO<sub>2</sub> greater than 0.6 was the only variable related to reduced diffusion capacity at 1 year.<sup>21</sup> The severity of lung injury was likely related to patterns of oxygen administration; however, this was a retrospective study of only 16 patients. More recently, a larger retrospective study by de Jonge and colleagues found inhospital mortality to be independently associated with mean FIO<sub>2</sub> during intensive care unit (ICU) stay after correction for severity of illness.<sup>22</sup> However, they also recognized that multiple confounders may not have been accounted for and that further work is required.

Singer and associates found no difference in respiratory variables in a prospective trial of 40 patients receiving either 100% or titrated O<sub>2</sub> after cardiac surgery.<sup>23</sup> In contrast, Barber and coworkers found that severely braininjured patients treated with FiO<sub>2</sub> of 1.0 had deterioration of respiratory variables when compared with those receiving FiO<sub>2</sub> of 0.21.<sup>24</sup> However, no postmortem differences were observed. Both studies were small and in isolated populations, with a number of sources of bias.

In summary, the earliest manifestation of hyperoxic injury to the lungs is retrosternal discomfort associated with tracheobronchitis. Subsequently, a syndrome analogous to ARDS develops, starting with an inflammatory phase and followed by a fibroproliferative phase. These data arise from volunteer studies, and it is unknown whether high FIO<sub>2</sub> negatively affects critically ill patients.

#### HYPERBARIC OXYGEN ADMINISTRATION

#### Central Nervous System Toxicity

Central nervous system (CNS) toxicity was first described by Paul Bert in 1877.<sup>25</sup> CNS toxicity is manifested by a number of symptoms, the most dramatic of which is an oxygen convulsion. These are generalized and tonic-clonic

#### Table 8-1 Oxygen Toxicity Associated with Recreational Diving

Symptoms	No. of Cases	Percentage
Convulsions	46	9.2
Twitching lips	303	60.6
Vertigo	44	8.8
Nausea	43	8.6
Respiratory disturbance	19	3.8
Dyspnea	8	
Cough	6	
Other	5	
Twitching, other than lips	16	3.2
Sensation of abnormality	16	3.2
Visual disturbance	5	1
Acoustic hallucinations	3	0.6
Paraesthesia	2	0.4

British Medical Journal May 17 1947. Oxygen Poisoning in Man by Kenneth W Donald D.S.C., M.D., M.R.C.P.

in nature. There is marked interindividual and intraindividual variability in time to symptom onset, but there appears to be a threshold around a partial pressure of oxygen ( $Po_2$ ) of 1.7 atm, below which convulsions do not occur (Table 8-1).

The immediate management of an oxygen convulsion is to remove the diver from the oxygen supply. During recompression for a diving related illness, a diver will generally be allowed to have three uncomplicated oxygen seizures before treatment is abandoned.

#### **Ocular Toxicity**

Patients receiving hyperbaric oxygen therapy (HBOT) for nondiving injuries such as nonhealing wounds may receive a prolonged treatment course lasting several weeks or months. Such patients may develop myopia, which is generally reversible.<sup>26,27</sup>

Cataract development in association with a prolonged course of HBOT (seven patients with exposures between 300 and 850 hours) was reported in 1984,<sup>28</sup> but it was not until 2007 that a case report was published which suggested the de novo formation of a cataract in a healthy female after 48 hyperbaric oxygen sessions.<sup>29</sup> Reduced glutathione plays a critical role in maintaining lens transparency, and cataract formation has been attributed to oxidation of glutathione in the lens stroma.

#### ASSESSMENT OF EXPOSURE: UNITS OF PULMONARY TOXIC DOSE

The relationship between Po<sub>2</sub> and duration of exposure was described mathematically by Bardin and Lambertson.<sup>30</sup> They defined a unit of pulmonary oxygen toxicity as the

Table 8-2 Units of Pulmonary OxygenToxicity versus Percentage Decrement inVital Capacity

Equivalent UPTD Units	Average Decrement in VC (%)
615	2
825	4
1035	6
1230	8
1425	10
1815	15
2190	20

Adapted from Harabin L, Homer D, Weathersby PK, et al. *Predicting Pulmonary*  $O_2$  *Toxicity: A New Look at the Unit Pulmonary Dose.* Bethesda, MD: Naval Medical Research Institute; December 1986.

degree of pulmonary toxicity incurred as a result of breathing 100% oxygen for 1 minute at 1 bar absolute pressure, based on vital capacity (VC) decrements (Table 8-2).

Both diving and recompression therapy involve breathing oxygen at variable partial pressures for various periods of time. The units of pulmonary toxic dose (UPTD) system allows these different exposures to be added together to produce an overall oxygen exposure for the treatment or dive. A general guideline is an acceptable limit of a 2% decrement in VC for divers and a 10% decrement in VC for patients undergoing recompression therapy.

The major limitation of the UPTD approach is that individual susceptibility and the degree of recovery between dives or treatments is not taken into account.

In summary, hyperbaric oxygen therapy has been associated with convulsions and the development of cataracts. However, the relatively low number of reported cases and the relatively high number of patients undergoing HBOT suggests that these adverse effects are rare. The UPTD system has been developed to measure the degree of oxygen exposure in at-risk patients. It is unclear whether this system is of value in critical care.

#### MANAGEMENT OF OXYGEN TOXICITY

The basic principle of management is early titration of FIO<sub>2</sub> to the lowest level possible while maintaining adequate tissue oxygenation. Practically, suggested targets of SpO<sub>2</sub> of 88% to 95% or a PaO<sub>2</sub> of 55 to 80 mm Hg (7.4 to 10.7 kPa) are commonly used.<sup>31</sup> A wide variety of therapeutic maneuvers may be used in those with advanced pulmonary disease such as maintenance of positive end-expiratory pressure (PEEP), prone positioning, alternative modes of ventilation, inhaled nitric oxide, and extra-corporeal membrane oxygenation. Many of these remain controversial, with no definite benefit on overall mortality yet demonstrated.

If the mechanism of tissue injury is consequent on increased ROS formation, enhancement of defenses against ROS should theoretically reduce damage and improve outcomes. This has been demonstrated in animal models.<sup>32–34</sup> White and colleagues demonstrated less morphologic changes in the lungs in response to hyperoxia in transgenic mice with elevated levels of superoxide dismutase.<sup>35</sup> However, the little available evidence in humans is conflicting. A small cohort study suggested that patients with lower plasma antioxidant levels had worse outcomes compared with those with normal levels,<sup>36</sup> whereas another small study suggested that patients with septic shock treated with glutathione and N-acetylcysteine had reduced markers of oxidative stress.<sup>37</sup> Suter and coworkers found that administration of N-acetylcysteine compared with placebo in acute lung injury improved systemic oxygenation and reduced requirements for ventilatory support, although it had no effect on development of ARDS or mortality.<sup>38</sup> Two further studies suggested that administration of N-acetylcysteine may improve some respiratory parameters but again did not have any effect on mortality.<sup>39,40</sup>

The difficulty arises when attempting to place limits on oxygen administration in light of either a significant oxygen requirement or clinical need for hyperbaric treatment. In the critically ill, significant hypoxia as a result of other insults and leading to development of ARDS will necessitate administration of high oxygen partial pressures, and the need to achieve adequate oxygen delivery far outweighs the little evidence available regarding toxic pulmonary effects of oxygen in this population. In hyperbaric treatments, a risk-benefit analysis should be undertaken on a case-by-case basis, taking into account the low and generally reversible incidence of oxygen toxicity.

In summary, if oxygen toxicity truly exists in the critical care population, the best means of treatment is prevention and the avoidance, when possible, of an FIO<sub>2</sub> greater than 0.6. However, there is insufficient evidence to support withholding higher FIO<sub>2</sub> levels if required to maintain "safe" arterial oxygen tension levels.

#### HYPEROXIA AND SURGICAL SITE INFECTIONS: IS OXYGEN BENEFICIAL?

Unlike the literature on oxygen toxicity in critical illness, which is fragmented and often anecdotal, there are a growing number of clinical and observational trials on the impact of high FIO2 in perioperative medicine. For example Hedenstierna's group and followers have exten-sively studied and defined absorption atelectasis<sup>18,41,42</sup> and techniques that can be used to avoid it.43,44 There are accumulating data that oxygen may beneficial in the prevention of surgical site infections. This is based on evidence that oxidative killing by neutrophils, the primary defense against surgical pathogens, depends critically on tissue oxygenation. Hopf and colleagues<sup>45</sup> performed a noninterventional, prospective study of subcutaneous wound oxygen tension (Psqo<sub>2</sub>) and its relationship to the development of wound infection in surgical patients. One hundred and thirty general surgical patients were enrolled, and Psqo<sub>2</sub> was measured perioperatively. There was an inverse relationship between wound oxygen tension and the risk for developing surgical site infections

(SSIs). They hypothesized that manipulating  $F_{IO_2}$  may increase  $P_{SQO_2}$  and reduce SSIs.

Greif and coworkers<sup>46</sup> randomly assigned 500 patients undergoing colorectal resection to receive 30% or 80% inspired oxygen during the operation and for 2 hours afterward. Anesthetic treatment was standardized, and all patients received prophylactic antibiotic therapy. Wounds were evaluated daily until the patient was discharged and then at a clinic visit 2 weeks after surgery. The arterial and subcutaneous partial pressure of oxygen was significantly higher in the patients given 80% oxygen than in those given 30% oxygen. The duration of hospitalization was similar in the two groups. Among the 250 patients who received 80% oxygen, 13 (5.2%; 95% confidence interval [CI], 2.4% to 8%) had surgical-wound infections, compared with 28 of the 250 patients given 30% oxygen (11.2%; 95% CI, 7.3% to 15.1%; P = .01). The absolute difference between groups was 6% (95% CI, 1.2% to 10.8%).

These data were confirmed by a smaller study from Spain. Belda and associates<sup>47</sup> undertook a double-blind, randomized controlled trial of 300 patients aged 18 to 80 years who underwent elective colorectal surgery. Patients were randomly assigned to either 30% or 80% FIO<sub>2</sub> intraoperatively and for 6 hours after surgery. Anesthetic treatment and antibiotic administration were standardized. A total of 143 patients received 30% perioperative oxygen, and 148 received 80% perioperative oxygen. Surgical site infection occurred in 35 patients (24.4%) administered 30% Fio<sub>2</sub> and in 22 patients (14.9%)administered 80%  $F_{IO_2}$  (P = .04). The risk for SSI was 39% lower in the 80% Fio<sub>2</sub> group (relative risk [RR], 0.61; 95% CI, 0.38% to 0.98%) compared with the 30% Fio2 group. After adjustment for important covariates, the RR of infection in patients administered supplemental oxygen was 0.46 (95% CI, 0.22% to 0.95%; P = .04).

Pryor and colleagues<sup>48</sup> claimed opposite results. This study included 165 patients undergoing general surgery, who were randomized to 30% or 80% oxygen. The overall incidence of SSI was 18.1%. In an intention-to-treat analysis, the incidence of infection was significantly higher in the group receiving  $FIO_2$  of 0.80 than in the group with  $FIO_2$  of 0.35 (25.0% versus 11.3%; P = .02).  $FIO_2$  remained a significant predictor of SSI (P = .03) in multivariate regression analysis. Patients who developed SSI had a significantly longer length of hospitalization after surgery (mean [SD], 13.3 [9.9] versus 6.0 [4.2] days; P < .001).

This study was criticized for a number of reasons. It is unclear whether the group assignment was truly blind. Tissue oxygenation was not blind. Wound infection was identified by retrospective chart review, a highly unreliable technique. There was no standardization of fluid therapy, temperature, or antibiotic prophylaxis. Patients receiving 80% oxygen were more likely to be obese, had longer operations, and lost more blood. All these factors may be associated with increased risk for SSI. Significantly more patients in the high FIO<sub>2</sub> group went back to the postanesthetic care unit intubated after surgery. Finally, the incidence of wound infections, at 25%, was high in the hyperoxic group compared with the study by Grief<sup>46</sup> but similar to the control group in the study by Belda.<sup>47</sup>

Maragakis and colleagues<sup>49</sup> undertook a case-control retrospective review of SSIs in patients undergoing spinal

surgery. Two hundred and eight charts were reviewed. The authors claimed that the use of an FIO<sub>2</sub> of less than 50% significantly increased the risk for SSI (odds ratio, 12; 94% CI, 4.5% to 33%; P < .001). This study has the same flaws as that by Prior and colleagues,<sup>48</sup> albeit with opposite results.

Myles and associates<sup>50</sup> enrolled 2050 patients into a study that randomized them to either Flo<sub>2</sub> of 80% or 30%, plus 70% nitrous oxide. Patients given a high Flo<sub>2</sub> had significantly lower rates of major complications (odds ratio, 0.71; 95% CI, 0.56% to 0.89%; P = .003) and severe nausea and vomiting (odds ratio, 0.40; 95% CI, 0.31% to 0.51%; P < .001). Among patients admitted to the ICU postoperatively, those in the nitrous oxide–free group were more likely to be discharged from the unit on any given day than those in the nitrous oxide group (hazard ratio, 1.35; 95% CI, 1.05% to 1.73%; P = .02). It is unclear whether these data represent a beneficial effect of oxygen or a detrimental effect of nitrous oxide.

In summary, as part of a multimodal prevention strategy that includes timing of antibiotic administration, maintenance of body temperature, and perhaps glycemic control, perioperative hyperoxia appears to reduce the risk for postoperative surgical site infections. Whether these data are applicable in the ICU has yet to be investigated.

#### AUTHORS' RECOMMENDATIONS

- High levels of oxygen at the cellular level result in the formation of ROS.
- ROS cause lipid peroxidation, oxidative injury to nucleic acid chains, and oxidative protein damage.
- The earliest manifestation of hyperoxic injury to the lungs is retrosternal discomfort associated with tracheobronchitis. Subsequently, a syndrome analogous to ARDS develops, starting with an inflammatory phase and followed by a fibroproliferative phase.
- Hyperbaric oxygen therapy has been associated with convulsions and the development of cataracts.
- The UPTD system has been developed to measure the degree of oxygen exposure in at-risk patients.
- If oxygen toxicity truly exists in the critical care population, the best means of treatment is prevention and avoidance, when possible, of an FiO<sub>2</sub> greater than 0.6.
- Perioperative hyperoxia appears to reduce the risk for postoperative surgical site infections. Whether these data are applicable in the ICU has yet to be investigated.

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# 9

# What Is the Role of Hyperbaric Oxygen Therapy in the Intensive Care Unit?

Stephen R. Thom

Hyperbaric oxygen (HBO<sub>2</sub>) therapy is a treatment modality in which a person breathes 100% O2 while exposed to increased atmospheric pressure. HBO2 treatment is carried out in either a monoplace (single patient) or multiplace (typically 2 to 14 patients) chamber. Pressures applied while in the chamber are usually 2 to 3 atmospheres absolute (ATA), the sum of the atmospheric pressure plus additional hydrostatic pressure equivalent to one or two atmospheres. Treatments typically are for 2 to 8 hours, depending on the indication, and may be performed from 1 to 3 times daily. Monoplace chambers are usually compressed with pure O2. Multiplace chambers are pressurized with air, and patients breathe pure O<sub>2</sub> through a tight-fitting face mask, a hood, or an endotracheal tube. During treatment, the arterial O<sub>2</sub> tension typically exceeds 2000 mm Hg, and levels of 200 to 400 mm Hg occur in tissues.<sup>1</sup>

#### MECHANISMS OF ACTION

When assessing the role of HBO<sub>2</sub> in critical care management, focus should be placed on mechanisms of action. Therapeutic mechanisms of HBO<sub>2</sub> are based on elevating hydrostatic pressure and the partial pressure of oxygen (Po<sub>2</sub>). Elevated hydrostatic pressure raises gas partial pressures in the body and causes a reduction in the volume of gas-filled spaces according to Boyle's law. This action has direct relevance to conditions such as arterial gas embolism and decompression sickness. Hyperoxygenation mediates most therapeutic actions in intensive care unit (ICU) cases, and effects are based on production of reactive species. A summary of these mechanisms is shown in Figure 9-1.

It is well accepted that reactive oxygen species (ROS) mediate O<sub>2</sub> toxicity, which for HBO<sub>2</sub> encompasses pulmonary injuries, central nervous system effects manifested by grand mal seizures, and ocular effects such as reversible myopia.<sup>2</sup> ROS and reactive nitrogen species (RNS) also serve as signaling molecules in transduction cascades, or pathways, for a variety of growth factors, cytokines, and hormones.<sup>3,4</sup> As such, reactive species can generate either positive or negative effects, depending on their concentration and intracellular localization. Because exposure to hyperoxia in clinical HBO<sub>2</sub> protocols is rather brief (typically about 2 hours/day), studies show that antioxidant defenses are adequate so that biochemical stresses related to increases in reactive species are reversible.<sup>5–7</sup> Treatments often include so-called air breaks, whereby a patient breathes just air for 5 minutes once or twice through the course of a treatment. This intervention has been demonstrated to enhance pulmonary O<sub>2</sub> tolerance.<sup>8</sup> Although more is still to be learned about the role ROS and RNS play in therapeutic responses to HBO<sub>2</sub>, this chapter briefly outlines what is known and then summarizes major categories of problems or processes in which controlled clinical trials have demonstrated clinical efficacy.

#### **GROWTH AND TRANSCRIPTION FACTORS**

Wound healing disorders are a concern in all aspects of medicine and can be a major factor for patients languishing in ICUs. This is especially true for those with underlying diabetes.<sup>9</sup> Further, review of data regarding wound healing provides a rationale for other indications in critically ill patients.

HBO<sub>2</sub> in current practice is used to treat refractory diabetic wounds and delayed radiation injuries. Common elements shared by both disorders include depletion of epithelial and stromal cells, chronic inflammation, fibrosis, an imbalance or abnormalities in extracellular matrix components and remodeling processes, and impaired keratinocyte functions.<sup>10,11</sup> Diabetic wound healing also is impaired by decreased growth factor production, whereas in postirradiation tissues, there appears to be an imbalance between factors mediating fibrosis and those promoting normal tissue healing.<sup>10,11</sup>

The effectiveness of HBO<sub>2</sub> as an adjuvant therapy for the treatment of diabetic lower extremity ulcerations is supported by six randomized trials and evaluations from a number of independent evidence-based reviews.<sup>12–14</sup> The pathophysiology of radiation injury is obviously different from that of diabetic wounds, but the varied tissue abnormalities have been likened to a chronic wound. The benefit of HBO<sub>2</sub> for radiation injury also has been shown in randomized trials and is supported by independent evidence-based reviews.<sup>15</sup> It is important to state that, for both



**Figure 9-1.** Overview of the therapeutic mechanisms of hyperbaric oxygen (HBO<sub>2</sub>). The two primary effects of HBO<sub>2</sub> are to reduce the volume of bubbles in the body and to elevate tissue oxygen tensions. The figure outlines effects that result from increased production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) because of hyperoxia. GFs, growth factors; HIF-1, hypoxia-inducible factor-1; HO-1, heme oxygenase-1; HSPs, heat shock proteins; SDF-1, stromal-derived factor-1; SPCs, stem-progenitor cells; VEGF, vascular endothelial growth factor.

diabetic wounds and radiation injuries, HBO<sub>2</sub> is used in conjunction with standard surgical management. By itself or if used only in the postoperative period, HBO<sub>2</sub> may be inadequate treatment.<sup>16</sup> Animal trials also have documented benefits of HBO<sub>2</sub>.<sup>17–19</sup> The basis for efficacy is only partially understood but appears to be a combination of systemic events as well as local alterations within the wound margin (see Fig. 9-1).

Neovascularization occurs by two processes. Regional angiogenic stimuli influence the efficiency of new blood vessel growth by local endothelial cells (termed *angiogenesis*) and stimulate the recruitment and differentiation of circulating stem-progenitor cells (SPCs) to form vessels de novo in a process termed *vasculogenesis*.<sup>20,21</sup> Clinical HBO<sub>2</sub> has effects on both these processes.

HBO<sub>2</sub> reduces circulating levels of proinflammatory cytokines under stress conditions (e.g., endotoxin challenge).<sup>22</sup> Further, in wounded tissues or isolated cells, HBO<sub>2</sub> increases synthesis of many growth factors. HBO<sub>2</sub> does not alter circulating levels of insulin, insulin-like growth factors, or proinflammatory cytokines (e.g., tumor necrosis factor- $\alpha$  [TNF- $\alpha$ ], interleukin-6 [IL-6], and IL-8) in normal healthy humans.<sup>22</sup> Vascular endothelial growth factor (VEGF) and angiopoietin, as well as stromal-derived factor-1 (SDF-1), influence SPCs homing to wounds and SPCs differentiating to endothelial cells.<sup>23,24</sup> Synthesis of VEGF, which is the most specific growth factor for neovascularization, has been shown to be increased in wounds by HBO<sub>2</sub>.<sup>25</sup> HBO<sub>2</sub> also stimulates synthesis of basic fibroblast growth factor and transforming growth factor- $\beta$ 1 by human dermal fibroblasts,<sup>26</sup> angiopoietin-2 by human umbilical vein endothelial cells,<sup>27</sup> and plateletderived growth factor (PDGF) receptor in wounds.<sup>28</sup> Extracellular matrix formation is closely linked to neovascularization, and it is another O<sub>2</sub>-dependent process.<sup>29</sup> Enhanced collagen synthesis and cross-linking by HBO<sub>2</sub> have been described, but whether changes are linked to the O<sub>2</sub> dependence of fibroblast hydroxylases versus some alteration in balance of wound growth factors, metalloproteinases, and inhibitors of metalloproteases is as yet unclear.<sup>29–31</sup>

Oxidative stress at sites of neovascularization will stimulate growth factor synthesis by augmenting synthesis and stabilizing hypoxia inducible factors-1 and -2 (HIF-1, HIF-2).<sup>32,33</sup> Hypoxia-inducible transcription factors are heterodimers of HIF-a and a constitutively expressed HIF-b (also called the aryl hydrocarbon receptor nuclear translocator [ARNT] subunit). Enhanced growth factor synthesis by HBO<sub>2</sub> is due at least in part to augmented synthesis and stabilization of HIFs.<sup>25</sup> This may seem paradoxical, but even under normoxic conditions, HIF activity is regulated by a variety of cellular microenvironmental modifications. It is well recognized that expression and activation of HIF-a subunits are tightly regulated, and their degradation by the ubiquitin-proteasome pathway typically occurs when cells are replete with O2.34,35 However, whether hypoxic or normoxic conditions prevail, free radicals are required for HIF expression.<sup>35–37</sup> In addition to ROS, synthesis of •NO is required for VEGF-mediated angiogenesis,<sup>38</sup> and many downstream effects of VEGF are stimulated by •NO.39,40

The influence  $HBO_2$  has on HIF isoform expression appears to vary based on chronology (e.g., looking early or late after wounding or an ischemic insult). One recent

model showing accelerated wound healing by HBO<sub>2</sub> reported lower HIF-1 levels at wound margins with reduced inflammation and fewer apoptotic cells. In contrast, higher levels of HIF-1 have been linked to elevated VEGF in wounds in response to hyperoxia.<sup>32</sup> Recently, exposure to HBO<sub>2</sub> was shown to elevate HIF-1 and HIF-2 levels in vasculogenic SPCs. The basis for this effect is augmented production of the antioxidant thioredoxin and one of its regulatory enzymes, thioredoxin reductase, in response to oxidative stress. Among other actions, thioredoxin has been shown to promote the expression and activity of HIFs.<sup>41</sup> HIF-1 and HIF-2 then secondarily stimulate transcription of many genes involved in neovascularization. These include SDF-1 and its counterpart ligand, CXCR4, as well as VEGF. A physiologic oxidative stress that triggers the same pathway is lactate metabolism.<sup>33</sup>

Bone marrow NOS-3 activity is required for SPC mobilization.<sup>42</sup> SPC mobilization is compromised by diabetes, apparently because NOS activity can be impaired due to responses related to hyperglycemia and a reduced presence of insulin.<sup>43,44</sup> In addition, radiation and chemotherapy, along with other factors such as age, female gender, and coronary artery disease, are known to diminish SPC mobilization.45-47 By stimulating •NO synthesis in bone marrow, HBO<sub>2</sub> mobilizes SPCs in normal humans and patients previously exposed to radiation.<sup>48</sup> Preliminary observations suggest the same is true for diabetic patients. In animal models, SPCs mobilized by HBO<sub>2</sub> home to wounds and accelerate healing.<sup>17,18</sup> HBO<sub>2</sub> also improves clonal cell growth of SPCs from humans and animals.48 Functional enhancements of SPCs by HBO<sub>2</sub> appear to be related to augmentation of HIF-1 and HIF-2 levels.

Therefore, to summarize,  $HBO_2$  can stimulate healing in refractory wounds and irradiated tissues. One oxidative stress response that triggers improved function, at least for SPCs, involves elevations of thioredoxin and thioredoxin reductase. These secondarily increase HIF-1 and HIF-2. The influence of  $HBO_2$  on HIFs in other cell types or tissues is variable. Increased synthesis of growth factors and collagen has been demonstrated. A separate free radical-based mechanism for augmentation of neovascularization by  $HBO_2$  involves bone marrow SPC mobilization that increases the number of circulating SPCs that may home to injured tissues.

#### ANTI-INFLAMMATORY EFFECTS OF HBO<sub>2</sub>

A variety of disorders can be loosely grouped to facilitate the discussion on mechanisms of HBO<sub>2</sub>, although this clearly does not address all elements of these complex pathophysiologic processes. Clinical HBO<sub>2</sub> protocols for these conditions are much shorter than for wound healing. Treatments occur for just a few days rather than weeks; are performed at higher O<sub>2</sub> partial pressures (about 2.5 to 3 ATA), and may occur multiple times in the same day.

Skin graft and flap failures may be due to ischemiareperfusion injuries. A prospective, blinded clinical trial found that administration of HBO<sub>2</sub> before and for 3 days after the procedure led to a 29% improvement in graft survival.<sup>49</sup> Although this is the only randomized clinical trial on skin grafts, numerous animal studies support its conclusions (see citations in reference 50). Clinical studies have documented significant survival enhancement with HBO<sub>2</sub> for extremity reimplantation and free tissue transfer and after crush injury.<sup>51,52</sup> Other clinical trials have shown reductions in coronary artery restenosis after balloon angioplasty and stenting,<sup>53</sup> decreased muscle loss after thrombolytic treatment for myocardial infarction,<sup>54</sup> improved hepatic survival after transplantation,<sup>55</sup> and a reduced incidence of encephalopathy seen after cardiopulmonary bypass and after carbon monoxide poisoning.<sup>56,57</sup>

As is the case with wound healing, there appear to be complex and perhaps overlapping mechanisms for therapeutic effects of HBO<sub>2</sub> (see Fig. 9-1). An early event associated with tissue reperfusion is adherence of circulating neutrophils to vascular endothelium. This process is mediated by  $\beta_2$ -integrins. When animals or humans are exposed to  $HBO_2$  at 2.8 to 3 ATA (but not to 2 ATA  $O_2$ ), the ability of circulating neutrophils to adhere to target tissues is inhibited temporarily.58-61 In animal models, HBO<sub>2</sub>-mediated inhibition of neutrophil  $\beta_2$ -integrin adhesion has been shown to ameliorate reperfusion injuries of brain, heart, lung, liver, skeletal muscle, and intestine, as well as smoke-induced lung injury and encephalopathy due to carbon monoxide poisoning.<sup>60,62–67</sup> It also appears that benefits of HBO2 in decompression sickness involve the temporary inhibition of neutrophil  $\beta_2$ -integrins in addition to the Boyle's law-mediated reduction in bubble volume.

Exposure to HBO<sub>2</sub> inhibits neutrophil  $\beta_2$ -integrin function because hyperoxia increases synthesis of reactive species derived from NOS-2 and myeloperoxidase, leading to excessive S-nitrosylation of β-actin.<sup>68</sup> This highly localized process occurs within neutrophils and is not observed in other leukocytes, probably because of a paucity of myeloperoxidase. β-Actin modification increases the concentration of short, non-cross-linked filamentous (F)-actin, alters F-actin distribution within the cell, and inhibits  $\beta_2$ -integrin clustering on the membrane surface. HBO<sub>2</sub> does not reduce neutrophil viability, and functions such as degranulation, phagocytosis, and oxidative burst in response to chemoattractants remain intact. 60,61,69 Inhibiting  $\beta_2$ -integrins with monoclonal antibodies also will ameliorate ischemia-reperfusion injuries but, in contrast to HBO<sub>2</sub> antibody therapy, causes profound immunocompromise.<sup>70,71</sup> Perhaps the most compelling evidence that HBO2 does not cause immunocompromise comes from studies in sepsis models, where HBO<sub>2</sub> has a beneficial effect.<sup>72,73</sup> HBO<sub>2</sub> does not inhibit neutrophil antibacterial functions because the G-protein-coupled inside-out pathway for activation remains intact, and actin nitrosylation is reversed as a component of this activation process.<sup>68</sup> The denitrosylation mechanism in neutrophils is an area of current investigation.

Monocyte-macrophages exhibit lower stimulusinduced proinflammatory cytokine production after exposure to HBO<sub>2</sub>. This is seen with cells removed from humans and animals exposed to HBO<sub>2</sub> and also when cells are exposed to HBO<sub>2</sub> ex vivo.<sup>74</sup> The HBO<sub>2</sub> effect on monocyte-macrophages may be the basis for reduced circulating cytokine levels after endotoxin stress.<sup>22</sup> The mechanism is unknown but could be related to HBO<sub>2</sub>-mediated enhancement of heme oxygenase-1 and heat shock proteins (HSP; e.g., HSP 70).<sup>7</sup> Hence, once again, an oxidative stress response appears to occur. There are additional mechanisms involved with beneficial HBO<sub>2</sub> effects in reperfusion models. HBO<sub>2</sub> augments ischemic tolerance of brain, spinal cord, liver, heart, and skeletal muscle by mechanisms involving induction of antioxidant enzymes and anti-inflammatory proteins.<sup>75–79</sup>

HIF-1 is responsible for induction of genes that facilitate adaptation and survival from hypoxic stresses.<sup>35</sup> Therefore, it has been a focus of interest when examining HBO<sub>2</sub> therapeutic mechanisms in ischemia-reperfusion models. HIF-1 is involved with proapoptotic as well as antiapoptotic pathways and, in brain, promotes astrocyte-mediated chemokine synthesis.<sup>80,81</sup> In several models, exposure to HBO<sub>2</sub> appears to ameliorate postischemic brain injury by decreasing HIF-1 expression.<sup>82</sup> When HBO<sub>2</sub> is used in a prophylactic manner to induce ischemic tolerance, however, the mechanism appears related to upregulation of HIF-1 and at least one of its target genes, erythropoietin.<sup>83</sup> Thus, as was the case in wound healing models, timing of HBO<sub>2</sub> application appears to influence cellular responses.

There has been a long tradition of considering HBO<sub>2</sub> therapy for a variety of highly virulent infectious diseases, such as necrotizing fasciitis and clostridial myonecrosis, with a view that the microorganisms involved were particularly sensitive to elevated Po<sub>2</sub>. Several retrospective cohort trials indicate there is a benefit to including HBO<sub>2</sub> with antibiotics and surgery for necrotizing fasciitis.<sup>84</sup> In the only multicenter retrospective study, survival was not statistically significant (30% mortality rate [9 of 30 patients] with HBO<sub>2</sub> and 42% [10 of 24 patients] without HBO<sub>2</sub>). Despite this observation, the authors support the use of HBO<sub>2</sub> because of an apparent selection bias between groups.<sup>85</sup> Retrospective comparisons examining efficacy of HBO<sub>2</sub> in clostridial myonecrosis support its use, but again there is ongoing debate.<sup>86</sup>

Most clinically significant anaerobic organisms are actually rather aerotolerant, and thus tissue O<sub>2</sub> tensions, even those achievable with HBO<sub>2</sub>, would be expected to be only bacteriostatic.<sup>87</sup> More likely therapeutic mechanisms include impairment of exotoxin production, which is O<sub>2</sub> sensitive and can be inhibited at tissue partial pressures achievable with HBO<sub>2</sub>,<sup>86</sup> and leukocyte killing, which is improved at progressively higher O<sub>2</sub> tensions.<sup>8</sup> A broader focus may be required to elucidate the as yet unclear pathophysiology of these serious infections and the role of HBO<sub>2</sub>. A recent study of streptococcal myonecrosis showed that host responses to even minor traumatic injuries increase expression of vimentin in muscle tissue, enhancing adhesion and sequestration of microorganisms.<sup>89</sup> There may be a role for intravascular plateletneutrophil aggregation with vascular occlusion in these infectious processes.<sup>90,91</sup> These issues are much closer to the pathophysiologic events seen with disorders such as ischemia-reperfusion injuries than traditional ideas in infectious diseases. There is ample room for further investigation.

#### MECHANISM SUMMARY

This brief review has highlighted beneficial actions of  $HBO_2$  and the data that indicate oxidative stress brought about by hyperoxia can have therapeutic effects. Figure 9-1 provides a summary of mechanisms, all of which appear to stem from elevations in reactive species. Although there has been substantial advancement of the field in recent years, more work is required to establish the breadth of  $HBO_2$  use in 21st century medicine. Investigations of fundamental mechanisms are still needed, and on the clinical front, patient selection criteria must be clarified to truly make  $HBO_2$  a cost-effective treatment modality.

#### COMMON INDICATIONS AND SUPPORTING CITATIONS

#### Arterial Gas Embolism and Decompression Sickness

Hyperbaric therapy has been used to treat disorders related to gas bubbles in the body for quite some time. In the 19th century, workers frequently were noted to experience joint pains, limb paralysis, or pulmonary compromise when they returned to ambient pressure. This condition-decompression sickness (DCS), caisson disease, or bends-was later attributed to nitrogen bubbles in the body, and recompression was found to relieve symptoms.<sup>92</sup> The mechanism, based purely on Boyle's law with reduction of gas bubble volume due to pressure, was later improved by adding supplemental oxygen to hasten inert gas diffusion out of the body. Similar observations were made at later times for scuba divers, who also are prone to develop arterial gas embolism (AGE) due to pulmonary overpressurization on decompression. Iatrogenic AGE has been reported in association with cardiovascular, obstetric-gynecologic, neurosurgical, and orthopedic procedures. Indeed, it can occur whenever disruption of a vascular wall occurs. Nonsurgical processes reported to cause AGE include overexpansion during mechanical ventilation, hemodialysis, and accidental opening of central venous catheters.

Treatment of gas bubble disorders includes standard support of airway, breathing, and circulation plus application of HBO<sub>2</sub>. Referral should be prompt, but even when treatments may be delayed for hours to days, a trial of therapy is recommended. Gas bubbles have been reported to persist for several days, and many reports note success when HBO<sub>2</sub> is begun after long delays. Controlled animal trials support efficacy of HBO<sub>2</sub>, but randomized clinical trials have not been done.<sup>93</sup>

#### **Carbon Monoxide Poisoning**

Carbon monoxide (CO) is the most common cause of injury and death by poisoning in the world.<sup>94</sup> The affinity of CO for hemoglobin to form carboxyhemoglobin (COHb) is more than 200-fold greater than that of  $O_2$ . CO-mediated hypoxic stress is a primary insult, but COHb values correlate poorly with clinical outcome.<sup>57,95,96</sup> Therefore, alternative mechanisms to explain the toxicity

of CO have been sought. Oxidative injury to brain after CO poisoning has been shown to occur in several animal models.<sup>97</sup> Excessive release of excitatory amino acids, such as glutamate, has been implicated as a component of CO-mediated brain injury.<sup>98–100</sup>

Survivors of acute CO poisoning are at risk for developing delayed neurologic sequelae that include cognitive deficits, memory loss, dementia, parkinsonism, paralysis, chorea, cortical blindness, psychosis, personality changes, and peripheral neuropathy. Delayed neurologic sequelae typically occur 2 to 40 days after poisoning. The incidence is 25% to 50% after severe poisoning.

Administration of supplemental oxygen is the cornerstone of treatment of CO poisoning. Oxygen inhalation will hasten dissociation of CO from hemoglobin and provide enhanced tissue oxygenation. HBO<sub>2</sub> causes carboxyhemoglobin dissociation to occur at a rate greater than that achievable by breathing pure oxygen at sea-level pressure. Additionally, HBO<sub>2</sub>, but not ambient pressure oxygen treatment, has several actions that have been demonstrated in animal models to be beneficial in ameliorating pathophysiologic events associated with central nervous system injuries mediated by CO. These include an improvement in mitochondrial oxidative processes,<sup>101</sup> inhibition of lipid peroxidation,<sup>102</sup> and impairment of leukocyte adhesion to injured microvasculature.<sup>60</sup> Compared with 1 ATA, HBO<sub>2</sub> treatment of animals poisoned with CO have a more rapid improvement in cardiovascular status, lower mortality,<sup>103</sup> and lower incidence of neurological sequelae.<sup>104</sup>

There are five prospective randomized trials that have assessed clinical efficacy of HBO<sub>2</sub> for acute CO poisoning.<sup>57,95,105–107</sup> Several failed to find benefit<sup>106,107</sup> but methodologic weaknesses have diminished their clinical impact. The current consensus is that HBO<sub>2</sub> treatment significantly reduces the incidence of delayed neurologic sequelae and, in retrospective comparisons, also appears to diminish acute mortality.<sup>108</sup> As yet, however, there is no agreement among hyperbaric practitioners as to the length of delay from poisoning beyond which there is no chance for benefit from HBO<sub>2</sub>.<sup>109</sup>

#### **Clostridial Myonecrosis (Gas Gangrene)**

Successful treatment of gas gangrene is highly dependent on prompt recognition and aggressive intervention. Mortality rates from 11% to 52% have been reported. There are four retrospective comparisons and 13 case series detailing the use of HBO<sub>2</sub>. Many were cited in a previous review.<sup>1</sup> Owing to difficulties in comparing patient groups, impartial assessment based on mortality or "tissue salvage" rates is difficult. Most authors comment on clinical benefit from treatment, and I share that opinion. Temporal improvement of vital signs in patients with gangrene can be among the most dramatic observations in day-to-day practice.

#### **Crush Injury**

A single randomized controlled trial involving 36 patients constitutes the limited experience with HBO<sub>2</sub> for acute traumatic peripheral ischemia and suturing of

severed limbs. This study demonstrated that HBO<sub>2</sub> improved healing and reduced infection and wound dehiscence.<sup>51</sup> In a case series of 23 patients, HBO<sub>2</sub> was deemed to improve limb preservation. This study also suggested that the change in transcutaneous tissue oxygen level from ambient to hyperbaric conditions predicted outcome. The rationale for considering HBO<sub>2</sub> is to temporarily improve oxygenation to hypoperfused tissues because hyperoxia-induced vasoconstriction can diminish edema formation. This latter mechanism has been demonstrated most convincingly in experimental compartment syndrome.

#### **Progressive Necrotizing Infections**

The use of HBO<sub>2</sub> for treatment of necrotizing fasciitis and Fournier gangrene, mixed aerobic-anaerobic infections, has been reported in six nonrandomized comparisons and three case series.<sup>85,110–117</sup> As with gas gangrene, variations in time of diagnosis and clinical status on admission compromise assessment of the existing literature. Most recently, Brown and associates reported a multicenter experience in which 30 patients received HBO<sub>2</sub> and 24 surgery and antibiotics only.<sup>85</sup> A trend toward increased survival was noted in the HBO<sub>2</sub> group (30% with HBO<sub>2</sub> and 42% without). However, the authors state their support for continued use of HBO<sub>2</sub> because of an apparent selection bias between groups and the limited power of the study. Animal trials have been difficult to assess because synergistic bacterial processes are difficult to establish. One report has found HBO<sub>2</sub> to potentiate the effect of antibiotics in streptococcal myositis.<sup>118</sup>

#### Thermal Burns

Some burn centers employ adjunctive HBO<sub>2</sub> to severe burns, but as controversy persists, this is not a universal practice. Documented benefits with HBO<sub>2</sub> in reducing partial- to full-thickness skin loss, hastening epithelialization, and lowering mortality in animal models have been reported. Randomized clinical trials, albeit with small patient numbers, have reported improved rates of healing, shorter hospitalization stays and reduced costs.<sup>119–121</sup> Uncontrolled series also have reported efficacy, but some studies have failed to find benefit.<sup>122–124</sup> The rationale for treatment has been based on reducing tissue edema and increasing capillary angiogenesis. The latter mechanism has not been shown directly with thermal injuries.

#### **AUTHORS' RECOMMENDATIONS**

- Mechanisms of HBO<sub>2</sub> related to production of ROS and RNS alter protein functions and also modify gene expression by modulating one or more transcription factors.
- HBO<sub>2</sub> can affect a variety of disease processes based on animal and clinical trials.
- Clinical efficacy of HBO<sub>2</sub> has been demonstrated in prospective randomized clinical trials, but more work is needed to elucidate its benefits in critical care.

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# 10 What Is the Clinical Definition of ARDS?

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Acute respiratory distress syndrome (ARDS) is a form of acute respiratory failure characterized by acute hypoxemia and by diffuse radiologic pulmonary abnormalities. ARDS is detected in various clinical settings, has multiple causes, and manifests with a variable course. Histopathologically, ARDS is characterized by disseminated, acute inflammatory damage to alveoli. This initially presents as interstitial and intra-alveolar edema with polymorphonuclear extravasation. With time, the process may evolve to fibrosis.<sup>1</sup> However, these clear histopathologic changes are not reflected in characteristic biologic, radiologic, or functional markers. Therefore, it is difficult to identify acute alveolar inflammation accurately. The diagnosis of ARDS in patients is made using a set of clinical criteria. Nonetheless, it has proved remarkably difficult to construct a system of definitions for ARDS. Indeed, none of the available criteria is completely satisfactory. Diagnostic criteria remain problematic owing to questionable validity (the ability to identify a group of patients with a certain condition and outcome) and reliability (the ability to identify a condition in a predictable manner). This is unfortunate because an adequate clinical definition of ARDS is needed for research (i.e., to select candidates for clinical trials) and intervention (i.e., to identify which patients should receive treatments supported by such trials). In fact, it is probable that the lack of valid and reliable ARDS definitions has contributed to the inconsistent results of many clinical studies<sup>2</sup> and to discrepancies observed in the incidence and mortality of this syndrome.<sup>3</sup> This chapter reviews the definitions for ARDS that have been employed to date, including the current American European Consensus Conference (AECC) criteria.<sup>4</sup> Their virtues and flaws are highlighted. Finally, hypothetical modifications for future clinical criteria are discussed.

#### **PREVIOUS DEFINITIONS**

ARDS was first reported in 1967 by Ashbaugh and colleagues.<sup>5</sup> They observed 12 patients displaying a clinical, physiologic, and pathologic course of events that was remarkably similar to the infantile respiratory distress syndrome. These patients presented with acute onset of severe dyspnea, tachypnea, oxygen refractory cyanosis, loss of lung compliance, and diffuse alveolar infiltration on chest radiograph. This pattern of clinical presentation was used to characterize this newly discovered acute

respiratory distress syndrome. Subsequently, Petty and coworkers in 1971 modified its name from "acute" to "adult" respiratory distress syndrome to differentiate it from its newborn counterpart.<sup>6</sup> In the two decades that followed, there were no standardized diagnostic criteria for ARDS, and the syndrome continued to be loosely defined. According to a systematic review published in 1996, only 50% of the published articles on the incidence and risk factors of ARDS used some definition of this syndrome.<sup>3</sup> When definitions were used, most were derived from Ashbaugh's description and included hypoxemia and bilateral chest infiltrates. Most authors distinguished ARDS from cardiogenic pulmonary edema based on the absence of clinical or measured left atrial hypertension. Although uniformly considered the most characteristic feature of ARDS, the definition of hypoxemia was not consistent among studies. Multiple variables (i.e., Pao<sub>2</sub>, Pao<sub>2</sub>/ FIO<sub>2</sub> ratio, or alveolar-arterial PO<sub>2</sub> gradient) and various discriminating values were used to define critical hypoxemia. Additionally, only a few studies required the presence of positive end-expiratory pressure (PEEP) to diagnose ARDS,<sup>7,8</sup> and therefore the response to ventilatory support was largely ignored.

A number of approaches to better characterize ARDS were proposed. Most were based on physiologic abnormalities, but they did not prove to be useful. The extracorporeal membrane oxygenation (ECMO) entry criteria were conceived to recruit patients with very severe acute respiratory failure into a randomized study on ECMO.9 Patients were enrolled in the study if they met either one of two different sets of criteria: Pao<sub>2</sub> less than 50 mm Hg with PEEP greater than or equal to 5 cm H<sub>2</sub>O and with  $F_{10_2}$  of 1 for at least 2 hours (fast criteria), or Pao<sub>2</sub> less than 50 mm Hg with  $F_{10_2}$  greater than or equal to 0.6 for at least 12 hours in conjunction with an intrapulmonary shunt fraction of more than 30% measured after 48 hours of maximal medical management (slow criteria). These criteria selected patients with a mortality rate of 90%. This was the goal of the approach but was not useful in other contexts. Subsequently, the ECMO criteria were used again to define severe ARDS, although, in a 1991 study, the death rate of patients selected in this manner was reported to be lower (55%) than in the original ECMO trial.<sup>10</sup> More recently, Murray and colleagues developed a lung injury score (LIS) to categorize the presence and the severity of the physiologic manifestations of ARDS and to document changes over time in the severity of the
process.<sup>11</sup> The LIS is a three-part assessment describing the state of lung injury, its severity, and associated conditions. The first part indicates whether the condition is acute or chronic; the second part (Table 10-1) stratifies the severity of lung injury using a score (ranging 0 to 4)

		Value
CHEST RADIOLOGY SCORE		
No alveolar consolidation		0
Alveolar consolidation, 1 quadrant		1
Alveolar consolidation, 2 quadrants		2
Alveolar consolidation, 3 quadrants		3
Alveolar consolidation, 4 quadrants		4
HYPOXEMIA SCORE		
Pao <sub>2</sub> /Fio <sub>2</sub>	≥300	0
Pao <sub>2</sub> /Fio <sub>2</sub>	225-299	1
Pao <sub>2</sub> /Fio <sub>2</sub>	175-224	2
Pao <sub>2</sub> /Fio <sub>2</sub>	100-174	3
Pao <sub>2</sub> /Fio <sub>2</sub>	<100	4
PEEP SCORE (WHEN VENTILATED)		
PEEP	$\geq 5$	0
PEEP	6-8	1
PEEP	9-11	2
PEEP	12-14	3
PEEP	≥15	4
RESPIRATORY SYSTEM COMPLIAN (IF AVAILABLE)	ICE SCORE	
Compliance	${\geq}80~\text{mL/}\\\text{cm H}_2\text{O}$	0
Compliance	60-79 mL/ cm H <sub>2</sub> O	1
Compliance	40-59 mL/ cm H <sub>2</sub> O	2
Compliance	20-39 mL/ cm H <sub>2</sub> O	3
Compliance	${\leq}19mL/\\cm~H_2O$	4

	Score
No lung injury	0
Mild to moderate	0.1-2.5
Severe lung injury (ARDS)	>2.5

PEEP, positive end-expiratory pressure.

Adapted from Murray JF, Matthay MA, Luce JM, Flick MR. An expanded definition of the adult respiratory distress syndrome. *Am Rev Respir Dis.* 1988;138:720-723.

that combines oxygenation, PEEP, radiologic appearance, and respiratory system compliance. Finally, the third part designates what underlying pathologies caused (when known) or are associated with lung injury. Advantages of the LIS included use of ventilator settings in the determination of severity. In particular, accounting for PEEP settings helped distinguish patients with ARDS from patients who have easily reversible conditions such as atelectasis or pulmonary edema from fluid overload. In addition, the LIS included bedside assessment of respiratory compliance. This variable, although typically low in ARDS, has been touted as an independent predictor of mortality.<sup>12</sup> Finally, the LIS introduced the concept that ARDS was not a single entity but rather included a spectrum of variable severity. Although the LIS offered a good pathophysiologic characterization of ARDS, its relative complexity and the lack of prospective validation have limited its use. However, an important trial of an "open" approach to mechanical ventilation in ARDS used a LIS of 2.5 or higher as a selection criterion.<sup>13</sup> Importantly, the LIS was a one-time assessment and did not assign a weight to the duration of physiologic changes.

#### **CURRENT AECC DEFINITION**

The AECC was convened in 1992. Its specific charge was to specify a set of definitions for ARDS<sup>4</sup> in order to simplify diagnosis and to standardize the selection of patients for clinical and epidemiologic studies (Table 10-2). The committee ultimately recommended a return to the original term acute (rather than adult) respiratory distress syndrome in recognition of the fact that ARDS is not limited to adults. An important addition was the introduction of new terminology to describe two severity levels based on the degree of oxygenation impairment. The term *acute* lung injury (ALI) was created to define a rather broad category of patients with a Pao2/Fio2 ratio of less than 300 mm Hg, whereas the term ARDS was reserved for the subset of patients who had the most severe impairment, with a Pao<sub>2</sub>/Fio<sub>2</sub> ratio of less than 200 mm Hg. It is important to understand that ALI and ARDS are not two separate entities because all patients with ARDS also have ALI (Fig. 10-1). No terminology was created for the intermediate form of ALI.

The AECC loosely defined radiologic criteria for ALI. These included the presence of bilateral infiltrates with a

Table 10-2 American European Consensus
Conference Definitions for ARDS and Acute
Lung Injury

Chest radiology	Acute onset, bilateral infiltrates
Hemodynamics	Pulmonary-artery wedge pressure of <19 mm Hg or the absence of clinical evidence of left atrial hypertension
Oxygenation	ALI: $Pao_2/Fio_2$ ratio < 300 ARDS: $Pao_2/Fio_2$ ratio < 200



**Figure 10-1.** Venn diagram showing the relative distributions of patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) within a larger population of patients with acute respiratory failure (ARF). (*Adapted from Luhr OR, Antonsen K, Karlsson M, et al. Incidence and mortality after acute respiratory failure and acute respiratory distress syndrome in Sweden, Denmark, and Iceland. The ARF Study Group.* Am J Respir Crit Care Med. 1999;159:1849-1861. Official Journal of the American Thoracic Society © American Thoracic Society.)

patchy or diffuse alveolar or interstitial pattern. Patients with hypoxemia due to volume overload or heart failure are not considered to have ALI. In fact, ALI is defined as "a syndrome of inflammation and increasing permeability that is associated with a constellation of clinical, radiologic, and physiologic abnormalities that is not associated with left atrial or pulmonary capillary hypertension." Therefore, the diagnosis of ALI requires that hydrostatic edema be excluded by clinical judgment or on a pulmonary artery occlusion pressure of less than 18 mm Hg. Finally, AECC criteria require that ALI be acute in onset and persistent, lasting days to weeks; be associated with one or more known risk factors; and be characterized by diffuse radiologic infiltrates and by arterial hypoxemia resistant to oxygen therapy alone. This excludes patients with chronic lung diseases such as interstitial pulmonary fibrosis or sarcoidosis.

### TESTING AND LIMITATIONS OF THE AECC CRITERIA

The AECC criteria are simple and broadly inclusive. As a result, they have been widely used to select patients for clinical and epidemiologic studies. One such investigation suggested that ALI and ARDS are more common than previously thought and carry a higher mortality than previously appreciated.<sup>14</sup> It is conceivable that the adoption of the AECC criteria resulted in improved patient care and increased awareness of the relevance of ARDS.<sup>15</sup> However, it can also be argued that the simplicity of the AECC criteria has compromised the validity and reliability of these criteria.<sup>16,17</sup> It is particularly difficult to determine whether this is so for ARDS because

there is no established gold standard for the diagnosis. Most therapeutic strategies for ARDS target the treatment of diffuse, acute lung inflammation and are typically tested in animal models reproducing this pattern. However, when human autopsy findings were used as a reference, the sensitivity and specificity of the AECC criteria in the prediction of diffuse alveolar damage were suboptimal.<sup>18</sup> In absence of a gold standard, clinical criteria can be assessed by testing their ability to identify a population of patients with distinct characteristics and outcomes. This is particularly crucial when selecting patients for clinical trials. The AECC criteria for ALI identify a population that amounts to 16% to 23% of all patients who undergo mechanical ventilation for longer than 24 hours<sup>19,20</sup> (see Fig. 10-1). About three fourths of ALI patients also have ARDS. However, it may be difficult to demonstrate a difference in mortality among ALI, ARDS, and other forms of acute respiratory failure.<sup>20,21</sup> There is increasing consensus that the AECC criteria have limitations that affect their ability to identify a population with homogeneous characteristics and prognosis. These limitations can be better understood by critically analyzing each of the definitions that compose the set of the AECC criteria.

#### Acuity of Illness

The AECC criteria loosely require "acuity" and exclude chronic respiratory failure. However, the lack of a specific definition of the timeline of acuity introduces subjectivity. It is clear that the boundaries can be fuzzy between an acute and a chronic process or between the onset of a new disease and an exacerbation of a chronic one. It has been proposed that a timeline of less than 1 week from onset define acute respiratory failure,<sup>16</sup> but this choice is itself quite arbitrary.

#### Chest Radiology

In studies involving expert clinicians, the interobserver agreement between participants asked to evaluate portable chest radiographs of intensive care unit (ICU) patients and decide whether they met the AECC radiologic criteria for ALI was only moderate.<sup>22,23</sup> This is problematic when patients are being selected for enrollment in a clinical trial. It is likely that distinguishing between the patterns of bilateral infiltrates required to diagnose ARDS and the radiologic appearance of other disease processes is difficult even for the trained clinicians. Bilateral pneumonic infiltrates, atelectasis, and hydrostatic edema all may be confused with inflammatory alveolar damage. This is particularly true when examining portable chest films. Further, ventilator settings and, in particular, the level of PEEP significantly affect the size and distribution of radiologic infiltrates. It has been suggested that the reliability of the radiologic criteria can be improved, not by defining the abnormalities themselves, but rather by eliminating the presence of ALI and ARDS when specific abnormalities are absent.<sup>22</sup> Chest computed tomography (CT) can better identify ground-glass opacities that likely represent alveolar inflammatory processes,<sup>24</sup> but its routine use remains limited.

#### Cardiogenic Edema

The AECC criteria for the diagnosis of ARDS require a critical pulmonary artery occlusion pressure (PAOP) of less than 18 mm Hg to exclude patients with hydrostatic pulmonary edema. Different problems exist with this approach. First, PAOP measurement poorly estimates pulmonary venous hypertension.<sup>25</sup> This most often reflects disagreement in the interpretation of tracings.<sup>26</sup> Additionally, an elevated wedge pressure in ventilated patients may be caused by elevated airway pressures rather than by left ventricular dysfunction. Further, the routine, widespread use of pulmonary artery catheterization has decreased over the years.<sup>27</sup> Finally, ARDS often occurs in an appropriately resuscitated patient, particularly one who is older and has some degree of cardiac dysfunction at baseline. AECC criteria also permit clinical diagnosis of left atrial hypertension, but again, criteria are vague and may result in further subjectivity. Echocardiography can be used to rule out ventricular dysfunction. However, respiratory failure and mechanical ventilation may increase subjectivity. Biomarkers such as natriuretic peptides have not yet proved useful in respiratory failure.<sup>28</sup> Therefore, the distinction between ARDS and hydrostatic pulmonary edema is most often made by inference and subjective clinical evaluation. This approach is rendered even more problematic by the lack of clear boundaries between hydrostatic and nonhydrostatic pulmonary edema. In fact, inflammatory lung injury can be accompanied by pulmonary venous hypertension, whereas hydrostatic pulmonary edema may occur at wedge pressures of less than 18 mm Hg in the presence of alveolar inflammatory damage.<sup>29</sup> One study has hypothesized that "capillary stress failure," endothelial disruption caused by markedly elevated pulmonary capillary pressures and perhaps mechanical ventilation, might result in fluid extravasation into the extracellular matrix.<sup>30</sup> When all is considered, it is unlikely that there is a sharp distinction between ARDS and hydrostatic pulmonary edema, and clinicians will continue to use a probabilistic approach to patient evaluation.

#### Hypoxemia

The oxygenation criteria for ALI and ARDS are problematic for several reasons. The AECC opted to require a Pao<sub>2</sub>/Fio<sub>2</sub> ratio of less than 200 mm Hg to diagnose ARDS. This value was chosen based on its use in trials that predated consensus conference. The PaO2/FIO2 threshold value of 300 mm Hg chosen for ALI was completely new and arbitrary. It was introduced to identify a subset of patients who had ALI but not ARDS and who might have better outcomes. However, it is not clear that this has occurred. Many published studies, especially those focusing on mortality, fail to differentiate patients with ALI from those with ARDS.<sup>20</sup> In two epidemiologic studies,<sup>14,19</sup> less than 30% of patients met criteria for ALI but not ARDS at the time of presentation. Up to 55% of these ALI-only patients progressed to develop ARDS. Although patients who did not become worse had better outcomes, those who did progress to ARDS had a mortality rate that was comparable with that in individuals presenting with

ARDS. Because it is impossible to predict which patients will later progress, the distinction between ALI and ARDS may not identify two groups of patients with different outcomes.

Recent clinical trials have employed a wide range of mechanical ventilation settings and modalities at the time of enrollment of patients into studies on ARDS and ALI. Approaches have included noninvasive respiratory support. The AECC criteria do not constrain ventilator settings and, in contrast to the LIS, do not account for the effects of different levels of PEEP on oxygenation. The Pao<sub>2</sub>/Fio<sub>2</sub> ratio was chosen to quantify hypoxemia because it is the simplest way to standardize Pao2 and limit variability due to different FIO2 settings. However, in certain pathophysiologic states, the PaO2/FIO2 ratio can vary significantly with changes in FIO2.<sup>31</sup> Indeed, all oxygenation variables, including shunt and alveolararterial Po2 gradient, are to some extent affected by Fio2 changes. Additionally, high FIO2 causes reabsorption atelectasis and a consequent increase in shunt fraction.<sup>32</sup> It may be that the response to changing FIO<sub>2</sub> is a better approach to patient characterization than a single blood gas determination.

The effect of ventilator settings on the selection of ARDS patients is illustrated by a study in which patients who initially met AECC criteria for ARDS were placed on pressure control ventilation with an FIO2 of 1 and a standardized level of PEEP.<sup>33</sup> After a period of 30 minutes, 24 of 41 patients had improvements in Pao<sub>2</sub>/Fio<sub>2</sub> to above 200 mm Hg and were considered "transient ARDS." These patients had a significantly lower mortality rate (12.5% versus 53%), a shorter duration of mechanical ventilation, and more ventilator-free days than patients who continued to meet criteria for ARDS. In a larger study, Villar and associates applied standardized ventilator settings to ARDS patients at the time of recruitment.<sup>34</sup> Patients who continued to meet AECC ARDS criteria after 24 hours on PEEP higher than 10 cm  $H_2O$  and  $F_{IO_2}$  of 0.5 or greater had higher mortality than patients whose Pao<sub>2</sub>/Fio<sub>2</sub> improved. Thus, the application of PEEP alone identified two patient populations with different outcomes. However, it was necessary to wait 24 hours for the differences between groups to be statistically significant. This suggests that there should be a period of observation before the diagnosis of ARDS.

In all, probably profound physiologic dissimilarities underlie the different outcomes observed in patients who responded to standardized ventilator settings and patients who did not. Typically, patients who do not improve their PaO<sub>2</sub>/FIO<sub>2</sub> in response to a high FIO<sub>2</sub> have greater intrapulmonary shunt,<sup>31</sup> and perhaps more pulmonary edema. However, patients who respond dramatically to a PEEP of only 10 cm H<sub>2</sub>O may have a different underlying pathophysiologic condition, as a cause of their hypoxemia. For example, atelectasis or hydrostatic edema responds well to moderate levels of PEEP. However, this is difficult to prove without further analysis. In addition, the oxygenation response to PEEP is affected by hemodynamic changes<sup>35</sup> as well as alveolar recruitment. Finally, it is possible that requiring observation for 24 hours identifies those patients who have conditions that are more easily treated than ARDS.

The mortality rate in patients who continue to meet ARDS criteria despite standardized ventilator settings is higher than that reported in recent studies that did not standardize PEEP and FIO<sub>2</sub>.<sup>34</sup> This observation sheds doubt on optimistic reports that the mortality from ARDS has been decreasing over time because comparisons are difficult.<sup>2</sup>

#### Possible Modifications to the ARDS Criteria

Various authors have suggested that the limitations inherent in the AECC criteria for ARDS are such that modification or change is needed. Indeed, a recent editorial<sup>15</sup> opined that the question is not whether these changes are needed but, given the available data, when this change should be implemented. The current lack of clinically applicable markers for diffuse alveolar damage and the low probability that such markers will soon become available mandate that ARDS criteria will continue to be based on clinical observations. Radiologic findings and easily obtainable measures of hypoxia such as the Pao<sub>2</sub>/Fio<sub>2</sub> ratio, despite all their problems, likely will continue to be used. The intended simplicity of the AECC criteria has been useful in standardizing entry criteria for clinical trials. However, this limiting approach may have oversimplified the physiologic assessment of ARDS patients. Recent evidence suggested that other variables, for example, compliance and dead space ratio, may be more robust independent predictors of mortality.<sup>12</sup> These variables, although more difficult to measure than Pao2/Fio2, can be obtained at the bedside. It is possible that their use, perhaps within a scoring system similar to the LIS, could improve ARDS criteria. However, each variable will need to be individually tested before its use.

There is some evidence that physiologic characteristics, response to therapy, radiologic appearance, and perhaps outcome may be affected by the etiology that precipitates ARDS.<sup>36,37</sup> If that is so, the etiology of ARDS should be better specified. It may be that ARDS is really two distinct syndromes: pulmonary or primary ARDS, arising in response to injury intrinsic to the lung, and extrapulmonary or secondary ARDS, precipitated by a process such as peritonitis that is remote from the lung. If so, the definition of ARDS should account for this. However, although this approach is physiologically sound, there are multiple obstacles preventing its application. One of the most important ones is the difficulty in establishing the pulmonary or nonpulmonary origin of the abnormality that triggers respiratory failure. In addition, the distinction between pulmonary ARDS and pneumonia is problematic.<sup>18</sup> Radiologic studies have suggested that the CT appearance of the lungs predicts patients' prognosis better than the etiology of their ARDS.<sup>38,39</sup>

Recent evidence hints that standardization of ventilator settings may be an appealing addition to the existing criteria used to diagnose ARDS. The addition of a minimal period of observation to confirm that hypoxemia is persistent has been used in at least one positive trial on mechanical ventilation.<sup>40</sup> The disadvantage is the delay in initiating definitive treatment or in recruiting patients into clinical trials. Additionally, the implications of a difference between a "transient" and "persistent" ARDS are somewhat unclear. It is possible that only the patients who do not improve on the standard settings have "real" ARDS.<sup>16,34</sup> However, it is equally likely that a positive response to increased PEEP is a characteristic of this syndrome and should not be a reason to exclude patients from either diagnosis or the potential benefit of treatment. Conversely, the current criteria, in which patients within a study may be significantly heterogeneous, will likely continue to generate investigations with results that are difficult to interpret.

Ferguson and associates used the Delphi technique to develop a modified definition of ARDS.<sup>41</sup> In contrast to the informal method used by the AECC, this is a multistep consensus-developing process that has been used in marketing and technology forecasting. In the Delphi technique, a group of experts is surveyed and feedback is provided. The results are used to initiate a new, more focused survey. Multiple iterations of this approach ultimately lead to consensus. Ferguson and associates used four survey rounds. The first round generated a series of criteria. In two subsequent rounds, the criteria were reduced. In a final round, participants arrived at a definitive evaluation that led to a set of provisional criteria (Table 10-3). These differed from the AECC criteria in multiple aspects, most noticeably in the standardization

	Defining Characteristic	Operational Definition
1	Hypoxemia	$Pao_2/Fio_2 < 200$ mm Hg with $PEEP \geq 10$
2	Acute onset	Rapid onset in <72 hr
3	Radiographic abnormalities	Bilateral airspace disease <sup><math>\dagger</math></sup> involving $\geq 2$ quadrants on frontal chest radiograph
4	Noncardiogenic in origin	No clinical evidence of congestive heart failure (including use of pulmonary artery catheter and/or echo if clinically indicated)
5	Decreased lung compliance	$\begin{array}{l} \mbox{Static respiratory system compliance} \\ < 50 \mbox{ mL/cm $H_2$O} (with patient $$sedated, tidal volume of $$mL/kg $$ideal body weight, PEEP $$= 10$) \end{array}$
6	Predisposition	Direct and/or indirect factor associated with lung injury <sup>‡</sup>

Table 10-3 Delphi Criteria for ARDS

\*ARDS is indicated by the presence of criteria 1-4 and one of 5 or 6.

<sup>&</sup>lt;sup>†</sup>Airspace disease is defined as the presence of one or more of the following: (1) air bronchograms, (2) acinar shadows (nodular opacities 4-10 mm in diameter with poor margination), (3) coalescence of acinar shadows, (4) silhouette sign (loss of definition of the heart border or hemidiaphragm, excluding that caused by lobar collapse).

<sup>&</sup>lt;sup>‡</sup>Direct lung injury: pneumonia, aspiration of gastric contents, fat emboli, near drowning, inhalational injury, reperfusion pulmonary edema after transplantation, or pulmonary embolectomy; indirect lung injury: sepsis, severe trauma with shock and multiple transfusions, cardiopulmonary bypass, transfusions of blood products, and severe burns.

PEEP, positive end-expiratory pressure.

Adapted from Ferguson ND, Davis AM, Slutsky AS, Stewart TE. Development of a clinical definition for acute respiratory distress syndrome using the Delphi technique. J Crit Care. 2005;20:147-154.

of PEEP requirements, the definition of a timeline for acute onset, and the introduction of more specific criteria for radiographic abnormalities. In an initial testing experience, the Delphi definitions were compared with the LIS and the AECC criteria and against autopsy findings of diffuse alveolar damage in 138 patients.<sup>42</sup> Although the Delphi criteria and the LIS had better specificity than the AECC criteria (respectively, 0.82 and 0.77 versus 0.51), the sensitivities of all three methods were comparable (between 0.83 and 0.69). Thus, the Delphi criteria are provisional and will need to be refined and further tested before clinical or investigational use.

In an attempt to rationalize patient recruitment in clinical trials, the use of "ad hoc" criteria has been advocated.<sup>16</sup> Patients would be chosen based on the scope of the study and on the intervention being investigated. If, for example, a study focused on the outcome effects of alveolar recruitment, patients would be recruited based on their response to recruitment maneuvers or to higher PEEP. Another example would be the use of cytologic markers of fibrosis to select candidates for a study on steroids in ARDS. Although appealing, this approach will further fragment study populations, and it is not clear that clinical outcomes improve. It also is possible that this method would yield a series of studies with good internal validity that could not be extrapolated to other conditions, thus resulting in poor external validity. Additionally, the clinical applicability of these sets of criteria likely would be limited.

#### AUTHORS' RECOMMENDATIONS

- ARDS is a condition characterized by acute hypoxemia, compromised respiratory mechanics, and widespread inflammation of both lungs.
- Diagnosis is, by necessity, clinically based.
- Current and past diagnostic criteria for ARDS have limited validity and reliability because they fail to select a population with homogenous outcomes.
- Currently, there is inadequate evidence to justify a radical change in these criteria.
- To recruit patients with uniformly severe outcomes, future clinical studies may benefit from the addition of standardized ventilator settings and, when possible, of an observation period as the requirement for the diagnosis of ARDS.
- Cautious selection of patients based on their physiologic, radiologic, or biologic characteristics may be appropriate for select clinical trials. However, understanding that the results thus obtained will be applicable only to patients with similar characteristics.

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## 11 What Is the Natural History of a Patient with ARDS?

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#### **HISTORY AND DEFINITIONS**

The increasing availability of positive-pressure ventilation in the 1950s and 1960s allowed physicians to support critically ill patients through previously fatal illnesses. In the early period of positive-pressure ventilation, however, a variety of reports described difficult cases that did not respond predictably to this intervention. In 1967, Ashbaugh and colleagues published their classic manuscript detailing the course of 12 patients with a syndrome of refractory hypoxemia, diffuse alveolar infiltrates, and decreased pulmonary compliance. Because of the syndrome's clinical and histopathologic similarities with an illness seen in premature infants, they termed this condition the *acute respiratory distress syndrome in adults*.<sup>1</sup>

In a subsequent manuscript, Petty and Ashbaugh redescribed the syndrome, denoted clinical features, and suggested principles of management. Through increasing experience, it became clear that many factors could precipitate the syndrome; it is not merely the lung's response to a pulmonary insult. They further noted that, in patients who did not survive the condition, extrapulmonary complications and organ failure-rather than respiratory failure-commonly caused the patients' demise. Their recommended management included strategies to improve gas exchange (i.e., volume-controlled ventilation, oxygen control, and the use of positive endexpiratory pressure [PEEP]) as well as interventions to prevent further pulmonary injury (i.e., treating the precipitating event fluid restriction, and corticosteroids).<sup>2</sup> Well-designed randomized controlled trials would be necessary to test these and other management techniques.

Throughout the ensuing decades, investigators conducted many observational studies and clinical trials to further characterize the course of, and evaluate therapy for, the adult (now *acute*) respiratory distress syndrome (ARDS). Unfortunately, no consensus definition for the syndrome existed.<sup>3</sup> As a result, the enrollment criteria varied, making interpretation of the results difficult.<sup>3</sup> In an attempt to standardize the definition of ARDS for both prognostic and research purposes, Murray and colleagues proposed a two-part definition including an acute lung injury (ALI) scoring system and identification of the disorders associated with the development of ARDS.<sup>4,5</sup>

Despite these efforts to provide a more refined definition of ARDS, the lack of a consensus definition was an obstacle to the design of both epidemiologic and clinical trials. In 1992, the American Thoracic Society and the European Society of Intensive Care Medicine formed the American-European Consensus Committee (AECC) on ARDS in an "attempt to bring clarity and uniformity to the definition of acute lung injury and ARDS." The members recommended that the acronym ARDS should refer to the "acute" (rather than "adult") respiratory distress syndrome because the syndrome had been described in patients of all ages. The consensus committee drafted the modern definition for ARDS (Table 11-1).<sup>6</sup> Although this definition draws a distinction between ALI and ARDS based on the severity of hypoxemia, the distinction is arbitrary, because both lie within a spectrum of the same process.

#### EPIDEMIOLOGY

Determining the incidence of ALI and ARDS is difficult, and estimates have varied greatly.<sup>3</sup> In 1972, the National Heart and Lung Institute estimated the incidence of ARDS to be 75 cases per 100,000 population per year.<sup>7</sup> Later incidence studies reported much lower rates, ranging from 1.5 per 100,000 to 17.9 per 100,000,<sup>8–12</sup> but methodologic differences make comparisons difficult to interpret. For example, each of these studies included a subset of hospitals in a specific geographic region, and follow-up was often less than 1 year. Further, each of these incidence studies used different definitions because most took place before the AECC definition.<sup>6</sup>

To address the limitations of previous incidence studies, investigators in King County (Seattle), Washington, designed a prospective cohort study to determine the incidence of and outcomes from ALI/ARDS. King County, because of its geographic location, presents a unique opportunity for population-based research because patients residing there are unlikely to travel outside the county for medical care. The King County Lung Injury Project (KCLIP) included 21 hospitals (all 18 hospitals of King County and 3 hospitals from adjacent counties) and followed patients enrolled between April 1999 and July 2000 for 12 consecutive months. To identify patients with ALI/ ARDS, investigators used the definitions recommended by the AECC on ARDS.<sup>6</sup> The KCLIP investigators estimated the incidence of ALI to be 78.9 per 100,000 person years (age adjusted to 2000 U.S. Census, 86.2 per 100,000 person years).<sup>13</sup>

#### Table 11-1 American European Consensus Conference Diagnostic Criteria for Acute Respiratory Distress Syndrome (ARDS) and Acute Lung Injury (ALI)

- Acute onset
- Bilateral infiltrates on chest radiograph consistent with pulmonary edema
- Hypoxemia
- ALI:  $Pao_2/Fio_2$  ratio  $\leq 300$
- ARDS:  $Pao_2/Fio_2$  ratio  $\leq 200$
- Absence of heart failure
  - No clinical evidence of left atrial hypertension
  - If measured, pulmonary arterial occlusion pressure  $\leq$  18 mm Hg

Data from Bernard GR, Artigas A, Brigham KL et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes and clinical trial Coordination. *Am J Respir Crit Care Med.* 1994;149:818-824.

#### MORTALITY

The acute mortality of ARDS has declined in the past four decades. Initial reports of ARDS-associated mortality rates varied from 50% to 75%. However, owing to variable definitions and approaches to management, it is difficult to compare these studies.<sup>14–16</sup> To assess the trends in the outcome of ARDS over time, Milberg and associates performed a single-center, retrospective cohort analysis of cases of ARDS from their institution between 1983 and 1993.<sup>16</sup> Overall mortality changed little between 1983 and 1987 (53% to 68%) but subsequently decreased to a low of 36% in the final year of the analysis. In 2000, the Acute Respiratory Distress Syndrome Network (ARDSNet) published their landmark, multicenter study of ventilation with two different tidal volumes. In this report, the standard-of-care arm had a crude mortality rate of 39% (the interventional arm revealed a reduced mortality rate of 31%).<sup>17</sup> Two subsequent studies performed by the ARDSNet revealed comparable rates of death before discharge from the hospital.<sup>18,19</sup>

The mortality rate in the ARDSNet-sponsored studies may not apply to the overall ALI/ARDS population because these studies excluded patients with such high-risk conditions as sickle cell disease, chronic liver disease, and neuromuscular disease.<sup>17–19</sup> In contrast to the design of the ARDSNet randomized, controlled trials, the KCLIP included *all* patients with ALI/ARDS (as defined by the AECC criteria<sup>6</sup>) in their mortality analysis. These investigators found an in-hospital morality rate of 38.5% in patients with ALI and 41.1% in patients with ARDSNet initial publication.<sup>17</sup>

### CLINICAL FEATURES AND PATHOPHYSIOLOGY

The normal lung is a compliant, air-filled union of structure and function that efficiently performs the task of gas exchange. In ALI/ARDS, the normal structure and function of the lung are disrupted, resulting in a noncompliant, fluid-filled organ that is inefficient in performing gas exchange. Although a wide variety of insults can initiate the process of ALI (Table 11-2), once initiated, three pathologically distinct stages characterize the syndrome: exudative, proliferative, and fibrotic.<sup>20</sup> Although these stages are distinct histologically, they are less distinct clinically and may overlap.

#### **Exudative Phase**

Acute respiratory failure and bilateral infiltrates consistent with pulmonary edema on chest radiograph characterize the initial, exudative phase of early ARDS. The most striking clinical features of early ARDS are severe hypoxemia and decreased pulmonary compliance,<sup>21</sup> usually requiring mechanical ventilation with high minute volumes. Pathologic examination reveals diffuse alveolar damage. Necrosis and apoptosis of type I pneumocytes lead to a denuded and profoundly abnormal alveolar epithelium. Eosinophilic hyaline membranes, composed of fibrin, plasma proteins, and cellular debris, form along the alveolar walls and are characteristic of the exudative phase.<sup>20</sup> Activated neutrophils and macrophages populate the injured alveolar spaces, whereas extravasated erythrocytes enter through the damaged capillary endothelium.<sup>22</sup>

The acute injury to both the capillary endothelium and alveolar epithelium leads to increased permeability and massive interstitial and alveolar edema. Because the endothelial and epithelial barriers no longer provide an

Table	11-2	Conditio	ns Ass	ociated	with	Acute
Lung	Injury	and the	Acute	Respira	tory	
Distre	ess Sv	ndrome				

Direct Lung Injury	Indirect Lung Injury
COMMON CONDITIONS	
Infectious pneumonia	Sepsis
Aspiration of gastric contents	Severe trauma
LESS COMMON CONDITIONS	
Inhalational injury	Transfusion-related lung injury
Pulmonary contusion	Cardiopulmonary bypass
Fat embolus	Acute pancreatitis
Amniotic fluid embolus	Severe, large- surface-area burns
Near-drowning	Drug overdose
RARE CONDITIONS REQUIRING SP CONSIDERATION	ECIAL
Miliary tuberculosis <sup>41</sup>	
Cryptogenic organizing pneumonia <sup>42</sup>	
Acute eosinophilic pneumonia <sup>43</sup>	

effective barrier to the movement of plasma proteins, the edema fluid has a characteristically high protein concentration. Increases in pulmonary capillary hydrostatic pressure can worsen the edema formation. Additionally, the damaged alveolar epithelium lacks the normal capacity to remove the edema fluid from the alveolar spaces.<sup>23</sup> These factors contribute to the severity and duration of pulmonary edema and injury in ARDS.<sup>24</sup>

#### **Proliferative Phase**

As early as 3 days after the onset of ARDS, the remaining uninjured type II pneumocytes begin to proliferate. This marks the onset of the proliferative phase of ARDS. Oxygen requirements typically decrease during this period as pulmonary edema resolves. However, the lung remains poorly compliant, and an increased dead space fraction necessitates high minute ventilation. Alveolar infiltrates may improve, whereas interstitial infiltrates remain on chest radiographs.<sup>25</sup> Microscopic examination of the lung reveals airspaces lined with cuboidal type II cells that cover the injured epithelial surface.<sup>20</sup> These pneumocytes may differentiate into type I cells, re-establishing the normal fluid transport mechanisms of the alveolus and promoting the process of healing and resolution.<sup>21</sup> During the proliferative phase of ARDS, in addition to type II pneumocytes, interstitial fibroblasts also proliferate.<sup>20</sup>

#### **Fibrotic Phase**

Although many patients experience an otherwise uneventful recovery from the proliferative phase of ARDS, some patients progress to a syndrome of fibrosing alveolitis and chronic respiratory failure. Recent clinical experience suggests that the incidence of fibrosing alveolitis may be decreasing with the advent and routine use of protective ventilatory strategies. Prolonged respiratory failure in patients with ALI/ARDS appears to indicate progressive pulmonary fibrosis because increasing alveolar fibrosis has been demonstrated in the lung tissue of those who persist on mechanical ventilation into day 10 of the illness. Extensive pulmonary fibrosis is evident by day 35.<sup>26</sup> Further, the progression to fibrosing alveolitis, as documented by biopsy, portends a poor prognosis when compared with patients without this finding.<sup>2</sup> Although most physicians consider the clinical features of pulmonary fibrosis to be delayed complications of ARDS, the process of fibrosis is initiated early in the course. Indeed, there may be evidence of interstitial fibrosis as early as 36 hours into the course of the illness,<sup>28–30</sup> and biomarkers of collagen production in the lung are elevated as early as the first day of ARDS.<sup>31</sup> This early biochemical and histopathologic evidence of fibrosis implies that the molecular mechanisms responsible for fibrosis are triggered early in the course of disease.<sup>24</sup>

#### LONG-TERM SEQUELAE

Survival rates for ARDS have improved in the past decade,<sup>13</sup> reflecting advances in supportive care and

ventilator management. Reductions in the acute mortality of ARDS have led to an increase in the population of ARDS survivors in the community. As this population has grown, the long-term consequences of the condition have become more apparent.<sup>32</sup>

#### Quality of Life and Health Care–Related Costs

Survivors' quality of life is of utmost concern in the treatment of any medical condition. Multiple studies have shown that health-related quality of life scores are consistently lower in survivors of ARDS than in the general population.<sup>33–35</sup> Serial quality of life measurements in ARDS survivors show improvement throughout the first year after discharge. Unfortunately, this improvement appears to abate in the subsequent year.<sup>34–36</sup> Additionally, survivors of ARDS frequently report symptoms of anxiety and depression that persist for years after the initial hospitalization.<sup>35</sup> Although there is initial improvement in quality of life throughout the first year after discharge, ARDS survivors do not reach the baseline quality of life measured in control subjects.

In addition to substantial emotional and behavioral costs, ARDS also places a profound economic burden on both survivors and society. Although the predominance of the direct costs of ARDS relate to the initial hospitalization, postdischarge rehabilitation and readmission also contribute to the total costs generated.<sup>34</sup> The total health care-related dollars spent on the condition represent only a fraction of the total economic burden of the illness because many survivors are unable to resume their previous professional activities. As Hopkins and colleagues demonstrated, about one third of survivors return to full-time employment or school, one third receive disability benefits, and one third retire or otherwise do not work.<sup>35</sup> Thus, the financial burden of ARDS reaches from the hospital to the workplace and reflects the physical, emotional, and cognitive consequences of the disease.

#### **Pulmonary and Neurocognitive Dysfunction**

Survivors of ARDS experience not only emotional and economic sequelae but also long-lived declines in pulmonary and neurocognitive function. Pulmonary dysfunction after ARDS is typically mild and may result in an array of defects in pulmonary function testing, although reductions in diffusing capacity are the most commonly observed aberration.<sup>37–39</sup> Patients with normal pulmonary function studies, including diffusing capacity, may exhibit marked abnormalities in exercise testing, indicating that this method may be most sensitive for detecting gas exchange abnormalities after ARDS.<sup>37,38</sup>

Although pulmonary function abnormalities after ARDS are typically mild, neurocognitive sequelae may be striking. Hopkins and associates demonstrated that *all* survivors of severe ARDS had neurocognitive impairment on hospital discharge, with cognitive impairment persisting in 78% at the 1-year follow-up.<sup>40</sup> Similar to other indices of recovery in ARDS, it appears that improvement in neurocognitive function occurs predominantly during

the first year after hospital discharge, with little increment after this time.  $^{35}$ 

Currently, the mechanisms underlying the long-term consequences of ARDS are largely unknown; however, research is under way to determine the etiology of these sequelae. As the acute management of ARDS improves and the population of survivors increases, the long-term consequences of this illness will rise. Further investigation into the mechanisms of emotional, physical, and neurocognitive dysfunction seen after hospital discharge are necessary to prevent these sequelae from undermining our advances in the acute management of ALI/ARDS.

#### CONCLUSION

ARDS remains a prevalent and often fatal condition in intensive care units across the world, with a high mortality rate. Since its initial description by Ashbaugh and colleagues in 1967, clinicians and researchers have made great progress in understanding the epidemiology, pathophysiology, and clinical course of the condition. Unfortunately, despite our increased understanding of the pathogenesis of ALI/ARDS, countless clinical trials, and the expenditure of tremendous medical resources, relatively few specific therapies for the condition exist. In fact, beyond supportive care and control of the predisposing condition, only a plateau pressure-limited low tidal volume ventilation strategy has been proved effective in reducing mortality. Among patients who survive the condition and return home, many have persistent physical and neurocognitive sequelae that lead to reduced quality of life and the increasing economic burden of the condition.

#### AUTHORS' RECOMMENDATIONS

- The AECC definition is the currently accepted definition of ALI/ARDS and is used in recent clinical trials that study the condition.
- ARDS is a common condition, with an incidence of 86.2 per 100,000 person years.
- Despite advances in our understanding of ALI/ARDS, the overall mortality rate of the condition remains about 30%.
- The clinical course of ALI/ARDS consists of three phases, which are histologically distinct but less distinct clinically.
- Long-term pulmonary and neurocognitive dysfunction is common in survivors of ALI/ARDS.

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## 12 Do Nonventilatory Strategies for Acute Lung Injury and ARDS Work?

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The inflammatory injury suffered by the alveolar epithelium-endothelium complex provides multiple potential therapeutic targets. The inflammatory process could be inhibited at any stage from the genome to inflammatory signaling to leukocyte activation. Similarly, the various pathophysiologic consequences of alveolar injury could be amenable to pharmacologic intervention. The injurious process affects local alveolar ventilation, gas diffusion, and perfusion leading to reduced compliance, ventilationperfusion mismatch, and respiratory failure. This chapter reviews the evidence for past, present, and potential future pharmacologic therapies for acute lung injury and acute respiratory distress syndrome (ALI/ARDS). Therapies can be classified as aiming to improve the pathophysiologic consequences of ALI/ARDS or as anti-inflammatory, although a large degree of overlap exists.

#### THERAPIES TO TREAT PATHOPHYSIOLOGIC CONSEQUENCES OF ALI/ARDS

#### Surfactant Deficiency

Surfactant is an endogenous mixture of phospholipids and proteins A to D produced by type 2 alveolar cells. It reduces alveolar surface tension, preventing alveolar collapse, and has anti-inflammatory and antimicrobial properties. Exogenous surfactant administration has been successfully used in neonatal respiratory distress syndrome, a condition of reduced surfactant production. Early trials in ARDS demonstrated physiologic improvements<sup>1–7</sup>; however, later phase 3 trials failed to show an improvement in mortality.<sup>8,9</sup> A meta-analysis of surfactant trials in ALI/ ARDS reported an increase in oxygenation without an improvement in duration of ventilation or mortality.<sup>10</sup>

Various reasons have been proposed for these results. Although the neonatal syndrome is due to reduced production, the situation is more complex in ALI/ARDS. Surfactant is affected by increased removal, altered composition, reduced efficacy, and reduced production. Potential limitations of these phase 3 studies include the use of suboptimal surfactant formulation, dose and duration of therapy, inadequate alveolar delivery, and late initiation of therapy. The effect of calfactant (a calf protein B and C-based surfactant) in ALI/ARDS is currently being studied (NCT00682500), whereas trials of Surfaxin (a synthetic protein B-based surfactant) (NCT00215553) and HL-10 (a pig protein B and C-based surfactant) (NCT00742482) have recently been terminated, and results are awaited. Pending new research, surfactant therapy is not recommended (Table 12-1).

#### Limitation of Generation of Alveolar Edema

Alveolar flooding is primarily dependent on three factors: capillary hydrostatic pressure, oncotic pressure, and alveolar-capillary permeability. Capillary permeability is increased in ALI/ARDS. Reducing hydrostatic pressure and increasing oncotic pressure may ameliorate the development of pulmonary edema.

Reducing capillary hydrostatic pressure targeted to pulmonary artery occlusion pressure (PAOP)<sup>11</sup> and central venous pressure (CVP)<sup>12</sup> may be associated with improved outcome in ALI/ARDS, although fluid management guided by a pulmonary artery catheter (PAC) compared with a central venous catheter offers no advantage in ALI/ARDS.<sup>13</sup> Both a positive fluid balance<sup>14–17</sup> and increased extravascular lung water (EVLW)<sup>18</sup> are associated with poor outcomes in ARDS. Guiding fluid therapy with EVLW measurement rather than PAOP may be better.<sup>19</sup>

Hydrostatic pressure may be reduced by restricting fluid intake, increasing fluid output with either diuretics or renal replacement therapy (RRT), or decreasing vasomotor tone with vasodilators. The phase 3 Fluid and Catheter Treatment Trial (FACTT) study demonstrated improvements in secondary outcomes such as duration of ventilation and intensive care unit (ICU) stay with a restrictive fluid strategy. Fluid balance was dictated by a protocol of diuretic administration based on filling pressures.<sup>12</sup> Total 7-day fluid balance was about 0 mL, compared with about 7000 mL in the liberal fluid strategy. Although there was no difference in mortality, importantly there was no increase in renal failure or organ hypoperfusion with fluid restriction.

Animal models have demonstrated reduced pulmonary edema through reductions in pulmonary vascular pressures and permeability with RRT. Two small observational studies

Recommended	Not Recommended as Routine Therapy	Investigational
Restrictive fluid strategy	Surfactant	Extravascular lung water-guided fluid strategy
Diuretics	Intravenous vasodilators	Renal replacement therapy
Low central venous pressure	Pulmonary artery catheter	Albumin β-Agonists Insulin Gene therapy Growth factors
	Inhaled NO Activated protein C Antithrombin III	Stem cells Inhaled prostacyclin Endothelin antagonists Almitrine Tissue factor pathway inhibitor Factor VIIai Heparin
	Steroids (for established ALI/ARDS) Ketoconazole Ibuprofen N-acetylcysteine Procysteine Lisofylline Sivelestat	Heparin Thrombomodulin Steroids (for early ALI/ARDS) Complement antagonism Interferon-β Anti-CD14 antibody Anti-CD18 antibody Pentoxifylline Granulocyte-macrophage colony-stimulating factor Depelestat Vitamins C and E Statins Renin-angiotensin system modulation
	Sivelestat	Granulocyte-macrophage colony-stimulating Depelestat Vitamins C and E Statins Renin-angiotensin system modulation Omega-3 fatty acids Induced hypothermia

#### Table 12-1 Summary of Nonventilatory Strategies for ALI/ARDS

\*Therapies with mixed results in clinical studies (e.g., steroids) require further evaluation before a specific recommendation can be made.

in humans have provided mixed results. Ten children with ALI/ARDS after bone marrow transplantation or chemotherapy treated with RRT had an 80% survival rate, in contrast to a historical survival rate of 15%.<sup>20</sup> Thirty-seven adults with renal failure and ALI/ARDS treated with RRT and a zero fluid balance had no pulmonary improvements within the first 24 hours of treatment.<sup>21</sup> The role of RRT in the management of ALI/ARDS remains uncertain.

The choice of fluid for resuscitation in ALI/ARDS remains unclear. Theoretically, a colloid with higher oncotic pressure would be more suitable than a crystalloid, but this has not been borne out in a large trial of albumin versus saline in critical illness.<sup>22</sup>

Hypoproteinemia is associated with the development of lung injury and is a marker of weight gain and death. Two small studies have investigated the use of furosemide with albumin infusions in hypoproteinemic patients with ALI. Both showed increases in total serum protein and more negative fluid balances with furosemide and albumin administration. This was associated with improved oxygenation, but there was no mortality benefit.<sup>23,24</sup>

Albumin also exerts antioxidant effects through its thiol group. Nonsurvivors of ALI/ARDS have reduced thiol values.<sup>25</sup> The infusion of albumin is associated with increased plasma thiol levels in sepsis<sup>26</sup> and ALI/ARDS<sup>27</sup> and decreased markers of oxidant injury.

A study is presently ongoing to investigate whether minimizing EVLW, measured by transpulmonary thermal indicator dilution using the Pulse Contour Cardiac Output (PiCCO) and directed by the FACTT diuretic algorithm, is superior to CVP-guided therapy (NCT00624650). A phase 2 study investigating the role of recombinant human atrial natriuretic peptide (Carperitide) in minimizing pulmonary edema in ARDS has recently been completed, and results are awaited (NCT00030121).

Lung injury is often heralded by a rise in pulmonary vascular resistance, with an imbalance between pulmonary vasoconstrictors and vasodilators being seen in animal endotoxin shock models. Intravenous adenosine reduces EVLW, whereas intravenous nitroprusside and nitroglycerin also reduce pulmonary edema generation, but at the expense of increasing ventilation-perfusion mismatch. To date, there is no clear evidence to support the role of vasodilator treatment in ALI/ARDS.

#### Maximizing Alveolar Fluid Clearance

Alveolar fluid clearance (AFC) is impaired in more than 50% of patients with ALI/ARDS, with this group having higher mortality rates.<sup>28</sup>  $\beta$ -Agonists upregulate AFC by increasing sodium ion transport from the alveolar space. A clinical trial of intravenous salbutamol in ALI/ARDS demonstrated reduced EVLW and a trend toward increased survival.<sup>29</sup> A retrospective study of salbutamol exposure in ALI suggested an association between higher exposure and improved outcome.<sup>30</sup>  $\beta_2$ -Agonists may exert several

other beneficial effects in ALI/ARDS, including increased surfactant secretion, decreased lung endothelial permeability, decreased airway resistance, and decreased airway pressures. A large United Kingdom multicenter study is in progress examining the effects of intravenous salbutamol on outcome in ALI/ARDS (ISRCTN38366450), whereas an Acute Respiratory Distress Syndrome Network (ARDSNet) inhaled  $\beta$ -agonist study has recently been terminated, and results are awaited (NCT00434993).  $\beta$ -Agonists are not currently recommended for treatment of ALI/ARDS.

Another potential future treatment is gene therapy to increase the expression of the ion channels and pumps needed for AFC. An animal study investigating overexpression of the  $\beta_1$ -subunit of the sodium-potassium adenosine triphosphatase (ATPase) pump demonstrated increased rates of AFC and improved survival.<sup>31</sup> If the alveolar epithelium is severely injured, cellular regeneration may be required before a functioning epithelial layer can be manipulated.

#### **Epithelial and Endothelial Repair**

Stem cells have the capacity for limitless self-renewal and differentiation. Embryonic stem cells are pluripotent and have the ability to differentiate into any cell type in the body, whereas adult stem cells are multipotent and have the ability to differentiate into several cell types, including cell types of other organ systems.

Stem cells provide three therapeutic opportunities.<sup>32</sup> First, endogenous stem cells may be stimulated by exogenously administered growth factors. Keratinocyte growth factor (KGF), hepatocyte growth factor, and transforming growth factor- $\alpha$  (TGF- $\alpha$ ) have all been shown to reduce the effects of ALI in animal models. Epidermal growth factor, TGF- $\alpha$ , and KGF can all upregulate AFC. KGF has other potentially useful effects, including cytoprotection, augmented surfactant secretion, and an antioxidant effect. The administration of exogenous growth factors has not yet been directly studied in human trials of ALI/ARDS. Vascular endothelial growth factor (VEGF) promotes angiogenesis and regulates vascular permeability. Genetic polymorphisms of the VEGF gene are associated with lower levels of VEGF and increased mortality in ALI/ ARDS.<sup>33</sup> Although VEGF increases alveolar permeability in ALI/ARDS,<sup>34</sup> its administration enhances alveola repair in vitro and in animal models. The role of VEGF in ALI/ARDS is being studied (NCT00319631).

Secondly, administration of exogenous stem cells, either embryonic or adult, can provide repair to an injured alveolus. Animal studies have been promising. In a lipopolysaccharide (LPS)-induced ALI/ARDS model, bone marrow progenitor cells localized to the site of injury and differentiated into endothelial and epithelial cells. Autologous transplantation of endothelial progenitor cells preserves endothelial function and maintains the integrity of the pulmonary alveolar-capillary barrier, whereas administration of mesenchymal stem cells reduces the severity of ALI/ARDS in mice.<sup>35</sup> Patients with pneumonia<sup>36</sup> and ALI/ARDS<sup>37</sup> have higher levels of endothelial progenitor cells, and these higher levels correlate with improved outcome. Mesenchymal stem cells were originally thought to act as a source of regenerative cells by differentiating into, and locally replacing, lethally injured cells. However, their primary mechanism of action may be through the secretion of growth factors, cytokines, and other signaling molecules to cause the trophic modulation of inflammation, cell death, fibrosis, and tissue repair.<sup>38</sup>

The third role of stem cells is their ability to deliver gene therapy to the injured lung. Endothelial progenitor cells have been used to deliver vasodilatory genes to the pulmonary vasculature with resultant decreases in PAOPs in experimental pulmonary hypertension. In one study, nontransfected mesenchymal stem cells reduced the severity of ALI/ARDS in a mouse LPS model, whereas administration of mesenchymal stem cells transfected with the human angiopoietin-1 gene only demonstrated a small additional improvement.<sup>35</sup> Human studies are awaited.

#### Vasodilators

Nitric oxide (NO) is an endogenous vasodilator produced by the endothelium. When administered by inhalation, it vasodilates the circulation of ventilated alveoli, thus potentially reducing shunt and pulmonary hypertension. Early studies demonstrated physiologic improvements with NO in ARDS<sup>39-43</sup>; however, mortality remained unchanged. Two meta-analyses showed no mortality benefit<sup>44,45</sup> and reported possible harm due to methemoglobinemia, toxic nitrogen compounds, increased pulmonary edema, rebound pulmonary hypertension, and renal failure. Because NO is expensive, possibly harmful, and without a mortality benefit, its routine use is not recommended, although it may have a place as salvage therapy for severe hypoxemia given its ability to increase oxygenation.<sup>46</sup>

Prostacylins are derivatives of arachidonic acid and have potentially beneficial effects, including vasodilation, inhibition of platelet aggregation, reduction of neutrophil adhesion, and inhibition of both macrophage and neutrophil activation. Inhaled prostaglandin I2 (PGI2; prostacyclin) has been compared with inhaled NO in ARDS.<sup>47–49</sup> PGI2 has similar efficacy and some advantages, including minimal systemic effects, absence of platelet dysfunction, easy administration, harmless metabolites, and no requirement for monitoring. No placebo-controlled randomized trial has yet studied PGI2 in ARDS, but an ongoing study aims to show that nebulized PGI2 (iloprost) decreases pulmonary hypertension selectively and improves oxygenation in ARDS (NCT00314548).

Intravenous prostacyclin in the form of PGE1 has also been investigated in ARDS. Although vasodilatory effects can cause hypotension and increase pulmonary shunting, prostacyclin is anti-inflammatory and can increase both cardiac output and oxygen delivery and improve oxygen extraction during reduced oxygen delivery. Early studies<sup>50–52</sup> in ARDS showed no significant benefit, although the dose delivered was questioned.<sup>53</sup> PGE1 was reformulated as liposomal PGE1 to increase pulmonary drug delivery and minimize side effects. Again, despite a promising preclinical study,<sup>54</sup> subsequent studies were negative.<sup>55,56</sup>

Endothelin-1 is a potent vasoconstrictor that has been implicated in the pathophysiology of lung injury. Tezosentan, an endothelin receptor antagonist, has been investigated in animal models of lung injury and with mixed results thus far.

#### Vasoconstrictors

Almitrine is a pulmonary vasoconstrictor that may increase hypoxic pulmonary vasoconstriction and reduce shunt. In a small ARDS study, oxygenation was improved, with minimal increase in pulmonary vascular pressures.<sup>57</sup> The combination of intravenous almitrine to decrease blood flow to hypoxic lung units and inhaled NO, to increase blood flow to ventilated lung units, has been investigated in both experimental lung injury and a small clinical study.<sup>58</sup> Both found the combination superior than either therapy alone at increasing Pao<sub>2</sub>, with a minimal rise in pulmonary artery pressure. Further research is required.

#### Coagulation

An imbalance between fibrinogenesis and fibrinolysis in ARDS results in widespread fibrin deposition in the alveolar airspace, interstitium, and blood vessels. Pulmonary intravascular thrombosis and vasoconstriction can lead to the development of increased pulmonary vascular dead space, a known independent predictor of mortality in ALI/ARDS. Several anticoagulants have been proposed as potential therapies in ALI/ARDS and have undergone investigation in animal models. Tissue factor pathway inhibitor (TFPI), factor VIIai, heparin, antithrombin III, activated protein C (APC), and thrombomodulin have all been shown to have beneficial effects at this level of investigation.<sup>59</sup>

Protein C levels are lower in patients with ALI/ARDS than normal controls, and the level of protein C correlates with clinical outcome.<sup>60</sup> However, a small randomized controlled trial of APC in ALI/ARDS did not reduce either duration of ventilation or mortality, although pulmonary vascular dead space was decreased.<sup>61</sup> A further study investigating APC in inflammatory and infectious ALI/ARDS is in progress (ISRCTN52566874). A phase 2 trial of recombinant TFPI demonstrated improvements in lung dysfunction score and survival.<sup>62</sup> Therapeutic modulation of the coagulation system is not recommended in ALI/ARDS.

#### ANTI-INFLAMMATORY THERAPY

#### Glucocorticoids

Steroids possess a myriad of anti-inflammatory properties stretching from the genome to the macrophage. In the 1980s, several trials unsuccessfully examined the role of short-course, high-dose methylprednisolone in preventing the development of ARDS in high-risk patients.<sup>63–66</sup> A trial of high-dose steroids early in the course of ARDS was negative,<sup>67</sup> but a recent study in 91 patients with prolonged low-dose methylprednisolone showed reduced inflammation and organ dysfunction, plus reduced duration of mechanical ventilation and ICU stay.<sup>68</sup>

Excessive alveolar fibrosis is a feature of established ARDS, and the antifibrotic properties of steroids have been investigated in this setting. Observational studies<sup>69–72</sup> showed promising results and were followed by a small randomized controlled trial that suggested a beneficial effect on outcome.<sup>73</sup> However, the ARDSNet Late Steroid Rescue Study demonstrated no overall effect on mortality,

with increased mortality when steroids were commenced 7 days after the onset of ALI/ARDS.<sup>74</sup> A recent metaanalysis<sup>75</sup> and systematic review<sup>76</sup> concluded that steroids have no role in preventing ARDS but may have a role in treating ARDS. Further studies are required to definitively answer this question, and studies of low-dose steroids in early ARDS are planned (NCT00562835 and NCT00773058). Corticosteroid therapy is covered in detail in Chapter 22.

#### Proinflammatory Mediator Inhibition

Eicosanoids are derivatives of arachidonic acid and act as proinflammatory mediators. They are produced through the activity of either 5-lipoxygenase to produce the leukotrienes or cyclooxygenase to produce prostanoids.

Ketoconazole is an imidazole antifungal agent with antiinflammatory properties, specifically an ability to block leukotriene and thromboxane A<sub>2</sub> synthesis, and an antimacrophage effect whereby proinflammatory cytokine secretion is reduced. Small studies reported positive results for the prevention of ARDS in high-risk patients.<sup>77–79</sup> A large subsequent study by the ARDSNet group of ketoconazole in 234 patients with ARDS demonstrated no beneficial effects.<sup>80</sup>

Ibuprofen is a nonsteroidal anti-inflammatory agent that inhibits cyclooxygenase. In a large sepsis study of 448 patients, ibuprofen diminished prostanoid production and was associated with a trend toward decreased duration of pulmonary dysfunction and ARDS, but this did not reach statistical significance.<sup>81</sup> Modulation of other inflammatory mediators has also been investigated, but to date, no treatment has been shown to effectively reduce mortality.

Complement can contribute to ALI/ARDS by the generation of C3a and C5a, which attract neutrophils to the lungs and activate them. Complement can also cause cellular injury through the production of the membrane attack complex, C5b-9. Complement receptor-1 is a cell surface receptor on erythrocytes and leukocytes that can inhibit both classic and alternative complement pathways. Animal studies have provided a basis for further investigation, and a human phase 1 study in 24 patients with ARDS has demonstrated the safety of recombinant soluble cytokine receptor-1 and its ability to inhibit the complement cascade.<sup>82</sup> Further studies are awaited.

Insulin has anti-inflammatory effects through inhibition of the proinflammatory transcription factor NFkB. In a rat model of endotoxin-induced ALI/ARDS, tight glycemic control to 90 to 110 mg/dL reduced the severity of lung injury.<sup>83</sup> The role of intensive insulin therapy in preventing ALI/ARDS by maintaining tight glycemic control (80 to 110 mg/dL) is being studied in a phase 2 trial (NCT00605696).

Other current studies of potential anti-inflammatory treatments include a trial investigating the safety, tolerability, and efficacy of recombinant human interferon- $\beta$  in ALI/ARDS (NCT00789685) and a phase 2 trial of IC14, a recombinant chimeric monoclonal antibody to CD14, to block CD14-medicated cellular activation in patients with sepsis-induced ALI (NCT00233207). This trial has recently been terminated, and results are awaited. Anti-inflammatory therapy for ALI/ARDS is not recommended.

Table 12-2 Summary of Omega-3 Polyunsaturated Fatty Acid (PUFA) Supplementation Studies in ALI/ARDS

Study	Omega-3 PUFA	Other Antioxidants	Number in Trial	Setting	Nonmortality Benefits	Absolute Mortality Reduction
Singer et al, 1986 <sup>86</sup>	EPA and GLA	Yes	100	ALI	Yes	No
Pontes-Arruda et al, 2006 <sup>87</sup>	EPA and GLA	Yes	156	Sepsis and ARDS	Yes	19%
Pacht et al, 2003 <sup>88</sup>	EPA and GLA	Yes	43	ALI/ARDS	Yes	Not reported
Gadek et al, 1999 <sup>89</sup>	EPA and GLA	Yes	146	ARDS	Yes	No
Elamin et al, 2005 <sup>90</sup>	EPA and GLA	Yes	16	ARDS	Yes	Not reported

EPA, eicosapentaenoic acid; GLA, γ-linolenic acid.

#### Immunonutrition

Nutrition plays various roles in the management of ALI/ ARDS. The use of a feed high in fat and low in carbohydrate can reduce carbon dioxide production and thus ventilatory requirements.<sup>84</sup> Enteral nutrition can stimulate gut and lung immunoglobulin A (IgA) defense mechanisms.<sup>85</sup> The omega-3 polyunsaturated fatty acids found in fish oil, eicosapentaenoic acid (EPA),  $\gamma$ -linolenic acid (GLA), and docosahexaenoic acid (DHA) can reduce the production of arachidonic acid from membrane phospholipids.

Clinical studies in ALI/ARDS have demonstrated the benefit of fish oil supplementation with reductions in pulmonary neutrophil infiltration, microvascular permeability, pulmonary vascular resistance, duration of ventilation and ICU stay, and improved mortality.<sup>86–90</sup> This benefit from fish oil supplementation in ARDS has been supported in a recent systematic review on immunonutrition.<sup>91</sup> Further studies of fish oils in ALI/ARDS are in progress in Spain (ISRCTN63673813) and the United States (NCT00351533) (NCT00609180). This latter ARDS-Net study will also investigate early versus late feeding as well as antioxidants in ARDS. These studies will inform the use of immunonutrition in ALI/ARDS. Omega-3 fatty acid–based nutrition may have a role to play in the management of ALI/ARDS (Table 12-2).

#### Anti–Adhesion Molecule Therapy

The adhesion of immune cells to the endothelium to facilitate diapedesis is a vital step in the accumulation of neutrophils in the alveolus. The blockage of adhesion molecules is a potential therapeutic target in ALI/ARDS. Blockage of CD18, a neutrophil adhesion molecule, has been shown to attenuate the development of experimental lung injury. To date, there are no human studies.

#### **Effector Cell Inhibition**

Pentoxifylline is a phosphodiesterase inhibitor with antiinflammatory effects, acting against both neutrophils and macrophages. A small phase 1 study of pentoxifylline in six ARDS patients did not show any advantage in either gas exchange or hemodynamic parameters.<sup>92</sup> Lisofylline is a pentoxifylline derivative with slightly differing anti-inflammatory mechanisms. Although it also inhibits neutrophil accumulation and downregulates pro-inflammatory cytokines, it additionally has an effect on reducing levels of oxidized free fatty acids. Animal studies of lisofylline in the treatment of ARDS were promising, but again, a large multicenter study by the ARDSNet group in 235 patients with ALI/ARDS was negative.<sup>93</sup>

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is involved in the development and homeostasis of alveolar macrophages. It also plays a role in the prevention of alveolar epithelial apoptosis. A small study of 10 patients with ALI demonstrated an improvement in oxygenation with GM-CSF over a 5-day period.<sup>94</sup> A further study of GM-CSF in ARDS is under way in the United States (NCT00201409)

Activated neutrophils release neutrophil elastase, which plays a key role in alveolar injury, leading to increased vascular permeability and alveolar flooding. EPI-hNE-4 is a neutrophil elastase inhibitor that improved pulmonary compliance without affecting immune function during Pseudomonas aeruginosa-induced pneumonia in rats. A phase 3 multicenter trial of Depelestat (EPIhNE-4) in ARDS has completed and is awaiting publication (NCT00455767). Sivelestat is a reversible, competitive inhibitor of neutrophil elastase. After promising animal studies, sivelestat underwent a phase 3 study, in which it improved pulmonary function and reduced duration of ICU stay, with trends toward a reduction in duration of mechanical ventilation and mortality.95 However, the international Sivelestat Trial in ALI Patients Requiring Mechanical Ventilation (STRIVE) study in 492 ALI patients was stopped prematurely after an increase in the 180-day all-cause mortality rate was noted. No pulmonary improvements occurred, and the 28-day mortality rate was not reduced.96

#### Antioxidant Therapy

Activated neutrophils and macrophages partly exert their injurious effects through the generation of reactive oxygen species. Pulmonary glutathione, an antioxidant, is reduced in ARDS. *N*-acetylcysteine and procysteine are precursors for glutathione, and their administration can replete pulmonary glutathione levels in ARDS. Small studies of *N*-acetylcysteine in ALI/ARDS reported mixed results,<sup>97–100</sup> whereas a study of procysteine in ARDS was halted in 1998 owing to increased mortality (unpublished data). *N*-acetylcysteine can also downregulate NFkB, with resultant reduction in neutrophil chemoattractant messenger RNA (mRNA) and alveolitis in a rat model of lung injury.

Vitamin C and E administration in the critically ill reduced duration of mechanical ventilation and ICU stay without decreasing the incidence of ARDS.<sup>101</sup>

#### Statins

Statins were introduced into clinical practice as cholesterollowering agents through inhibition of HMG-CoA reductase and have since been shown to possess pleiotropic actions both dependent and independent of HMG-CoA reductase inhibition. Statins exert beneficial effects on inflammation and coagulation as well as epithelial, endothelial, and immune cells function.<sup>102</sup> Several retrospective studies have demonstrated that prior statin therapy is associated with improved survival in sepsis, including pneumonia.<sup>103-107</sup> Patients with ALI/ARDS receiving treatment with a statin during admission had a 73% lower odds of death, although this failed to reach statistical significance (odds ratio, 0.27; 95% confidence interval, 0.06 to 1.21; P = .09).<sup>108</sup> In contrast, another study suggested no benefit.<sup>109</sup> A recent study has shown pretreatment with a statin<sup>110</sup> reduces pulmonary markers of inflammation in an inhaled LPS-induced model of lung injury in healthy volunteers. The ongoing phase 2 HARP-prevention (ISRCTN56543987) and Hydroxymethylglutaryl-CoA reductase inhibition in Acute lung injury to Reduce Pulmonary oedema and inflammation (HARP) (ISRCTN70127774) studies are investigating the effect of simvastatin in the prevention and treatment of ALI/ARDS and will further inform this area. Several groups, including the ARDSNet and the Irish Critical Care Trials group are currently considering undertaking multicenter studies to address the role of statins in ALI/ARDS.

#### Angiotensin-Converting Enzyme Inhibitors

The SARS epidemic led to the discovery of a novel coronavirus, the receptor for which is a variant of the angiotensinconverting enzyme (ACE) implicating the renin-angiotensin system (RAS) in ALI/ARDS. ACE converts angiotensin I into angiotensin II, and angiotensin II acting through the angiotensin I receptor mediates vasoconstriction, alveolar permeability, and lung injury. ACE2 degrades angiotensin II, and therefore excessive ACE activity or ACE2 deletion is associated with worse lung injury.

Genetic observational studies in humans have supported the concept that the RAS system is important in the development and outcome of ALI/ARDS. ACE DD genotype is associated with increased ACE activity and worse outcome in ALI/ARDS.<sup>111–113</sup> A retrospective study has shown that prior treatment with an ACE inhibitor was associated with decreased mortality in patients requiring hospitalization for community-acquired pneumonia.<sup>107</sup> Therapeutic modulation of the RAS with recombinant ACE2, ACE inhibition, and angiotensin I receptor blockade with losartan attenuate pulmonary inflammation in rodent models of LPS-induced ALI/ARDS and ventilatorinduced lung injury. Human studies are awaited.

#### **Induced Hypothermia**

Hypothermia decreases metabolism by 25% at 33°C, reducing oxygen consumption and carbon dioxide production and thus ventilatory demand. It also decreases proinflammatory gene transcription and exerts an anti-inflammatory effect. In animal models, induced hypothermia reduces the expression of intracellular adhesion molecule-1, interleukin-1β levels, the pulmonary accumulation of neutrophils, and histologic lung damage. Several case reports have documented the successful use of hypothermia (33° to 34°C) for severe ALI/ARDS.<sup>114–116</sup> To date, there has been only one small study of 19 patients with sepsisassociated severe ALI/ARDS treated with induced hypothermia. The mortality rate was reduced by 33% at a mean temperature of 33.7 °C. The reduction in body temperature was associated with a reduction in alveolar-arterial oxygen gradient, heart rate, and cardiac index and an increase in oxygen extraction, although interestingly, oxygen consumption remained unchanged.<sup>117</sup> Further research is required.

#### REASONS THAT PHARMACOLOGIC THERAPY IS INEFFECTIVE IN ALI/ARDS

Despite repeated promising preclinical and clinical phase 1 and 2 studies of therapies for ALI/ARDS, no nonventilatory strategy has yet convincingly been shown to improve outcome. The many reasons for the scientific failure of translation from bench to bedside include limitations of animal models, poorly understood human factors, study methodologic flaws, and the use of oxygenation as an outcome measure in a condition in which only a small minority die from refractory hypoxemia.<sup>118,119</sup> The use of pharmacologic agents as adjuncts to increase oxygenation allowing the limitation of injurious ventilation may be associated with improved outcomes, but this remains to be tested.

#### AUTHORS' RECOMMENDATIONS

- Despite promising scientific advances, nonventilatory strategies for ALI/ARDS remain elusive.
- The best evidence we have is for minimizing pulmonary edema through fluid restriction when appropriate.
- Other therapies may occasionally be justified as salvage therapy in severe ALI/ARDS, but with the knowledge that their risk-to-benefit ratio remains unclear.

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### What Are the Pathologic and Pathophysiologic Changes That Accompany Acute Lung Injury and ARDS?

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Ashbaugh and Petty first described the adult respiratory distress syndrome in 1967. Their report provided the clinical details of 12 patients with acute respiratory failure and severe hypoxemia, poor lung compliance, and diffuse infiltrates on chest radiograph.<sup>1</sup> This common and often fatal condition has become known as acute respiratory distress syndrome (ARDS) and, more generally, acute lung injury (ALI). Since then, despite attempts to understand the pathophysiology underlying ALI, the gravity of this illness remains significant, with an attributable mortality of more than 74,000 patients per year in the United States.<sup>2</sup> The National Institutes of Health (NIH) have concentrated their efforts on understanding the pathophysiology of lung injury in hopes of identifying therapeutic targets and new management strategies for this devastating condition.<sup>3</sup> This chapter provides an overview of historical and current advances in the pathology and physiology of ALI.

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#### PATHOLOGY OF ACUTE LUNG INJURY

ALI patients develop protein-rich edema that floods into the lung because of disruptions to the barriers that protect the alveolar-capillary units (Fig. 13-1).<sup>4,5</sup> Cell types relevant to this disease process are the alveolar epithelium, capillary endothelium, and inflammatory cells. Lung biopsies from ALI patients display an alveolar cellular infiltrate rich with neutrophils, macrophages, and erythrocytes in addition to disrupted alveolar epithelium and denuded basement membranes lined by fibrin-rich hyaline exudates (Fig. 13-2).<sup>4–6</sup> Cell death, epithelial hyperplasia, inflammation, and disordered coagulation and fibrinolysis also have been pathologically described and are collectively termed *diffuse alveolar damage*.<sup>7,8</sup>

Injury to the alveolar epithelial barrier has several adverse consequences. The alveoli fill with pulmonary edema fluid that contains serum proteins and proteases that disable surfactant.<sup>9,10</sup> Surfactant dysfunction contributes to inhomogeneous airspace collapse. In addition, cuboidal type II alveolar epithelial cells, which cover about 10% of the alveolar surface area, have a number of

important functions. These include the production of surfactant and ion transport. Injury to alveolar type II cells impairs surfactant production and turnover and may contribute to pulmonary edema by creating an imbalance in normal fluid transport. The radiographic diagnosis of ALI is consistent with this pathology because atelectasis and bilateral infiltrates may be patchy and asymmetrical, and they typically spare nondependent lung zones.<sup>11,12</sup>

The alveolar compartment also plays a role in the regulation of intra-alveolar coagulation and fibrinolysis.<sup>13–15</sup> Alveolar epithelial cells in culture exposed to bronchoalveolar lavage (BAL) fluid from ALI/ARDS patients respond with increased tissue factor activity, messenger RNA (mRNA), and protein levels.<sup>13</sup> Tissue factor (TF) is a potent stimulator of the extrinsic coagulation cascade that eventually leads to thrombin formation and fibrin deposition. TF activity and alveolar fibrin deposition were increased in serial BAL specimens in a baboon model of ALI, demonstrating increased coagulation and diminished fibrinolysis.<sup>16</sup> BAL fluid from ARDS patients increased TF activity when compared with patients with interstitial lung diseases and with healthy controls.<sup>17</sup>

A procoagulant state also is observed in the lung endothelial compartment. Lung biopsy specimens of ALI patients contain microthrombi within pulmonary capillaries in addition to capillary endothelial injury.<sup>4,5</sup> Injury and activation of the pulmonary microvasculature is reflected in elevated plasma levels of von Willebrand factor (vWF) antigen. This marker of endothelial cell activation and injury is associated with increased mortality in both adults and children.<sup>18,19</sup> Plasma endothelin-1, another marker of endothelial cell activation and injury, also is elevated in ALI patients.<sup>20-22</sup> In addition, Ware and colleagues recently reported an increase in mortality in association with low plasma protein C levels and elevated plasma plasminogen activator inhibitor-1 levels.<sup>23</sup> These biomarker studies provide additional evidence that disordered coagulation and fibrinolysis are involved in ALI.

Another pathologic source of lung injury is mechanical ventilation. Heterogeneity from the uneven distribution



**Figure 13-1.** A pictorial representation of the injured alveolus in the acute phase of ALI and ARDS (*right*) in comparison with the normal alveolus (*left*). Bronchial and alveolar epithelial cells are necrotic and sloughing in the injured alveolus. The basement membrane is denuded, and there is formation of hyaline membranes. Neutrophils adhere to the injured capillary endothelium and marginate through the interstitium into the airspace. The airspace is filled with a protein-rich pulmonary edema fluid and pictured with multiple cellular responses. Inactivated surfactant and fibrin deposition is depicted. Alveolar macrophages secrete cytokines; interleukin-1 (IL-1), IL-6, IL-8, and IL-10; and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ). The macrophage is also shown secreting other cytokines, including IL-1, IL-6, and IL-10. Activated neutrophils release pro-inflammatory molecules such as platelet-activating factor (PAF), oxidants, proteases, and leukotrienes. MIF, macrophage inhibitory factor. (*From Ware LB, Matthay MA. The acute respiratory distress syndrome*. N Engl J Med. 2000;342:1334-1349. © 2000 Massachusetts Medical Society. All rights reserved.)

of injury and edema predisposes the lung to alveolar overdistention and shear stress on epithelial cells during ventilation.<sup>24</sup> High tidal volume ventilation may cause a disruption of the alveolar-capillary barrier from tensile strain and shear stress.<sup>25–27</sup> Mechanical forces on the lung can increase local inflammation by release of proinflammatory cytokines.<sup>28</sup> In 2000, a National Heart, Lung and Blood Institute (NHLBI)-sponsored clinical trial of 861 patients reported that a lower tidal volume ventilation strategy with a plateau pressure limit reduced mortality of ALI patients by 22% compared with higher conventional tidal volumes.<sup>29</sup> The results of this trial transformed clinical practice by emphasizing the need for lung-protective ventilation. Based on experimental work, lung-protective lower tidal volume ventilation may function by reducing injury to both the alveolar epithelium and the lung endothelium.<sup>30</sup> Levels of proinflammatory cytokines and markers of endothelial and epithelial cell injury in ALI patients were attenuated in patients treated with the

lower tidal volume strategy compared with controls who received conventional mechanical ventilation.<sup>23,31,32</sup>

Mechanical ventilation also has been associated with systemic injury. Studies suggest that alveolar overdistention predisposes to failure of nonpulmonary organs secondary to a proinflammatory state.<sup>33–35</sup> After intratracheal acid aspiration and injurious mechanical ventilation, rabbits developed both renal and hepatic injury.<sup>36</sup> Apoptosis was visualized in the kidneys, and pulmonary and systemic levels of proinflammatory cytokines were elevated. In a murine model of ventilator-associated lung injury, ventilation strategy altered pulmonary and systemic organ cytokine expression.<sup>37</sup> Both the kidney and the liver expressed interleukin-6 (IL-6) and vascular endothelial growth factor receptor-2 during high tidal volume ventilation but not with low tidal volume. Clinically, nearly one fourth of ALI patients from the NHLBI-sponsored clinical trials of low tidal volume ventilation, ketoconazole, and lisofylline developed acute kidney injury in the first 4 days



**Figure 13-2.** Histologic analysis during the acute phase (**A**) and the fibrosing-alveolitis phase (**B** and **C**) of ALI and ARDS. **A**, High-power light micrograph of a lung-biopsy specimen demonstrating intra-alveolar red cells and neutrophils as well as characteristic hyaline membranes. **B**, Low-power light micrograph shows diffuse granulation tissue in the distal airspaces with pronounced inflammatory cell infiltrate. **C**, Higherpower view of dense hyaline membranes and diffuse alveolar inflammation consistent with diffuse alveolar damage. (*Reproduced with permission from Dr. Martha Warnock, UCSF Professor Emeritus.*)

of study enrollment.<sup>38</sup> Further, acute kidney injury in the setting of ALI has been associated with more than a three-fold increase in the odds of death. This high mortality underlines the importance for further exploration of the link between pulmonary and distal organ injury.

#### PHYSIOLOGIC CHANGES THAT CHARACTERIZE ACUTE LUNG INJURY

Classically, the physiologic elements that manifest in ALI are rapid-onset hypoxemia, increase in pulmonary dead space ventilation, and reduced lung compliance. Together these features increase work of breathing and overwhelm metabolic needs, leading to severe respiratory failure.

A number of experimental and clinical studies have established increased permeability pulmonary edema as a physiologic hallmark of early ALI.<sup>39–41</sup> Flooding of the alveolar airspaces impairs adequate ventilation, resulting in hypoxemia from ventilation-perfusion inequality and intrapulmonary shunt.<sup>1,42,43</sup> Right-to-left shunting also may occur from reabsorption atelectasis secondary to alveolar denitrogenation,<sup>44</sup> in which pure inspired oxygen washes out nitrogen in alveoli that would otherwise provide the bulk of total gaseous pressure to stent open the alveoli. The sum of partial pressures of trapped gas in the alveoli exceeds the venous gas partial pressures, leading to a rapid diffusion into the blood and subsequent collapse of the alveoli.<sup>45</sup>

More recently, an increase in physiologic dead space has been recognized as a prominent component of the physiology of early ALI. An increase in pulmonary dead space results from damage to the pulmonary microvascular bed. Direct injury or microthrombus leads to compromised blood flow to the alveoli. This impairs the lung's ability to excrete carbon dioxide, wasting ventilation.<sup>4,23,46,47</sup> Several studies have demonstrated elevated dead space fractions in ALI patients.<sup>12,48–51</sup> Nuckton and colleagues found that an elevated dead space fraction was an early independent predictor of death in 179 mechanically ventilated patients with ARDS (Fig. 13-3).<sup>50</sup> This finding has been confirmed in a more recent study.<sup>51</sup> These data emphasize the clinical importance of endothelial injury in the pathophysiology of ALI/ARDS.

Reduction in thoracic compliance is another physiologic consequence of increased permeability pulmonary edema. Quasi-static respiratory compliance measured in the lung is defined as the mechanical effort required to distend the lung. The lung is stiff because of protein-rich pulmonary



**Figure 13-3.** Mortality according to quintile of pulmonary dead space fraction observed in 179 patients with ARDS. (*From Nuckton TJ, Alonso JA, Kallet RH, et al. Pulmonary dead-space fraction as a risk factor for death in the acute respiratory distress syndrome.* N Engl J Med. 2002;346:1281-1286. © 2002 Massachusetts Medical Society. All rights reserved.)

edema fluid, cellular infiltrate, and a reduction in functionally active surfactant. Quasi-static respiratory compliance measurements in ALI patients are lower than normal. These measurements, along with higher pulmonary dead space fraction, independently predict worse clinical outcomes.<sup>50</sup> Patients develop an increased work of breathing that often requires assisted ventilation.<sup>50,52</sup> Improvement of oxygenation in ALI patients also has been investigated with the use of an optimized level of positive end-expiratory pressure (PEEP).<sup>43,53</sup> Functional residual capacity has been shown to increase with PEEP,<sup>43</sup> likely from recruitment of collapsed alveoli.<sup>54</sup> Despite promising animal experiments,<sup>25</sup> the prophylactic use of PEEP of 8 cm H<sub>2</sub>O in a randomized controlled trial of patients at risk for ARDS did not show benefit in preventing or reducing the severity of ALI.<sup>55</sup> In a prospective, randomized, multicenter trial, the result was similar without further survival improvement in ALI patients who received higher PEEP levels.<sup>5</sup>

Other physiologic indices have been investigated as indicators of severity of illness in ALI. Measures of hypoxemia, although integral to the definition of ALI, have not been shown to be of consistent prognostic value. The Pao<sub>2</sub>/Fio<sub>2</sub> ratio has been considered in a number of studies, but this too failed to predict clinical outcomes reliably.<sup>29,40,57-59</sup> A four-point lung injury scoring system was published in 1988 to quantify physiologic impairment of the injured lung.<sup>60</sup> The score is derived from the level of PEEP,  $PaO_2/$ FIO<sub>2</sub> ratio, static lung compliance, and degree of infiltrates based on chest radiograph. Although the lung injury scoring system has not been predictive of clinical outcomes,<sup>57,58</sup> in a recent trial by the Acute Respiratory Distress Syndrome Network, a fluid conservative therapy strategy was associated with a significant decrease in the lung injury score.<sup>61</sup> Thus, there appears to be a benefit to measurement of pulmonary physiologic parameters in clinical trials, and the prognostic value of these parameters in the clinical setting should be further evaluated.

#### RESOLUTION OF PULMONARY EDEMA FLUID IS CRITICAL TO RESOLUTION OF ACUTE LUNG INJURY

Several different types of studies have demonstrated increased permeability of both epithelium and endothelium in ALI patients and animal models. As stated previously, damage to the capillary endothelium and alveolar epithelium in ALI patients results in flooding of the alveoli with protein-rich pulmonary edema fluid. Specifically, electron microscopy has demonstrated denuded epithelium and diffuse alveolar damage.<sup>4,5</sup> Increased permeability through the damaged microvasculature of ALI patients has been confirmed by studies with radiolabeled tracer proteins.<sup>62</sup> Hemodynamic and lung lymph flow measurements in large animal models demonstrate an increase in lung vascular permeability with proteinrich pulmonary edema following clinically relevant causes of ALI.<sup>39,63–65</sup> Altered lung vascular permeability has also been studied with cultured human endothelial cells.<sup>66,67</sup> Monolayers of human endothelial cells have increased permeability as measured by albumin flux when exposed to the plasma of ARDS patients.<sup>67</sup>

Clinical studies have shown the importance of resolution of pulmonary edema fluid to clinical outcomes and the role of the intact alveolar epithelium in this process. In a group of 34 mechanically ventilated patients, the resolution of pulmonary edema was associated with net fluid clearance across the epithelial barrier based on serial measurements of pulmonary edema protein content.<sup>68</sup> In a larger study of 79 ALI patients, serial measurements of pulmonary edema and plasma demonstrated that maximal alveolar fluid clearance was associated with a better prognosis, including lower mortality and a shorter duration of mechanical ventilation (Fig. 13-4).<sup>69</sup> Most ALI patients had impaired alveolar fluid clearance.

The concept of a damaged alveolar epithelium and disrupted lung fluid balance has led to a novel therapeutic



**Figure 13-4.** Hospital mortality of 79 patients with ALI or ARDS in relation to two groups of alveolar fluid clearance: maximal (≥14%/ hour) and impaired/submaximal (<14%/hour). *N*, number of patients. (*Reproduced with permission from Ware LB, Matthay MA. Alveolar fluid clearance is impaired in the majority of patients with acute lung injury and the acute respiratory distress syndrome.* Am J Respir Crit Care Med. 2001;163:1376-1383. Official Journal of the American Thoracic Society.)

concept in patients with ALI. Primary edema formation and accumulation may be increased from lung vascular permeability, but because alveolar fluid clearance balances the formation of pulmonary edema, patients may have time to recover from the primary cause of lung injury. Experimental studies demonstrated that  $\beta_2$ -agonists can accelerate the resolution of alveolar edema.<sup>70,71</sup> In a small randomized controlled double-blinded trial of 40 ALI patients, intravenous salbutamol significantly reduced extravascular lung water compared with placebo.<sup>72</sup>

A large multicenter trial is under way to evaluate the potential benefits of inhaled albuterol in ALI patients. Future large, prospective, randomized trials may improve our understanding of ALI and further reduce mortality from this common condition.

#### CONCLUSION

The pathologic and physiologic findings of ALI account for the complex and too often demise of patients suffering from this syndrome. The main physiologic features of lung injury are high-permeability protein edema, increased pulmonary dead space, and poor lung compliance. Pathologically, the integrity of the alveolar and capillary barriers is altered by injury and inflammation. In addition, alveolar epithelial cell functions of fluid clearance and surfactant production are disrupted by injury, thus contributing to pulmonary edema. Impaired coagulation and fibrinolysis and injurious mechanical ventilation can also contribute to lung injury. Several clinical trials have led to progress in our understanding and treatment of this syndrome of acute respiratory failure.

#### AUTHORS' RECOMMENDATIONS

- The pathology of lung injury includes disruption of the alveolar epithelial and capillary endothelial barrier by inflammation and both direct and indirect sources of injury.
- The physiology of lung injury involves hypoxemia from pulmonary ventilation-perfusion mismatch and intrapulmonary shunting, increased pulmonary dead space, and decreased lung compliance.
- Increased permeability pulmonary edema is the hallmark of ALI, although the quantity of lung edema can be increased by elevated lung vascular pressures.
- Understanding physiologic and pathophysiologic mechanisms of ALI will further our understanding of the treatment and management of this disease.

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# 14 Is Acute Lung Injury a Single Syndrome?

#### Adam Fang, Jason D. Christie

The definitions of acute respiratory distress syndrome (ARDS) and acute lung injury (ALI) have evolved since their first description by Ashbaugh and colleagues.<sup>1</sup> Currently, the American-European Consensus Conference (AECC) defines ALI as a syndrome with an acute onset, bilateral infiltrates on chest radiograph, Pao<sub>2</sub>/Fio<sub>2</sub> ratio of 300 or less, and pulmonary artery wedge pressure of 18 mm Hg or less.<sup>2</sup> The AECC definition has helped standardize the way clinicians and researchers systematically identify patients with the ALI syndrome by grouping them into a homogeneous population. However, many investigators argue that, given its diffuse nature, ALI may not be best viewed as a single comprehensive syndrome but rather as a collection of related subsyndromes that vary by etiology and clinical setting.<sup>3–8</sup>

ALI is a syndrome. A syndrome can be defined as "a group of signs and symptoms that occur together and characterize a particular abnormality or condition or a set of concurrent things (as emotions or actions) that usually form an identifiable pattern."9 The word is derived from Greek for "run together." A feature of ALI, like many other clinical syndromes, is that it is a paradigm: "a collection of beliefs shared by scientists, a set of agreements about how problems are to be understood."<sup>10</sup> In forming the consensus AECC definition, the working group set the ALI paradigm for future research. Nonetheless, ALI is a paradigm that warrants further examination. For example, endophenotypes of the ALI syndrome may be more useful for uncovering clinical associations, determining prognoses, or defining patients more appropriately for clinical trials.<sup>7,8</sup> This chapter examines the evidence for ALI as a single syndrome and questions whether there is sufficient evidence to suggest a paradigm shift in the ALI syndrome definition.

#### EPIDEMIOLOGY

A number of studies have demonstrated associations of different predisposing factors with the development of ALI. These include sepsis, multiple transfusions, aspiration of gastric contents, pneumonia, and trauma. More recently, there has been an interest in categorizing patients based on the mechanism of lung injury, as a "direct" or "pulmonary" insult to the alveolar epithelium or an "indirect" or "extrapulmonary" insult in response to a systemic inflammatory response (Table 14-1).<sup>6</sup> A major thrust in defining subgroups of ALI has come from Gattinoni and colleagues; these investigators have popularized the terms *ARDSp* for ARDS due to pulmonary disease and *ARDSexp* for ARDS due to extrapulmonary disease.<sup>7,8</sup>

Although overall case fatality has declined considerably in recent years, ALI remains a common and fatal respiratory condition.<sup>11</sup> Both the prevalence of and mortality from ALI vary widely, in part reflecting variation in precipitating factors and study design differences (Table 14-2). Although prior studies had reported an incidence between 3 and 75 cases per 100,000 person-years,<sup>12-15</sup> Rubenfeld and colleagues, in a well-constructed epidemiologic study, reported in 2005 an age-adjusted incidence of 86.2 cases per 100,000 person-years.<sup>11</sup>

A limitation in estimating the differences in incidence of pulmonary and extrapulmonary sources is that these distinctions may not be mutually exclusive. For example, consider the patient with ALI following lobar pneumonia and concurrent septic shock. In fact, the potential overlap of this categorization limits the utility of separating ALI into categories. Nonetheless, most studies indicate that ARDS from pulmonary causes is more prevalent than that from extrapulmonary causes, representing 47% to 75% of all cases.<sup>7,16–20</sup> Other studies do not support this and suggest a greater prevalence of extrapulmonary causes<sup>21–23</sup> or no difference in the prevalence of the two.<sup>24</sup> Pneumonia was the most common cause of ARDSp. This is followed by aspiration and traumatic pulmonary contusion. Sepsis was the most common precipitant of ARDSexp.<sup>15</sup> Rubenfeld and colleagues noted that the incidence of ALI changed as age increased.<sup>11</sup> Despite this, in each decade, the incidence was highest for ALI due to sepsis. However, a number of subjects had sepsis that arose from a pulmonary source. This further emphasizes that the distinction between ARDSp and ARDSexp categorization may not be clear.

The overall mortality rate from ALI is about 35% to 40%.<sup>15,25,26</sup> Mortality differences between ARDSp and ARDSexp have been reported, but once again there is variability (see Table 14-2). One study reported an increased mortality in ARDSp, whereas others demonstrated no differences between ARDSp and ARDSexp.<sup>7,16–20,24</sup> Most studies have found the trauma population to have the lowest mortality rate. This may be due to younger age, fewer comorbidities, and less systemic organ damage but,

#### Table 14-1 Risk Factors and Conditions Associated with Acute Lung Injury

Direct or Pulmonary Lung Injury	Indirect or Extrapulmonary Lung Injury
Pneumonia	Sepsis
Aspiration of gastric	Severe trauma
contents	Multiple bone fractures
Near-drowning	Flail chest
Toxic inhalation injury	Head trauma
Fat emboli	Burns
Pulmonary contusion	Multiple transfusion
-	Drug overdose
	Acute pancreatitis
	After cardiopulmonary bypass
	Intravascular disseminated
	coagulopathy

even after statistical adjustment for these factors, traumarelated ALI still appears to have lower mortality.

#### RADIOLOGY

A number of studies have used chest radiography and computed tomography (CT) to support the hypothesis that the radiologic pattern is different in ARDSp and ARDSexp. Patchy densities likely representing pulmonary consolidation predominant in radiographs from patients with ARDSp.16 CT evaluations of patients with ARDSp characteristically demonstrate an even balance between diffusely distributed ground-glass opacification (in craniocaudal and sternal-vertebral directions). Consolidation in ARDSp favors the vertebral-basal lung segments, with 50% more consolidation present in ARDSp than in ARD-Sexp (Fig. 14-1, 14-2).<sup>8</sup> In contrast, patients with ARDSexp characteristically have hazy and diffuse lung densities on chest radiographs, likely representing interstitial edema and atelectasis. Ground-glass opacification in the central (hilar) third of the lung is observed on CT scans, and



**Figure 14-1.** Computed tomography scan of patient with ARDS due to pulmonary disease (i.e., aspiration pneumonia) demonstrating extensive consolidation with normal lung and ground-glass opacification. (*Courtesy of M. Cereda, M.D.*)

40% had more extensive ground-glass infiltrates than ARDSp (Fig. 14-3). $^{8}$ 

Within the broad group of patients with ARDSp, there are differences in lung morphology. CT scans classified by Goodman and colleagues showed that communityacquired pneumonia has two prevalent patterns.<sup>17</sup> Some of these patients have extensive consolidation and air bronchograms in the dependant lung regions with ground-glass opacification. Others have homogenous diffuse interstitial and alveolar infiltration without atelectasis (Fig. 14-4). Conversely, patients with nosocomial pneumonia often present with dense consolidation around the dependent portions of the lung, whereas the remaining lung appears substantially normal.<sup>8</sup> Taken together, these imaging studies demonstrate that there are significant variations in the radiologic appearances of ALI. In turn, these differences suggest the potential for different therapeutic responses (see "Treatment Response").8

Study	No. of Subjects	Prevalence of ARDSp (%)	Prevalence of ARDSexp (%)	Mortality of ARDSp (%)	Mortality of ARDSexp (%)
Suchyta et al, 1992 <sup>22</sup>	215	47	53	51	54
Gattinoni et al, 1998 <sup>7</sup>	21	57	43	50	44
Squara et al, 1998 <sup>21</sup>	586	44	56	60	61
Goodman et al, 1999 <sup>17</sup>	33	67	33	27	0
Jardin et al, 1999 <sup>19</sup>	37	78	22	21	75
Villar et al, 1999 <sup>18</sup>	56	39	61	36	47
Eisner et al, 2001 <sup>24</sup>	902	50	50	36	34

Table 14-2 Prevalence and Mortality of ARDSp and ARDSexp from Studies Specifically Addressing This Issue

ARDSp, acute respiratory distress syndrome due to pulmonary disease; ARDSexp, acute respiratory distress syndrome due to extrapulmonary disease.



**Figure 14-2.** Computed tomography scan of a patient with ARDS due to pulmonary disease (i.e., pneumonia) showing extensive consolidations in the dependent regions and normal aeration in the non-dependent regions.



Figure 14-3. Computed tomography scan of a patient with ARDS due to extrapulmonary disease (i.e., trauma) illustrating diffuse pulmonary infiltrates with prominence of ground-glass opacities.



**Figure 14-4.** Computed tomography scan of a patient with ARDS due to pulmonary disease (i.e., community-acquired viral pneumonia), demonstrating homogeneous diffuse interstitial and alveolar infiltration, without significant atelectasis. Also present are pneumomediastinum and extensive subcutaneous emphysema. (*Courtesy of P. Lanken, M.D.*)

#### BIOMARKERS

ALI may be initiated by injury to the lung endothelium or epithelium, triggering an inflammatory response involving cytokines, chemokines, and other inflammatory mediators. The amplification of injury leads to inflammatory cell influx and leakage of protein- and fibrin-rich fluid into the lungs. This activates thrombotic and antifibrinolytic pathways favoring fibrin deposition with microthombosis.<sup>27–29</sup> The resultant physiologic effects include impaired lung compliance, mismatched ventilation-perfusion, increased pulmonary dead space ventilation, and arterial hypoxemia.

Although this basic pathophysiology appears to be common despite the precipitating factor, studies of plasma biomarkers demonstrate circulating differences that reflect at-risk diagnoses (Table 14-3). Whether these differences are due to severity of injury to the epithelium or endothelium or simply due to the different pathophysiology of the underlying syndromes is not known. Further, circulating levels of biomarkers may not be reflective of cell or tissue pathophysiology. Nonetheless, although not specifically addressing differences between direct and indirect injury, studies of circulating mediators have shown variability when sepsis, trauma, or pneumonia is the precipitating factor.

Most studies have focused on differences between septic and nonseptic subjects or between traumatic and nontraumatic inflammation. Levels of intracellular adhesion molecule-1 (ICAM-1), von Willebrand Factor (vWF), and Eselectin have been shown to be higher in nontrauma patients compared with trauma patients.<sup>30,31</sup> This suggests different patterns of endothelial injury. Pulmonary epithelial stimulation and injury, as assessed by levels of surfactant protein D (SP-D) in the circulation, were highest in patients with pneumonia and lowest in those with trauma.<sup>32</sup> Although some data are conflicting among studies, baseline levels of interleukin-6 (IL-6), IL-8, and IL-10 appear to be higher in patients with sepsis and pneumonia, whereas patients who sustained trauma had the lowest cytokine levels,<sup>33</sup> although these differences were not as apparent in a large secondary analysis of Acute Respiratory Distress Syndrome Network (ARDS-Net) subjects.<sup>31</sup> Further, differences in the degree of thrombosis and antifibrinolysis depend on the cause of ARDS. Ware and associates found that the levels of protein C, an endogenous plasma anticoagulant that promotes fibrinolysis and inhibits thrombosis, are lower and thrombomodulin levels are higher in patients with ALI due to sepsis compared with lung injury secondary to other causes.<sup>34</sup> In contrast, Calfee and colleagues found no differences in plasma protein C and type 1 plasminogen activator inhibitor levels between trauma and nontrauma patients, although differences in other circulating inflammatory markers were significant.<sup>31</sup> Taken together, these changes suggest that sepsis and trauma have different patterns of circulating markers. However, the utility of these markers in defining different patterns of ALI in clinical practice remains unclear.

#### **RESPIRATORY MECHANICS**

Respiratory mechanics appear to differ when ALI is incited by varying causes. A study by Gattinoni and colleagues that partitioned airway, lung, and chest wall mechanics

Study	Method	No. of Patients	Results
Moss et al, 1996 <sup>30</sup>	Prospective cohort study	55	Higher concentrations of vWF antigen, ICAM-1, and soluble E-selectin in sepsis patients than in trauma patients who developed ARDS
Ware et al, 2003 <sup>34</sup>	Retrospective cohort study	45	Patients with ARDS from septic causes had lower levels of protein C and higher levels of thrombomodulin compared with patients with ARDS from nonseptic causes
Eisner et al, 2003 <sup>32</sup>	Secondary analysis of multicenter RCT	565	SP-D highest in patients with pneumonia and lowest in those with trauma-associated ALI
Parsons et al, 2005 <sup>33</sup>	Secondary analysis of multicenter RCT	861	Baseline cytokine levels of IL-6, IL-8, and IL-10 were consistently higher in patients with sepsis and pneumonia than in patients with other clinical risk factors for ALI
Calfee et al, 2007 <sup>31</sup>	Secondary analysis of multicenter RCT	1451	Trauma patients with ALI had lower concentrations of ICAM, vWF, SP-D, and soluble TNFR-1 compared with nontrauma patients with ALI

Table 14-3 Results of Studies Evaluating Levels of Biomarkers in ARDS of Varying Etiologies

ALI, acute lung injury; ARDS, acute respiratory distress syndrome; ICAM-1, intercellular adhesion molecule-1; IL, interleukin; RCT, randomized controlled trial; SP-D, surfactant protein-D; TNFR-1, tumor necrosis factor receptor-1; vWF, von Willebrand factor.

revealed that chest wall and lung elastance in ARDSp was different than in ARDSexp.<sup>7</sup> In ARDSp, the measured elastance of the lung was higher, indicating a stiffer lung. In contrast, chest wall elastance in ARDSexp was higher than in ARDSp, although this difference may result from increased intra-abdominal pressure due to case mix of this study, in which most of the ARDSexp subjects had abdominal sepsis as their precipitating factor.<sup>8</sup> These results were consistent in a later study by this group evaluating lung recruitment, detailed in the next section of this chapter.

#### TREATMENT RESPONSE

Differences in underlying radiology, pathology, and respiratory mechanics of ALI might affect the response to treatment. The results of many small clinical studies have not led to major therapeutic advances,<sup>35–49</sup> perhaps owing to the heterogeneity of the populations studied. Currently, lung protective mechanical ventilation and supportive intensive care are the major treatments that provide survival benefit for patients with ALI.<sup>50</sup> The ARDSNet lung protective strategy appeared to have been effective in all patients with ALI irrespective of differences in clinical risk factors or precipitating factors, including pulmonary versus nonpulmonary ALI as well as infection-related versus non–infection-related disease.<sup>24</sup> Based on these findings, Eisner and colleagues proposed that the low tidal volume strategy can be applied to all patients with ALI.<sup>24</sup>

Several studies have demonstrated different effects of recruitment maneuvers in patients with extrapulmonary ARDS.<sup>51–54</sup> In these studies, improvement in gas exchange was greater among those with ARDSexp than ARDSp (see Chapter 19). Different morphology of the lung, assessed by CT scan, may explain these observed differences in part.<sup>55,56</sup> Using CT in 68 patients with ALI, Gattinoni and coworkers demonstrated that the effect of PEEP on lung recruitment was associated with the percentage of potentially recruitable lung.<sup>57</sup> This, in turn, varied

according to inciting insult. Higher PEEP levels (>15 cm  $H_2O$ ) appeared more beneficial in patients with a higher percentage of potentially recruitable lung, including mostly individuals with pneumonia-induced ARDS. Conversely, lower PEEP levels (<10 cm  $H_2O$ ) appeared more advantageous in those with a lower percentage of potentially recruitable lung, as appears to occur in sepsis-induced ALL.<sup>57</sup> Therefore, lower levels of PEEP may be adequate in ARDSexp compared with ARDSp. Nonetheless, additional clinical studies are needed to determine effects of different levels of PEEP on patients with ALI incited by different insults.

The effects of prone positioning on respiratory function in ALI likewise may be related to the specific precipitating insult. Two studies showed that the increase in oxygenation in response to prone positioning was greater in ARDSexp than in ARDSp.<sup>20,58</sup> Lim and colleagues reported that the effects of prone positioning on static respiratory compliance was greater in patients with ARDSexp than in those with ARDSp.<sup>58</sup>

#### CONCLUSION

Although classifying ALI as a single syndrome is a useful paradigm, there may be future utility in categorizing ALI based on the inciting factor (e.g., sepsis or trauma) or into dichotomous categories, such as ARDSp and ARDSexp. The level of evidence for "lumping" or "splitting" ALI is variable. For example, although some observational studies have shown different mortality and circulating biomarkers associated with different subsets of ALI, the value of lung protective ventilation was independent of precipitating factor. Radiographic and CT images demonstrate distinct patterns between ARDSp and ARDSexp, and although lung protective ventilation appears to work universally for all patients with ALI, the optimal level of PEEP and/or use of prone positioning may depend on the specific precipitating factor. Therefore, speculation persists regarding whether future therapies may be better designed to address different ALI endophenotypes. Similarly, future observational and translational studies using ALI as an outcome, such as genetics research, may require careful attention to differences in precipitating factors. Further, as in the evolution of the syndrome definitions of myocardial infarction or Wegener granulomatosis, incorporation of biomarkers may help refine future definitions of ALI.

#### AUTHORS' RECOMMENDATIONS

- ALI may be a useful paradigm for treatment trials when viewed as a single syndrome entity.
- The level of evidence for splitting the syndromic definition of ALI by precipitating factor is variable and consists mostly of observed differences in incidence, outcome, treatment response, and plasma biomarkers.
- Overlap of precipitating factors, such as in the case of pneumonia with concurrent sepsis, limits the operational utility of endophenotype categorization within the ALI definition.
- There is no evidence that the ARDSNet low-stretch ventilation protocol has differential therapeutic effects on mortality in ALI arising from different precipitating factors.
- Differences in recruitability and imaging in ALI patients may identify different ALI endophenotypes for future clinical trials.
- Differences in ALI endophenotypes are appropriate future directions of research aimed at risk, diagnosis, prognosis, and therapy of ALI.

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## 15 What Is the Best Mechanical Ventilation Strategy in ARDS?

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Acute respiratory distress syndrome (ARDS) is the catastrophic response of the lung to an injury that results in severe respiratory failure. It has been recognized as a clinical entity in adults for more than 40 years<sup>1</sup> and affects more than 100,000 adults in the United States every year.<sup>2</sup> Despite intensive management, outcomes remain poor. Reported mortality rates in observational studies persist at between 40% and 50%, and long-term morbidity affects most survivors.<sup>3,4</sup>

#### PATHOPHYSIOLOGY AND CLINICAL FEATURES OF ARDS

The damage to the lungs in ARDS can occur after a direct insult to the lung (pulmonary ARDS) or due to indirect damage through the alveolar epithelium (extrapulmonary ARDS). Patients with ARDS generally share several constant characteristics that identify the condition. First, ARDS typically develops after exposure to at least one of a well-known list of risk factors (Table 15-1).<sup>5</sup> Second, ARDS has an acute onset and is persistent over time. One of the most relevant clinical features is the presence of bilateral pulmonary airspace opacities in the chest radiograph. Severe impairment of gas exchange with hypoxemia and decrease of pulmonary compliance are also hallmarks of ARDS. The underlying cause of ARDS is extremely complex and to date is incompletely understood. It appears to involve the initiation of an inflammatory cascade within the alveolar-capillary endothelium or epithelium, and a wide range of inflammatory cells, cytokines, and chemokines have been implicated in this process. At least in its early stages, ARDS represents the pathologic state of diffuse alveolar damage (DAD).6-8 There is damage to both endothelial and epithelial layers<sup>6,8–11</sup> of the alveolar-capillary membrane with resultant edema and alveolar flooding rich in proteins and hemorrhage, leading to hyaline membrane formation and fibrosis.<sup>6,10</sup> These changes can overlap and evolve over hours to days and result in a loss of the barrier and gas exchange functions of the lung (Table 15-2).<sup>6,8,12-14</sup> The clinical consequence is a severe heterogeneous injury to the lung that results in refractory hypoxemia and decreased lung compliance. Mechanical ventilation in this scenario is challenging because it is necessary to support respiratory function while minimizing further lung injury that may be associated with mechanical ventilation.

The most widely used definition of ARDS is that proposed by the American-European Conference Committee (AECC), published in 1994 (Table 15-3).<sup>15</sup> ARDS is defined by the acute onset of hypoxemia (with  $Pao_2/Fio_2$  ratio < 200), the presence of bilateral infiltrates on chest radiography consistent with pulmonary edema, and pulmonary capillary occlusion pressure higher than 18 mm Hg or the clinical absence of left atrial hypertension. This definition has well-known limitations<sup>16</sup>; some of the criteria used in this definition are a matter of strong debate,<sup>17</sup> and there is relatively poor correlation with tissue diagnosis of DAD.<sup>18</sup>

#### STRATEGIES FOR THE MANAGEMENT OF ARDS

When Ashbaugh and colleagues first described ARDS in 1967,<sup>1</sup> mechanical ventilation was already considered central to successful management. Evidence from clinical and experimental data has proved that ventilatory technique can contribute to lung injury and increased mortality. To date, there is no etiologic treatment available that can act on the pathogenic events that underlie the disease. Therefore, the focus of respiratory support by mechanical ventilation in patients with ARDS and acute lung injury (ALI) is to provide acceptable gas exchange while simultaneously minimizing further injury to the lung.

#### **Conventional Ventilation**

Traditionally, most patients received mechanical ventilation using a standard approach of volume-controlled ventilation with tidal volumes ranging from 10 to 15 mL/kg. Notably, the use of positive end-expiratory pressure (PEEP) has varied throughout the years but has rarely exceeded 10 to 15 cm H<sub>2</sub>O. An end-inspiratory airway pressure of less than 50 cm H<sub>2</sub>O was considered acceptable in the absence of pneumothorax or surgical emphysema.<sup>19</sup> The principal aim of this traditional strategy was to achieve normal physiologic indices as measured through arterial blood gas analysis.

However, the original description of ARDS recognized the importance of PEEP and its association with lower mortality.<sup>1</sup> Seven years later, Webb and Tierney published data demonstrating that high peak inflation pressures severely damaged the lung in rats, thus confirming the existence of ventilator-induced lung injury, and demonstrated

Table	15-1	Risk	Factors	and	Conditions
Assoc	iated	with	ARDS		

Direct Lung Injury	Indirect Lung Injury
FREQUENT RISK FACTOR	RS
Pneumonia Aspiration of gastric contents	Sepsis Severe trauma with shock or prolonged hypotension Multiple transfusion
LESS FREQUENT RISK FA	ACTORS
Inhalational injury Pulmonary contusion Fat emboli Near drowning	Acute pancreatitis Cardiopulmonary bypass Severe burns Intravascular disseminated

\*After pulmonary transplantation or pulmonary thromboendarterectomy.

coagulopathy

Cranial trauma

Drug overdose

#### Table 15-2 Pathologic Features of ARDS

Exudative Phase	Proliferative Phase
Diffuse alveolar collapse	Resolution and healing or fibrosis
Intrapulmonary shunt	Destruction of capillary network
Low ventilation-perfusion ratios	Increased alveolar dead space
Decreased compliance	High ventilation-perfusion ratios
Hypoxemia	Hypercarbia
PEEP more effective in reversing hypoxemia	PEEP less effective, may worsen hypercarbia

PEEP, positive end-expiratory pressure.

Reperfusion pulmonary

edema\*

## Table 15-3 American-European ConsensusConference Definition of Acute Lung Injuryand ARDS

	Oxygenation*	Front Chest Radiograph	PAWP <sup>†</sup>
Acute lung injury	$\frac{\text{Pao}_2/\text{Fio}_2 \text{ ratio}}{\leq 300 \text{ mm Hg}}$	Bilateral infiltrates	≤18 mm Hg
ARDS	$Pao_2/Fio_2$ ratio $\leq 200 \text{ mm Hg}$	Bilateral infiltrates	$\leq$ 18 mm Hg

\*Irrespective of positive end-expiratory pressure level.

<sup>†</sup>No evidence of left auricle hypertension or heart failure. Acute onset is required.

PAWP, pulmonary artery wedge pressure.



**Figure 15-1.** Computed tomography scan of an ARDS patient showing regional differences in lung parenchyma involvement.

that PEEP could attenuate this damage.<sup>20</sup> In the 1980s, the use of computed tomography (CT) in ARDS clearly showed that consolidation in lungs affected by ARDS was not as uniform as suggested by the plain radiograph. An example of this particular heterogeneous distribution of lung damage and consolidation is shown in Figure 15-1. There is an appreciable volume of preserved lung and alveolar spaces that could be particularly vulnerable to high inflation pressures and volume because it could be receiving most of the inflation volume. In the acutely injured lung, less than 50% of the lung may contribute to gas exchange. These observations led to the concept of the "baby lung" as a functional entity.<sup>21,22</sup> The concept conveniently illustrates that healthy regions of lung parenchyma bear more stress and strain than the collapsed and consolidated regions, which are somewhat protected from overdistention. Repeated overdistention of this smaller preserved lung during tidal ventilation was causative in lung injury. Key developments in the field of ARDS ventilation are summarized in Table 15-4.

All this cumulative knowledge led to a consensus for the development of a ventilation strategy for lung protection in early 1993.<sup>23</sup> The consensus was important in providing recommendations for clinical practice, defined the state of the art of mechanical ventilation in 1993, and continued to stimulate clinical research conducted in the field over the next decade. Today, we would regard conventional ventilation for a patient with ARDS to consist of two essential principles, each of which will be discussed in more detail below:

- *Lung protection:* ventilation with low tidal volume (VT) and low airway plateau pressure (Pplat; surrogate of alveolar pressure) employing "permissive hypercapnia" when necessary
- *Lung recruitment:* using high PEEP to recruit collapsed alveolar units and avoid further injury to the lung associated with high alveolar volume swings (volutrauma). This general principle has been included under the concept of open lung ventilation. Application of extremely high PEEP for short periods of time has been proposed as a method to achieve further recruitment (recruitment maneuvers).

Table 15-4 Key Research Landmarks in ARDS			
Study	Key Development		
Ashbaugh et al, 1967 <sup>1</sup>	The "original description" of ARDS suggesting a common pathway of lung injury irrespective of the initial injury		
Webb & Tierney, 1974 <sup>20</sup>	An animal study illustrating the relationship among inflation pressure, PEEP, lung histology, and gas exchange. Confirmed the existence of ventilator-induced lung injury		
Dreyfuss et al, 1988 <sup>36</sup>	Illustrated that inflation volume in mechanical ventilation may cause greater damage than airway pressure		
Hickling et al, 1990 <sup>37</sup>	Advocated adopting pressure-limited ventilation and permissive hypercapnia strategies in ARDS management		
Bernard et al, 1994 <sup>14</sup>	American-European Consensus Conference on ARDS published the current definition of ARDS and acute lung injury.		
Tremblay et al, 1997 <sup>38</sup>	Introduction of the concept of biotrauma: high tidal volume ventilation without PEEP releases proinflammatory cytokines from lung tissue.		
Amato et al, 1998 <sup>26</sup>	Small RCT showing a decrease in mortality associated with low tidal volume ventilation and positive end- expiratory pressure.		
NIH/ARDSNet, 2000 <sup>27</sup>	Large trial confirming reduced mortality in ARDS patients ventilated with low tidal volumes. It concluded the debate raised by earlier conflicting smaller trials.		
Gattinoni et al, 2001 <sup>39</sup>	The use of computed tomography in ARDS patients showed the heterogenicity of the lung injury.		

#### Lung-Protective Ventilation

Mechanical ventilation with low tidal volumes, and the subsequent decrease in transpulmonary pressure, is associated with a decrease in mortality. Despite evidence from animal studies, early clinical research published in the late 1990s by Stewart,<sup>24</sup> Brower,<sup>25</sup> and Amato<sup>26</sup> and their colleagues delivered conflicting results. The National Institutes of Health and Acute Respiratory Distress Syndrome Network (NIH/ARDSNet) trial, published in 2000, marshalled the resources necessary for a large randomized controlled trial (RCT) to end the equipoise. The results showed a 9% absolute reduction in mortality rate in patients ventilated VT of 6 mL/kg and Pplat of less than 30 cm H<sub>2</sub>O compared with VT of 12 mL/kg and Pplat of less than 50 cm  $H_2O$ .<sup>27</sup> Tidal volumes were based on the calculation of predicted body weight for each individual patient, calculated using the Devine formula for both male and female patients. Volumes were adjusted between 4 and 8 mL/kg to maintain the plateau pressure below 30 cm H<sub>2</sub>O, and hypercapnia could ensue, although a pH above 7.30 was targeted.

In 2006, the Acute Respiratory Insufficiency: España Study (ARIES) investigators compared the use of low tidal volume ventilation and high PEEP with standard ventilation in a population persistently meeting criteria for ARDS at 24 hours of mechanical ventilation.<sup>28</sup> Tidal volume in the study group (5 to 8 mL/kg) and PEEP replicated those of an earlier trial by Amato,<sup>26</sup> whereas the control group received lower levels of PEEP and more moderate tidal volumes (9 to 11 mL/kg of predicted body weight). This trial was stopped early after demonstrating both decreased intensive care unit (53.3% versus 32%) and hospital mortality (55.5% versus 34%).<sup>28</sup> Current guidelines strongly underline the use of low tidal volume ventilation and low pressures with permissive hypercapnia as needed in the management of ARDS and ALI. Table 15-5 summarizes the features of key studies that provide a strong body of evidence in this regard.

Limitation of airway pressure, specifically plateau pressure (pressure measured after the inspiratory pause in volume-controlled cycles) is an integral part of a lungprotective ventilation strategy. Traditionally, high airway pressures were avoided because of the risk for gross barotrauma. Although this remains essentially true, there is also sufficient evidence of inflammatory lung damage associated with large *volume* changes in the alveoli. Current targets of this approach in mechanical ventilation for ARDS are low tidal volume (in the range of 4 to 8 mL/kg of predicted body weight) and an airway plateau pressure below 30 cm H<sub>2</sub>O when this can be achieved.

#### Lung Recruitment

The rationale for the use of PEEP lies with the theoretical basis for loss of lung compliance in ARDS patients. Four mechanisms have been proposed to explain the beneficial effect of PEEP in the injured lung: (1) increased functional residual capacity, thereby increasing the size of the so-called baby lung and reducing risk for volutrauma; (2) redistribution of alveolar lung water; (3) improved ventilation-perfusion mismatching; and (4) alveolar recruitment. As stated previously, the use of PEEP is also postulated to be protective in preventing the cyclical collapse of alveoli with tidal ventilation, splinting open alveoli throughout the respiratory cycle, and avoiding atelectrauma. Although there is general agreement among experts that some amount of PEEP is beneficial, an assertion supported by observational data,<sup>29</sup> exactly what level of PEEP should be used has remained a contentious issue for decades.

In recent years, several RCTs have examined this issue explicitly. Studies by Amato and colleagues<sup>26</sup> and Villar and coworkers<sup>28</sup> used a significantly higher PEEP in their study groups than in their controls (13.2 versus 9.3 cm H<sub>2</sub>O, and 14.1 versus 9.0 cm H<sub>2</sub>O, respectively); however, it is unclear how much (if any) of the survival benefits seen in these trials was attributable to a higher level of PEEP versus the lower tidal volumes that were also employed. Three large RCTs have now been published

 Table 15-5 Overview of Study Design and Findings of Major Randomized Controlled Trials Involving

 Comparison of Mechanical Ventilation with Low versus High Tidal Volume in ARDS and Acute

 Lung Injury

Study*	No. of Patients	Tidal Volume (mL/kg PBW)	PEEP (cm H <sub>2</sub> O)	Mortality (%)	<b>P</b> Value
Amato et al, 1998 <sup>26</sup>					
Conventional	24	12	$8.7\pm0.4$	72	
Protective	29	<6	$16.4\pm0.4$	38	P < .001
Stewart et al, 1998 <sup>40</sup>					
Conventional	60	$10.7\pm1.4$	$7.2\pm3.3$	47	
Protective	60	$7.0\pm0.7$	$8.6\pm3.0$	50	N.S.
Brochard et al, 1998 <sup>41</sup>					
Conventional	58	$10.3\pm7.7$	$10.7\pm2.3$	38	
Protective	58	$7.1 \pm 1.3$	$10.7\pm2.9$	47	N.S.
Brower et al, 1999 <sup>42</sup>					
Conventional	26	$10.2\pm0.1$	_	46	
Protective	26	$7.3\pm0.1$	_	50	N.S.
ARDS Network, 2000 <sup>27</sup>					
Conventional	429	$11.8\pm0.8$	$8.6\pm3.6$	40	
Protective	432	$6.2\pm0.9$	$9.4\pm3.6$	31	P = .007

\*Conventional: study group receiving mechanical ventilation with higher tidal volume; protective: study group receiving mechanical ventilation with low tidal volume.

N.S., differences not statistically significant; PBW, predicted body weight; PEEP, positive end-expiratory pressure.

in which the question of PEEP level for lung protection has been isolated, with all patients in both groups receiving low tidal volumes in the range of 6 mL/kg.<sup>30–32</sup> In both the ALVEOLI trial<sup>30</sup> and the Lung Open Ventilation Study (LOVS),<sup>31</sup> PEEP was determined according to higher and lower PEEP-FIO<sub>2</sub> tables, whereas the ExPress trial compared lower levels of PEEP (5 to 9 cm H<sub>2</sub>O) with higher levels set to achieve a plateau pressure of 28 cm H<sub>2</sub>O.<sup>32</sup> In keeping with the original open-lung approach, the LOVS trial also employed recruitment maneuvers.

The ALVEOLI and ExPress trials were stopped early because of perceived low likelihood of achieving nominal statistical significance (futility), and this likely contributed to the large baseline imbalance in age (5 years, favoring the low PEEP group) in the ALVEOLI trial. The three trials are summarized in Table 15-6. In addition to the mortality results displayed, the LOVS and ExPress trials also demonstrated important reductions in the use of rescue therapy for refractory hypoxemia. Furthermore, the number of ventilator-free days in the ExPress trial was higher in the higher PEEP group. Taken together, these results suggest a possible survival benefit to high-PEEP strategies, particularly among patients with the most severe forms of ARDS. Although there is strong evidence and agreement in favor of the use of moderate or high PEEP, the optimal level of PEEP to apply in ARDS patients and the most appropriate method to titrate PEEP have not been determined.

*Lung recruitment* refers to the dynamic process of reopening collapsed alveoli through an intentional increase in transpulmonary pressure. This recruitment effect can be achieved through a variety of maneuvers that apply high and sustained airway pressures for a short period of time (e.g., 40 cm H<sub>2</sub>O for 40 seconds). Such maneuvers appear to improve oxygenation at least in the short term in most patients; however, the optimal pressure, duration, and frequency of such maneuvers are not yet determined.<sup>33–35</sup> It is important to note that adverse events such as transient hypotension, barotrauma, and dysrhythmia are well described, and evidence of or high risk for barotrauma or unilateral lung involvement can be considered also as possible contraindications to these recruitment maneuvers. To date, routine use of recruitment maneuvers in ARDS patients is not supported by the available evidence; however, they may be useful in certain individual patients, when performed by experienced clinicians. Other modes of ventilation, such as bilevel and airway pressure release ventilation (APRV), have been proposed as tools to achieve ongoing lung recruitment while still preserving the purported benefits of spontaneous breathing. Currently, however, insufficient data exist to make a recommendation about the advisability of their use; further study is also needed here.

#### ADJUNCTS TO VENTILATION IN ARDS

Multiple interventions have been described and investigated during the past 40 years as adjuncts to conventional ventilatory management, including both ventilatory and nonventilatory adjuncts. The list is extensive and includes independent lung ventilation, maintaining spontaneous ventilation, high-frequency ventilation, continuous positioning therapy, prone position, extracorporeal membrane
#### Table 15-6 Randomized Trials of Open Lung Strategies (No Confounding Interventions)

#### A. SUMMARY OF STUDY PATIENTS AND INTERVENTIONS **Patients** Mode RMs **Pplat** Study Ν PEEP ALVEOLI<sup>30</sup> 549 $Pao_2/Fio_2 < 300$ Open lung High (PEEP/FIO2 chart) AC No $\leq$ 30 cm H<sub>2</sub>O Control Low (PEEP/FIO2 chart) AC No $\leq 30 \text{ cm H}_2\text{O}$ LOVS<sup>31</sup> 983 $Pao_2/Fio_2 < 250$ PC Open lung High (PEEP/FIO2 chart) Yes $\leq 40 \text{ cm H}_2\text{O}$ Control Low (PEEP/FIO2 chart) AC No $\leq$ 30 cm H<sub>2</sub>O ExPress<sup>32</sup> 767 $Pao_2/Fio_2 < 300$ Open lung To keep Pplat 30 cm H<sub>2</sub>O AC No 28-32 cm H<sub>2</sub>O Control 5-12 cm H<sub>2</sub>O AC No $\leq$ 32 cm H<sub>2</sub>O

#### **B. SUMMARY OF METHODOLOGIC FEATURES**

Study	Randomization	Baseline Differences	Similarity in Other Aspects of Care	Intention- to-Treat	Stopped Early
ALVEOLI	Central automated	Age, by 5.5 yr (lower control group)	VT 6 mL/kg PBW weaning	Yes	Yes
LOVS	Central automated	Age, by 2 yr (higher control group)	VT 6 mL/kg PBW weaning	Yes	No
ExPress	Central automated	None	VT 6 mL/kg PBW weaning	Yes	Yes

#### **C. MORTALITY**

Study	Timing	Group Rates (%)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
ALVEOLI				
Open lung	Hospital	27.5	1.11	0.91
Control		24.9	(0.84-1.46)	(0.69-1.20)
LOVS				
Open lung	Hospital	36.4	0.90	0.97
Control		40.4	(0.77-1.05)	(0.84-1.12)
ExPress				
Open lung	28 days	27.8	0.89	N/A
Control		31.2	(0.72-111)	

CI, confidence interval; RMs, recruitment maneuvers; RR, risk ratio; PBW, predicted body weight; Pplat, plateau pressure; VT, tidal volume.

oxygenation, inhaled NO, partial liquid ventilation, aerosolized prostacyclin, surfactant, and multiple anti-inflammatory drugs and antioxidants among others. Most of these are covered in other chapters in this book.

#### CONCLUSION

Ventilatory strategies that minimize damage to the lung are essential to reducing the morbidity and mortality from ARDS. There is strong evidence that the manner in which ARDS patients are ventilated has a great effect on their mortality. Limiting tidal volumes and inspiratory pressures is a fundamental tenet of lung protection, along with at least low-moderate levels of PEEP. Attempts to open the lung using higher levels of PEEP with or without recruitment maneuvers may be beneficial, but definitive data are lacking. The role of additional adjuncts such as high-frequency ventilation and prone positioning is still unproved and requires further evaluation.

#### AUTHORS' RECOMMENDATIONS

- Ventilator-associated lung injury is an important contributor to mortality in patients with ALI and ARDS.
- Goals of ventilation in ARDS have evolved to achieving acceptable gas exchange while minimizing further injury to the lung.
- Use of lower tidal volumes (4 to 8 mL/kg of predicted body weight) and targeting airway plateau pressure below 30 cm H<sub>2</sub>O should be considered key factors in lung-protective ventilation.
- Although it appears that some PEEP should be used, just how much PEEP to apply to which patients remains controversial.

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# 16 Is Permissive Hypercapnia Helpful or Harmful?

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Traditional approaches to the CO<sub>2</sub> management of adults with acute respiratory failure have focused on the potential for hypercapnia to exert deleterious effects. Support for this paradigm derived from the association between hypercapnia and adverse outcome in diverse clinical contexts, including cardiac arrest, sepsis, and neonatal asphyxia. However, this approach has been increasingly questioned, particularly in the setting of acute severe respiratory failure. Mechanical ventilation strategies that reduce the intensity of mechanical ventilation, resulting in a respiratory acidosis—termed permissive hypercapnia improve outcome.<sup>1,2</sup> Consequently, permissive hypercapnia has been progressively accepted in critical care for patients requiring mechanical ventilation. Conventionally, the protective effect of ventilatory strategies incorporating permissive hypercapnia is considered to be due solely to reduction in lung stretch, with hypercapnia "permitted" in order to achieve this goal. However, hypercapnia is a potent biologic agent with the potential to exert both beneficial and harmful effects. Furthermore, it is possible to minimize the potential for hypercapnia in the context of low-stretch ventilatory strategies by manipulating the respiratory frequency. Because outcome in the critically ill patient appears to be related to the development of multiorgan failure, as opposed to simply lung injury, it is also necessary to determine the effects of hypercapnia on systemic organs.<sup>3</sup> To address these issues, it is necessary to consider the physiologic effects of hypercapnia, recent insights that have emerged from studies in preclinical models, and data from clinical studies.

#### PHYSIOLOGIC EFFECT OF HYPERCAPNIA

#### **Respiratory System**

Hypercapnic acidosis increases parenchymal lung compliance in experimental models, likely owing to improved surfactant secretion or activity.<sup>4</sup> Hypercapnic acidosis improves matching of ventilation and perfusion and increases arterial oxygenation by this mechanism.<sup>5</sup> Of concern, hypercapnic acidosis can increase pulmonary vascular resistance and worsen pulmonary hypertension. In ARDS, permissive hypercapnia appears to increase shunt, which appears to be due to a reduction in tidal volume and airway closure rather than to hypercapnia per se.<sup>6</sup> In contrast, in animal models, CO<sub>2</sub> administration improves ventilation-perfusion matching and increased arterial oxygenation.<sup>7,8</sup> Hypercapnia directly dilates small airways but also stimulates vagal-mediated large airway constriction,<sup>9</sup> with an overall relatively minor net effect on airway resistance.<sup>10</sup>

Hypercapnic acidosis impairs diaphragmatic function through effects on afferent transmission or integrity with short-term exposure to moderate hypercapnia.<sup>11</sup> The clinical effect of this potentially deleterious effect of hypercapnia, especially with regard to weaning from ventilation, has yet to be explored.

#### Cardiovascular System

The direct depressant effects of hypercapnic acidosis on the cardiovascular system are counterbalanced by its stimulatory effects on the sympathetic nervous system. Hypercapnic acidosis directly reduces the contractility of cardiac<sup>12</sup> and vascular smooth muscle.<sup>9</sup> However, hypercapnia-mediated sympathoadrenal effects, including increased preload and heart rate, increased myocardial contractility, and decreased afterload, lead to a net increase in cardiac output.<sup>9,13</sup> Hypercapnia also results in a net increase in Pao2 and increases global O2 delivery by elevating cardiac output. Regional, including mesenteric, blood flow is increased also.<sup>14</sup> This increases organ oxygen delivery. Hypercapnia and acidosis shift the hemoglobin-oxygen dissociation curve rightward, reducing the oxygen affinity of hemoglobin, and may cause an elevation in hematocrit level,<sup>15</sup> further increasing tissue oxygen delivery. Concurrent reduced cellular respiration and oxygen consumption observed during acidosis may further improve the oxygen supply-demand balance, particularly in the setting of compromised supply.<sup>16</sup>

#### **Central Nervous System**

Hypercapnia is a potent ventilatory stimulant. Hypercapnic acidosis improves cerebral tissue oxygenation by augmenting Pao<sub>2</sub> as well as cerebral blood flow.<sup>17</sup> Hypercapnic acidosis causes precapillary cerebral arteriole dilation, a function attributed to the acidosis rather than the hypercapnia.<sup>11</sup> Hypercapnic acidosis-mediated increases in cerebral blood flow are a clear concern in the setting of reduced intracranial compliance, in which increased global cerebral blood flow may critically elevate intracranial pressure.

#### ROLE OF PERMISSIVE HYPERCAPNIA IN ADULT CRITICAL CARE

#### Acute Respiratory Distress Syndrome

The only therapeutic intervention to convincingly demonstrate a significant reduction in mortality in patients with acute respiratory distress syndrome (ARDS) and acute lung injury (ALI) is lung protective mechanical ventilation. The potential for protective lung ventilation strategies incorporating permissive hypercapnia to improve survival in patients with ARDS was suggested initially by Hickling and colleagues.<sup>18,19</sup> Two studies by this group, one retrospective<sup>18</sup> and the other prospective,<sup>19</sup> strongly indicated that adoption of a low tidal volume approach was beneficial.

Of the five prospective randomized controlled trials of protective ventilatory strategies<sup>1,2,20–22</sup> carried out in the past decade, two demonstrated an effect of ventilator strategy on mortality,<sup>1,2</sup> although three did not.<sup>20–22</sup> Although to some extent, permissive hypercapnia developed in all the trials, there was much variability (Table 16-1). Therefore, although it is clear that ventilation strategy can definitely effect mortality—in the positive trials—there is no discernible relationship between levels of hypercapnia and survival among these data.

The database of the largest of these studies<sup>1</sup> has been subsequently analyzed to determine whether, in addition to the effect of tidal volume, there might also be an independent effect of hypercapnic acidosis.<sup>23</sup> Mortality was examined as a function of permissive hypercapnia on the day of enrollment using multivariate analysis and controlling for other comorbidities and severity of lung injury. It was found that permissive hypercapnia reduced mortality in patients randomized to the higher tidal volume but not in those receiving lower tidal volumes.<sup>23</sup> These are the first clinical data suggesting potential direct beneficial effects of hypercapnia in ARDS patients. However, although these clinical observations support a body of basic science on the beneficial effects of hypercapnic acidosis, they do not confirm them. Further appropriately designed randomized clinical studies are needed to elucidate the direct effect of permissive hypercapnia on ALI.

#### **Acute Severe Asthma**

Controlled hypoventilation with permissive hypercapnia has been integral part of the management of severe

Table 16-1 Ventilatory Strategies and Management of CO<sub>2</sub> in Clinical Trials

asthma since it was first described by Darioli and Perret in 1984.<sup>24</sup> In fact, the use of permissive hypercapnia for status asthmaticus predates its use in ARDS/ALI. Permissive hypercapnia facilitates a reduction of dynamic hyperinflation during mechanical ventilation in acute severe asthma by allowing an increase in the expiratory time, a reduction in inspiratory flow rates, and a reduction in tidal volume, and has been demonstrated to significantly reduce dynamic hyperinflation.<sup>25</sup> Others have supported the case for morbidity and mortality being reduced when permissive hypercapnia is adopted for those with severe asthma who require mechanical ventilation,<sup>26</sup> and modest levels of permissive hypercapnia (mean highest levels 62 mm Hg) are routinely employed for patients with acute severe asthma admitted to intensive care units in Europe.<sup>27</sup>

#### Chronic Obstructive Pulmonary Disease

The rationale for the use of permissive hypercapnia in chronic obstructive pulmonary disease (COPD) is similar to that for acute severe asthma; that is, it is permitted to minimize the potential for dynamic hyperinflation during mechanical ventilation. However, there are no clinical trials of permissive hypercapnia in COPD.

#### ROLE OF PERMISSIVE HYPERCAPNIA IN PEDIATRIC CRITICAL CARE

#### Neonatal Respiratory Distress Syndrome

Acute respiratory failure in the preterm newborn results from parenchymal stiffness due to immaturity and surfactant deficiency and may be complicated by adverse events such as sepsis and meconium aspiration. Ventilation strategies involving permissive hypercapnia are well tolerated in premature newborns and appear to lower the risk for chronic lung disease.<sup>28</sup> In contrast, the presence of hypocapnia at 48 and 96 hours of life in neonates with respiratory failure has been demonstrated to be the best predictor of bronchopulmonary dysplasia.<sup>29,30</sup>

Mariani and colleagues reported beneficial effects of hypercapnia in infants with neonatal respiratory distress syndrome.<sup>31</sup> Preterm infants were randomly allocated to a target Paco<sub>2</sub> between 35 and 45 mm Hg or between 45 and 55 mm Hg for the first 96 hours of life. Infants randomized to permissive hypercapnia required less

Study	Mortality Benefit	Control PaCO <sub>2</sub> (mm Hg, mean $\pm$ SD)	Protective $PaCO_2$ (mm Hg, mean $\pm$ SD)	Buffering Permitted
ARDSNet, 2000 <sup>1</sup>	Yes	$35.8\pm8.0$	$40.0\pm10.0$	Yes
Amato et al, 1998 <sup>2</sup>	Yes	$36.0\pm1.5$	$58.0\pm3.0$	No
Stewart et al, 1998 <sup>22</sup>	No	$46.0\pm10.0$	$54.5\pm15.0$	No
Brochard et al, 1998 <sup>20</sup>	No	$41.0\pm7.5$	$59.5 \pm 19.0$	No
Brower et al, 1999 <sup>21</sup>	No	$40.1 \pm 1.6$	$50.3\pm3.5$	Yes

intensive ventilation and weaned significantly faster from mechanical ventilation. No obvious adverse effects were seen, although it must be recognized that such a small study would not detect serious but rare adverse effects. A larger, multicenter factorial trial of permissive hypercapnia and dexamethasone in extremely low-birthweight infants was stopped early because of unanticipated nonrespiratory adverse events related to dexamethasone therapy. There was a trend toward a lower incidence of death and chronic lung disease in the permissive hypercapnia group. Of importance, only 1% of permissive hypercapnia group patients required mechanical ventilation at 36 weeks' gestational age, compared with 16% in the routine group (P < .01).<sup>32</sup> However, the reduced sample size limits the conclusions that can be drawn from this study. Finally, a multicenter study of premature neonates in Denmark (1994 to 1995) reported that a ventilatory strategy incorporating permissive hypercapnia and early use of nasal continuous positive airway pressure and surfactant reduced the incidence of chronic lung disease.<sup>33</sup> A randomized multicenter study has been started by the National Institute of Child Health and Development Neonatal Research Network. This trial, which aims to include 1310 premature infants, will determine whether a strategy involving early continuous positive airway pressure and permissive hypercapnia will increase survival without bronchopulmonary dysplasia at 36 weeks' gestational age compared with conventional ventilatory strategy combined with early surfactant therapy.<sup>34</sup>

#### **Congenital Diaphragmatic Hernia**

Congenital diaphragmatic hernia occurs in about 1 of every 3000 to 4000 births. The degree of pulmonary hypoplasia and severity of the pulmonary vascular abnormality are the major factors influencing survival. In most centers until the early 1990s, ventilatory strategies were focused on controlling pulmonary hypertension with aggressive hyperventilation and alkalinization. The demonstration by Wung and associates that use of high ventilator pressures and hyperventilation in the newborn with pulmonary hypertension leads to impaired cardiopulmonary physiology and the development of ventilator-induced lung injury led to a paradigm shift in the management of these infants.35 Consequently, the avoidance of barotrauma to the hypoplastic lung has assumed increasing importance, and ventilation strategies involving permissive hypercapnia are increasingly used.<sup>36</sup>

To date, the only available data on permissive hypercapnia in patients with congenital diaphragmatic hernia comes from retrospective studies. Wung and associates have shown that limiting airway pressures during conventional ventilation allowing Paco<sub>2</sub> levels to rise up to 60 mm Hg combined with delayed surgery resulted in increased survival rates by 19% and decreased use of extracorporeal membrane oxygenation (ECMO) by 29%.<sup>37</sup> Kays and colleagues also demonstrated that introduction of a low-pressure ventilatory strategy accepting Paco<sub>2</sub> levels of up to 80 mm Hg significantly improved survival.<sup>38</sup> With this approach, in combination with the concept of delayed operation, this group reported 78% survival among 60 patients with congenital diaphragmatic hernia. This was significantly better than the 15% survival rate in the hyperventilation group and 44% survival rate in the hyperventilation and ECMO group (P < .0001). A larger study carried out by Wilson and colleagues showed a significant rise in survival rate with the introduction of permissive hypercapnia (from 44% to 69%, P < .007). This was not influenced by delayed surgery or the institution of ECMO.<sup>39</sup> Two further studies were carried out by Boloker and coworkers<sup>40</sup> and Bagolan and colleagues<sup>41</sup> with similar results. Boloker and coworkers showed an overall survival rate of 75.8% in 120 patients with congenital diaphragmatic hernia treated with spontaneous ventilation and permissive hypercapnia (60 to 65 mm Hg).40 Similarly, Bagolan and colleagues demonstrated that permissive hypercapnia (40 to 60 mm Hg) was associated with a substantial increase in survival (45.8%, P < .02), decreased barotrauma, and decreased mortality at 6 months.<sup>41</sup> In contrast, the earlier introduction of high-frequency oscillatory ventilation, which readily controls Paco<sub>2</sub>, appeared to have minimal effect.<sup>41</sup> Despite the limitations of these studies, the finding of a clear survival benefit with newer treatment protocols involving permissive hypercapnia is persuasive.

#### Persistent Pulmonary Hypertension of the Newborn

Persistent pulmonary hypertension of the newborn is a clinical syndrome of multi-factorial etiology characterized by hypoxemia secondary to elevated pulmonary vascular resistance and right-to left shunting of blood across foramen ovale and/or ductus arteriosus. Persistent pulmonary hypertension is seen in the setting of neonatal sepsis, meconium aspiration and severe neonatal respiratory failure and can occur in an idiopathic form in term and near-term neonates. Traditional management has emphasized the use of hyperventilation to decrease pulmonary arterial pressure. Two case series reported that short term hyperventilation resulting in pH levels greater than 7.6 was accompanied by decreased pulmonary arterial pressures and increased arterial PaO2. 42,43 Since then, the resultant hypocapnia has been clearly associated with adverse neurologic outcome in survivors, in terms of increased sensorineural hearing loss<sup>44</sup> and low psychomotor developmental scores.<sup>45–47</sup>

In marked contrast to this traditional approach, Wung et al described lower than previous mortality, and reduced incidence of chronic lung disease, in 15 neonates suffering from persistent fetal circulation in severe respiratory failure.<sup>35</sup> The ventilation strategy aimed to maintain adequate PaO2 ( $\geq$  50 mm Hg) and to reduce barotrauma by limiting inflation pressure in combination with permissive hypercapnia (PaCO<sub>2</sub> 40-60 mm Hg). All neonates survived and only one infant developed chronic lung disease as defined by the infant's need for supplemental oxygen beyond 30 days of life.<sup>35</sup> Dworetz et al, in a retrospective study of 40 infants, found that survival in the sickest infants with pulmonary hypertension improved from 17% to 90% (P < 0.02) when less aggressive ventilation was

used.<sup>48</sup> In a more recent study, Marron et al reported 100% survival in a case series of 34 infants with a diagnosis of severe pulmonary hypertension and severe respiratory failure at birth managed with permissive hypercapnia.<sup>49</sup> Subsequent detailed neurologic and audiologic testing of 27 of these patients revealed a good neurologic outcome, with average IQ within the normal range, no cases of sensorineural hearing loss and a relatively low incidence of neurologic abnormalities not attributable to birth asphyxia. Only two infants developed bronchopulmonary dysplasia and neither required supplemental oxygen at follow up.<sup>49</sup>

#### **Congenital Heart Disease**

Approximately 30,000 infants are born with congenital heart disease (CHD) in the United States each year. Control of CO<sub>2</sub> traditionally has played an integral role in the management of patients with complex congenital heart defects. Impaired neurodevelopmental outcome remains the major cause of morbidity in survivors after heart surgery. In this regard, the potential of hypercapnia to improve brain and other systemic organ oxygenation is increasingly recognized. Licht et al have demonstrated that low cerebral blood flow (CBF) in neonates with severe congenital heart defects is associated with periventricular leukomalacia. This was reversible when CO<sub>2</sub> was administered.<sup>50</sup> Furthermore, the addition of inspired CO<sub>2</sub> increased cerebral oxygenation and mean arterial pressure compared with reducing FiO<sub>2</sub> in hypoplastic left heart syndrome<sup>51</sup> and following cavopulmonary connection<sup>52</sup> respectively. Hypoventilation has also been demonstrated to improve systemic oxygenation after bidirectional superior cavopulmonary connection, potentially via a hypercarbia-induced decrease in cerebral vascular resistance, thus increasing cerebral, superior vena caval and pulmonary blood flow.<sup>53</sup> Finally, a more detailed recent study demonstrated that without altering tidal volume or mean airway pressure, addition of CO<sub>2</sub> to the inspired gas resulted in improved cerebral blood flow and systemic oxygenation following cavopulmonary connection.<sup>54</sup> Taken together, these studies raise the potential that inhaled  $CO_2$  might have a future therapeutic role in this context.

### CONTROVERSIES AND AREAS OF UNCERTAINTY

#### Permissive Hypercapnia and Intracranial Pressure Regulation

A key concern is the potential for hypercapnia-induced increases in cerebral blood flow to critically elevate intracranial pressure.<sup>55</sup> Intracranial hypertension constitutes a relative rather than an absolute contraindication to permissive hypercapnia. Consideration should be given to the insertion of an intracranial pressure monitor or a jugular venous oximetry catheter because these can facilitate the gradual titration, or avoidance, of permissive hypercapnia in a patient with a brain injury.<sup>55</sup>

### Permissive Hypercapnia and Pulmonary Vascular Resistance

Clinical conditions predisposing to pulmonary hypertension should be considered a relative rather than absolute contraindication to permissive hypercapnia. Concerns about significant pulmonary hypertension can be dealt with most rationally by measuring the degree of pulmonary hypertension or its sequelae (e.g., right ventricular failure, tricuspid regurgitation, or increased right-to-left shunting) and the effect of hypercapnia on pulmonary vascular resistance, and then titrating the degree of hypercapnia accordingly. In this context, monitoring with transthoracic echocardiography or placement of a pulmonary artery catheter may be indicated.

#### Permissive Hypercapnia: Role of Buffering

Buffering of the acidosis induced by hypercapnia remains a common, albeit controversial, clinical practice. There is evidence that the protective effects of hypercapnic acidosis in ARDS are a function of the acidosis rather than elevated  $CO_2$ .<sup>56,57</sup> Buffering may simply ablate any protective effects of acidosis while not addressing the primary problem. Specific concerns exist regarding sodium bicarbonate, the buffer used most frequently in the clinical setting. Although the physiochemical effect of NaHCO<sub>3</sub> is to increase the strong ion difference, the net effect is the generation of  $CO_2$ . Hence, NaHCO<sub>3</sub> is an inappropriate therapy in patients with hypercapnic acidosis. Tromethamine (THAM) may be a better choice of buffer if available, in situations in which buffering of a hypercapnic acidosis is considered.<sup>58</sup>

### Permissive Hypercapnia: Upper Limits of Tolerability

Although there is no consensus on the level of hypercapnia that is safe, most physicians avoid  $Paco_2$  levels higher than 100 mm Hg. The major concern of permissive hypercapnia at extreme high levels is related to the vasodilatory effects of  $CO_2$  on cerebral vessels because this may increase intracranial pressure and aggravate preexisting intracranial hypertension in patients with brain pathology. In the absence of cerebral disease, extreme permissive hypercapnia, to levels of 150 to 200 mm Hg,  $Paco_2$  has been reported to be well tolerated for periods of several hours (about 10 hours), in patients with status asthmaticus in several case series with no immediate or late consequences.<sup>26</sup> However, caution is warranted: case reports exist implicating hypercapnia in the causation of subarachnoid hemorrhage<sup>59</sup> and cerebral edema.<sup>60</sup>

#### PERMISSIVE HYPERCAPNIA AT THE BEDSIDE: PRACTICAL ISSUES

The practical application of hypercapnia in the critically ill patient with severe respiratory failure requires consideration of a number of issues. *First*, in regard to clinically acceptable limits for Paco<sub>2</sub> and pH, there is considerable evidence that patients generally tolerate hypercapnic acidosis to pH values of 7.2 and lower very well. The reported levels of Paco<sub>2</sub> and pH (mean maximal Paco<sub>2</sub> 67 mm Hg; mean pH, 7.2) in the study of Hickling and associates<sup>20</sup> reflect reasonable initial goals. However, a more useful approach is to individualize Pco<sub>2</sub> and pH goals in each patient, with great care required in settings in which hypercapnia may have deleterious effects, such as the setting of combined lung and head injury.

Second, the rapid induction of hypercaphic acidosis in ARDS patients can have profound adverse hemodynamic effects.<sup>58</sup> Therefore, when instituting permissive hypercapnia, the degree of hypercapnia should be gradually titrated upward over a period of at least several hours, until the ventilatory goals to minimize the potential for ventilator induced lung injury have been achieved. Third, in regard to altering the ventilatory strategy to produce permissive hypercapnia, the first priority in ARDS patients is to reduce tidal volumes in order to reduce plateau pressures below 30 cm H<sub>2</sub>O when possible. Tidal volumes should be reduced to 6 mL/kg ideal body weight and may need to be decreased further if plateau pressures remain unacceptably high.<sup>1</sup> Higher positive endexpiratory pressure (PEEP) levels do appear to exert beneficial effects in ARDS patients.<sup>61</sup>

*Fourth*, the effect of the disease process on the optimal ventilatory strategy must be considered. The management of ventilatory rate will differ in patients with ARDS/ALI compared with acute bronchial asthma or COPD. ARDS/ALI is characterized by a predominance of alveoli with short time constants due to low compliance with normal airways resistance. Therefore, it is possible to ventilate at relatively high ventilatory rates and to prolong inspiration to maintain oxygenation. Conversely, asthma or COPD is characterized by a predominance of alveoli with long time constants due to normal or elevated compliance with high airways resistance. In these patients, greater time is required for alveolar emptying in expiration in order to reduce the risk for auto-PEEP and dynamic hyperinflation. This is achieved by using lower respiratory rates and by prolonging expiration to allow complete alveolar emptying.

#### **AUTHORS' RECOMMENDATIONS**

- Hypercapnia is the inevitable consequence of low-stretch ventilation strategies that have been associated with improved outcomes in ARDS.
- Evidence also supports the use of permissive hypercapnia strategies in acute severe asthma and chronic obstructive airways disease.
- Hypercapnia is a potent biologic agent, and there is increasing evidence from laboratory studies that hypercapnia may attenuate lung and systemic organ injury.
- The potential for hypercapnia to exert deleterious physiologic effects when intracranial compliance is reduced or when increases in pulmonary vascular resistance may be deleterious must be considered.
- There is no clinical evidence to support the clinical practice of buffering hypercapnic acidosis with sodium bicarbonate.
- A clearer understanding of the effects and mechanisms of action of hypercapnia is central to determining its safety and therapeutic utility.

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# 17 Do Patient Positioning in General and Prone Positioning in Particular Make a Difference in ARDS?

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Changes in posture and position invariably accompany activity in healthy adults, with likely salutary effects on physiology. Similar changes in orientation during illness have important effects on cardiovascular and pulmonary physiology due to interactions between gravitational forces and chest mechanics. Such changes can improve oxygenation in patients with hypoxemic respiratory failure and may reduce the risk for ventilator-associated pneumonia. In this chapter, we review the salient effects of positioning on respiratory physiology and outline the clinical evidence supporting active positioning as a therapeutic or supportive intervention.

#### EFFECTS OF POSITION ON NORMAL RESPIRATORY PHYSIOLOGY

#### **Airspace Mechanics**

Gravity interacts with thoracic structures and transdiaphragmatic forces to modulate regional lung volume, distribution of ventilation, and ventilation-perfusion matching.<sup>1,2</sup> The local transpulmonary pressure gradient (alveolar pressure – pleural pressure), in concert with the corresponding regional lung compliance, is the major determinant of regional lung volume. Under "relaxed" conditions, the total aerated lung volume is denoted as functional residual capacity (FRC). During active inspiration, the transpulmonary pressure gradient determines the regional distribution of inspiratory flow, an important component of both ventilation-perfusion matching and the distribution of peak alveolar strain during positive-pressure ventilation. Conversely, at end expiration (or during the respiratory phase in the context of pulmonary pathology), an unfavorable transpulmonary pressure gradient arising from abnormal pleural or diaphragmatic mechanics can promote airspace collapse, compromising oxygenation by increasing shunt fraction. Regardless of the position, regional pleural pressure tends to be less negative, and therefore alveolar dimensions are smaller in the dependent than in the nondependent lung regions.

Positional changes affect the gradients of regional pleural pressure and thus regional lung volume. For example, the heart rests on the lungs in the supine position and primarily on the sternum in the prone position.<sup>3</sup> This partially explains the observation that gravitational pleural pressure gradients are consistently less in the prone than the supine position.<sup>4</sup> In addition, the prone position reduces the pressure the abdominal contents exert on the diaphragm, a pressure that is transmitted to the pleural space. Consequently, when in the supine position, the dorsal lung regions are surrounded by a less negative pleural pressure (and a smaller transpulmonary pressure gradient). The prone position results in a more negative pleural pressure adjacent to the dorsal lung zones. The increased ventral pleural pressure in the prone position has less effect on FRC because there is "less lung" anterior to the heart. The improved aeration of the dorsal lung regions, combined with the smaller effect of cardiac weight on the ventral lung regions, tends to increase FRC. This effect is significant in healthy subjects because FRC is reduced by about 30% on transition from the sitting to the supine, horizontal posture.<sup>5</sup> Anesthesia or neuromuscular blocking agents tend to enhance this effect, presumably by reducing the tone of the diaphragm. When compared with the horizontal supine position, total FRC is about 20% greater in the lateral decubitus and prone positions.<sup>5,6</sup> Not surprisingly, abdominal distention and obesity modulate the consequences of a change in posture on the respiratory system, and prone positioning may help offset the consequences of reclining on FRC and gas exchange.<sup>7,8</sup>

In healthy, spontaneously breathing adults, ventilation distributes preferentially to the dependent lung regions in the upright, supine, prone, and lateral decubitus position. This effect is partially attributable to the phasic swings in pleural pressure that attend respiratory muscle activity.<sup>2</sup> In contrast, elimination of the normal phasic changes in pleural pressure that accompany pharmacologic paralysis and mechanical ventilation of healthy patients<sup>9,10</sup> or altered parenchymal characteristics in the setting of lung injury<sup>11,12</sup> can markedly attenuate or even reverse the predominantly dependent distribution of

ventilation. Changes in the distribution of ventilation during positive-pressure mechanical ventilation of nonparalyzed, partially assisted patients are complex. They vary with the specifics of the applied ventilatory support and regional lung mechanics. For instance, positive endexpiratory pressure (PEEP) can help redistribute ventilation in the dependent regions in patients with ARDS, but only if those regions are recruitable and the level of PEEP used is sufficient to maintain alveolar patency. Active diaphragmatic contraction, through its effects on pleural pressure, can increase transpulmonary pressure and help preserve alveolar patency.

#### Distribution of Blood Flow and Ventilation-Perfusion Ratio

Until recently, gravity was thought to be the main determinant of blood flow distribution within the lungs. It has now been shown that perfusion tends to distribute preferentially to the dorsal regions both in the supine and prone positions. This distribution cannot be explained by gravity alone.<sup>13,14</sup> Regional differences in vascular development and geometry<sup>15</sup> and in vasoregulation by nitric oxide<sup>16</sup> appear to contribute to regional distribution of perfusion within the lungs.

Modulation of airspace events, combined with the less marked effect of gravity on distribution of pulmonary blood flow, render the overall ventilation-perfusion ratio  $(\dot{V}/\dot{Q})$  sensitive to position.<sup>17</sup> Overall, the ventilation-perfusion relationship is less favorable in the supine than in the upright and prone positions. The effects of recumbency on oxygenation are complex and depend on the interrelationship of closing volume, FRC, and tidal volume.<sup>18</sup> Interindividual variations in the relations between these variables contribute to the variable effects of reclining on Pao<sub>2</sub> between subjects.

#### POSITIONING IN CRITICALLY ILL PATIENTS WITH RESPIRATORY FAILURE: GENERAL OVERVIEW

Judicious positioning of critically ill patients might reduce atelectasis, improve gas exchange, and decrease the threat of ventilator-associated pneumonia. The lateral and prone positions have the potential to improve gas exchange in selected patients with respiratory failure. Head-up positioning (tilting the patient upright) to alleviate diaphragmatic compression by the abdominal contents recently has been demonstrated to have some benefits. We briefly review the mechanisms that best account for these observations and the outcome studies when available with an emphasis on prone position, which is the best studied position in the intensive care unit (ICU).

### Respiratory Effects of Frequent Posture Changes

In anesthetized dogs, immobility is associated with a deterioration of gas exchange that can be prevented by turning every half hour.<sup>19</sup> Frequent changes in position are likely to be similarly important in maintaining normal respiratory

function in humans. The impact of frequent positional changes has been tested in the clinical arena using continuous oscillating beds with promising results. Such "kinetic therapy" appears to be well tolerated hemodynamically and has been reported to improve oxygenation,<sup>20</sup> decrease the risk for atelectasis and pulmonary infections,<sup>21,22</sup> and reduce the duration of intubation and resource use in trauma patients.<sup>19,23</sup> Kinetic therapy also has been used to treat established atelectasis.<sup>24</sup> A reduction in the incidence of pneumonia and improved oxygenation was observed in medical ICU patients.<sup>25,26</sup> It has been suggested that this modality may improve outcome in the sickest patients  $(P = .056 \text{ for a subgroup with an APACHE 2 score} > 20)_{r}^{27}$ but the data are not yet conclusive. Most available studies are of relatively small size and have important limitations. Thus, the results are not always consistent. For instance, use of a kinetic therapy bed has been associated with more frequent infectious complications, respiratory failure, and more ventilator support days in patients with thoracolumbar spinal column injuries.<sup>28</sup> The efficacy of position changes in protecting pulmonary function<sup>29</sup> and improving outcome is still uncertain, making its role in patient management somewhat unclear.

#### Lateral Position

Because both perfusion and ventilation distribute preferentially to the dependent lung during active breathing,  $\dot{V}/\dot{Q}$  mismatching and intrapulmonary shunting can be significantly reduced by lateral positioning of patients with unilateral or asymmetrical lung disease with the good lung down.<sup>30–32</sup> This therapeutic adjunct may significantly improve Pao2 and even preclude the need for intubation and mechanical ventilation<sup>30</sup>; arterial and mixed venous oxygen content increase without significant hemodynamic changes with the good lung down.<sup>33</sup> Rarely, critically ill patients fail to improve with the good lung down, (paradoxically) improve with the bad lung down, or develop arrhythmias, hypotension, or a marked reduction in  $Svo_{2}$ ,<sup>34</sup> necessitating prompt return to the supine position. The slight and usually transient decrements in Svo<sub>2</sub> reported after postural changes in critically ill patients is unlikely to explain the occasional persistent failure of blood gases to improve with the good lung down. Atelectasis due to unusual pressure distributions generated by the abdominal contents or increased pressure transmission to the thorax is more likely responsible. In such circumstances, PEEP may prove beneficial. Fortunately, in patients with predominant unilateral alveolar condensation or flooding, PEEP is less likely to detrimentally affect the distribution of perfusion in the lateral than in the supine position. When supine, an inappropriately high level of PEEP may redistribute blood flow to the diseased lung by promoting zone 1 conditions in the spared lung.<sup>3</sup> In unilateral pneumonia, however, PEEP may help limit contamination of the good lung by the diseased lung<sup>3</sup> and theoretically may be more helpful if used in combination with the lateral position in these circumstances.

The practice of positioning patients with the good lung down has notable exceptions. Children, some patients with chronic airflow obstruction (chronic obstructive pulmonary disease),<sup>37</sup> and anesthetized-paralyzed patients

share a tendency to have higher ventilation to the nondependent lung. In the presence of a moderate unilateral pleural effusion, V/Q matching during spontaneous breathing appears to be similar in the lateral position with the affected side up or down,<sup>32</sup> suggesting that moderate pleural effusions have little effect on gas exchange. Studies of regional lung function in seated patients with unilateral pleural effusions demonstrate that although the overall lung volume on the side of effusion is reduced, the residual volume (RV)-to-total lung capacity (TLC) ratio and FRC/TLC ratios on both sides are very similar.<sup>38</sup> This may explain the poor correlations among posture, pleural effusion size, and gas exchange in patients with unilateral pleural effusion without marked underlying infiltrates or hypoxemia. Patients with whole-lung collapse secondary to unilateral central airway obstruction may not improve or may even deteriorate when positioned with the spared lung down.<sup>39</sup> Patients with unilateral massive pulmonary embolism requiring mechanical ventilation have been reported to have better gas exchange with the diseased lung down.<sup>40</sup> Finally, lateral positioning with the good lung down is contraindicated in hemoptysis and lung abscess, for fear of spillage into the unaffected lung.

#### Elevation of the Head of the Bed

Elevating the head of the bed can improve oxygenation in ARDS, probably by promoting lung recruitment at the bases.<sup>41</sup> In 16 patients with ARDS, vertical positioning (trunk elevated at 45 degrees and legs down at 45 degrees) increased Pao<sub>2</sub> significantly from 94  $\pm$  33 mm Hg to 142  $\pm$ 49 mm Hg, with an increase higher than 40% in 11 patients. The semirecumbent position may also help reduce gastric content aspiration<sup>42</sup>; conversely, head position at less than 30 degrees in the first 24 hours of intubation was found to be an independent risk factor for developing ventilatorassisted pneumonia.43 In a subsequent randomized prospective trial, the semirecumbent position was reported to significantly reduce the rate of ventilator-associated pneumonia (odds ratio, 6.8 for the supine body position).<sup>44</sup> Based on this evidence, head-of-the-bed elevation has been endorsed by medical societies such as the Society of Critical Care Medicine. Notably, the feasibility and true efficacy of this intervention have been called into question.45,46 Pragmatic questions remain unanswered: for example, How many hours per day must the head of the bed be elevated? What is the optimal angle of head of the bed elevation? However, given that head of the bed elevation is cheap, benign, and potentially helpful, it appears a reasonable intervention even in the absence of definitive data.

#### PRONE POSITION IN ARDS

#### Physiology and Physiopathology of Prone Positioning

In 1976, Piehl and Brown first described improved oxygenation in patients with acute hypoxemic respiratory failure who were ventilated in the prone position.<sup>47</sup> This has been confirmed in subsequent studies; overall, oxygenation improves in about two thirds of patients when placed in the prone position.<sup>48</sup> The mechanisms underlying this improvement have been most extensively studied in large animal models. Complex interactions between regional aeration and the modulation of perfusion during positive-pressure ventilation determine the effects of prone positioning on gas exchange.

The improved oxygenation accompanying prone positioning appears primarily related to *regional* differences in FRC in the face of a relatively unchanged distribution of dorsal-ventral perfusion. The largest proportion of pulmonary blood flow is directed to the dorsal lung regions in both the supine and prone positions.<sup>13</sup> Moreover, the predominance of dorsal perfusion is preserved when the animal is turned prone.<sup>49</sup> In a canine model of lung injury induced by oleic acid, the prone position was found to improve gas exchange by reducing shunt.<sup>50</sup> In the setting of lung injury, both animals and patients with ARDS tend to have less aerated lung in the dependent regions due to the effects of gravity on the edematous lungs. The time constant of the dependent collapsed or flooded lung units is such that tidal ventilation distributes preferentially to the "open" nondependent lung units,<sup>11</sup> namely, to ventral regions when supine and to dorsal regions when prone. Accordingly, the increase in FRC seen when an injured animal or patient is turned prone (owing to changes in transpulmonary pressure favoring "opening" of the now nondependent dorsal regions; see earlier) is accompanied by an increase in perfusion to aerated lung units, with an accompanying decrease in shunt fraction.

In addition, positive-pressure ventilation tends to create West zone 1 or 2 conditions and can redistribute blood flow from the nondependent region to the dependent regions. Positive airway pressure decreases the vertical perfusion gradient when in the prone position, whereas it increases the vertical perfusion gradient in the supine position.<sup>51</sup> Positive-pressure ventilation of regionally heterogeneous ARDS lungs creates opposing gradients of ventilation and perfusion along the vertical axis, promoting  $\dot{V}/\dot{Q}$  mismatch and shunting. This effect of positive pressure is more marked in the supine position than in the prone position. Indeed, regional ventilation and perfusion (Vr/Qr) assessed by single-photon emission computed tomography showed that the prone position improved dorsal Vr to a greater extent than ventral Vr, whereas Qr remained essentially unchanged.<sup>52</sup> In other words, recruitment of dorsal lung units associated with preserved dorsal perfusion largely explains why prone positioning improves gas exchange in experimental models and why an overall increase in FRC is not required for prone positioning to improve  $\dot{V}/\dot{Q}$  matching (see later).53

Additional factors may, however, contribute to the improved gas exchange afforded by prone positioning. The pleural pressure gradient is smaller along the vertical axis,<sup>4</sup> and pleural pressure is more negative in the dependent regions in the prone than in the supine position.<sup>54</sup> This favors lung recruitment and accounts for the rise in FRC sometimes observed after turning to the prone position.<sup>55</sup> The effect of prone positioning on gas exchange during positive-pressure ventilation of pharmacologically

paralyzed subjects appears to be further modulated by changes in thoracoabdominal compliance that accompany the prone position. Pelosi and associates found that the improvement in oxygenation attending prone positioning correlated with a high supine thoracoabdominal compliance. A very compliant anterior chest tends to redistribute the tidal volume toward the nondependent, less wellperfused lung regions, promoting V/Q mismatching in the supine position. Constraint of the flexible ventral chest wall by contact with the bed during prone positioning "stiffens" the anterior chest wall. Such stiffening redirects tidal ventilation toward the better perfused dorsal regions, improving  $\dot{V}/\dot{Q}$  matching.<sup>56</sup> These data do not suggest that minimizing abdominal contact, as proposed by some, is a prerequisite for improved gas exchange. Finally, the properties of the lung (e.g., cause of ARDS) or phase of the disease (edema versus fibrosis) tend to alter the response to prone positioning.<sup>57</sup> Generally, patients in the early edematous phase of ARDS are more likely to experience improved gas exchange when turned prone than patients who have developed pulmonary fibrosis.

Which of these mechanisms prevails in individual patients and best accounts for the improved Pao<sub>2</sub>/Fio<sub>2</sub> ratio associated with prone positioning is not always clear but is potentially important. It has been suggested that a reduction Paco<sub>2</sub> following prone positioning may indicate the presence of recruitment and improved outcome.<sup>56</sup> Better recruitment distributes a given tidal volume to a larger number of alveoli, thereby reducing alveolar strain and the risk for epithelial and endothelial injury. Along these lines, Mentzelopoulos and coworkers measured tidal transpulmonary pressures as a function of end-expiratory lung volume to assess lung mechanical stress and found the latter index to be reduced during prone positioning.<sup>59</sup> The more uniform distribution of blood flow may also be important given the potential importance of ventilation and perfusion interaction in the pathogenesis of ventilator-induced lung injury.60 Regardless of the mechanisms, prone positioning has been found to attenuate ventilator-induced lung injury in large animals with normal<sup>61</sup> or injured lungs.<sup>62</sup> Overall, the protective effect of prone positioning is consistent with the post hoc findings of Gattinoni and colleagues, who reported reduced mortality in a subset of patients who received excessive tidal volume (large tidal volume relative to the size of lung) either because of the large tidal volume used (largest tidal volume subgroup) or the small size of the lungs (severest form of ARDS subgroup).<sup>63</sup>

#### **Prone Position and Outcome**

Despite its capacity to improve oxygenation in most patients with acute lung injury (ALI) or ARDS, the effect of prone positioning on patient outcome remains uncertain. To our knowledge, six randomized trials<sup>64–69</sup> addressing the effect of prone positioning on outcomes have been published. Characteristics and main results of these trials are summarized in Table 17-1. None of these studies showed an overall reduction in mortality from ALI or ARDS. Data from one study suggested that prone position may improve outcome in subgroups of patients with severe ARDS<sup>64</sup> and multivariate analysis of data from another study showed that randomization to the supine position was an independent risk factor for mortality.<sup>68</sup>

Four meta-analyses have been published recently, and the following conclusions were reached: Prone position clearly improves oxygenation but does not reduce overall mortality or the duration of mechanical ventilation.<sup>70-73</sup> Prone position does not increase the rate of major complications.<sup>70–73</sup> Pressure ulcers were found to be significantly more common in two meta-analyses.<sup>70,71</sup> Prone position does not appear to reduce the incidence of ventilatorassociated pneumonia. As indicated previously, the studies by Gattinoni<sup>64</sup> and Mancebo<sup>68</sup> and colleagues suggested a reduced mortality rate in a subgroup of severe ARDS patients with the highest SAPS II score (>50). Pooled together, the data suggest that prone position can significantly reduce the mortality in the sickest patient (odds ratio, 0.29; 95% confidence interval, 0.12 to 0.70).73 Ongoing trials are under way. These may or may not confirm reported findings.

Overall, current randomized trials are difficult to compare (e.g., patients enrolled had different causes of ARDS, levels of severity, and stages in the course of disease), and prone positioning lacks standardization in regard to its duration and to ventilatory strategy.<sup>72</sup> Clearly, more studies are needed to determine whether prone position can reduce ARDS-related mortality to define the target population who might benefit from this intervention to establish the optimal daily duration and timing of prone positioning in the course of ARDS and to elucidate the ventilatory strategy that most effectively uses the physiologic changes that occurred in the prone position.

#### Addendum

Since this chapter was written, the results of an additional randomized multicentric controlled trial which included 342 adult patients with ARDS was published.<sup>74</sup> Prone and supine patients from the entire study population had similar 28-day (31.0 percent vs. 32.8 percent) and 6-month (47.0 percent vs. 52.3 percent) mortality rates, despite higher complication rates in the prone group. Similar outcome were reported for patients with moderate hypoxemia in the prone and supine groups at 28 days (25.5 percent vs. 22.5 percent) and at 6 months (42.6 percent vs. 43.9 percent). The mortality of patients with severe hypoxemia favored prone positioning: 28-day mortality was 37.8 percent (prone group) and 46.1 percent (supine group), while their 6-month mortality was 52.7 percent (prone group) and 63.2 percent (supine group).

"Do the findings of this trial, together with those of previous studies, represent the end of the prone position technique? Undoubtedly, the data of the present trial together with previous results clearly indicate that prolonged prone positioning, in the unselected ARDS population, is not indicated as a treatment. However, its potential role in patients with the most severe hypoxemia, for whom the possible benefit could outweigh the risk of complications, must be further investigated, considering the strong pathophysiological background, the post hoc result of our previous study, the most recent meta-analysis, and the favorable trend observed prospectively in this study,"<sup>74</sup>

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### Table 17-1 Summary of Randomized Controlled Trials

					OL	JTCOME		COMPLICATIONS	
Study	Type of Respiratory Failure	No. of Subjects (Supine/ Prone)	Study Design	Duration of Daily Prone Positioning	Mortality	Results (Supine/ Prone; n/n) (%)	VAP (%)	Major Respiratory Complication (Extubation and ET Tube Obstruction) (%)	Pressure Sores (%)
Gattinoni, 2001 <sup>48</sup>	ALI and ARDS	152/152	MRC	$7 \pm 1.8$ hr for 10 days	10 days	73/152 (48) vs. 77/152 (51)	NA	10 vs. 8	36 vs. 28
Guerin, 2004 <sup>65</sup>	Acute hypoxemic respiratory failure	378/413	MRC	8 hr/day for 4 days (range, 2-6 days)	28 days	119/378 (32) vs. 134/413 (32)	24 vs. 21	16 vs. 20	50 vs. 42
Voggenreiter, 2005 <sup>66</sup>	ALI and ARDS (trauma)	19/21	SR	$11\pm5\mathrm{hr}$	ICU	3/19 (16) vs. 1/21 (5)	89 vs. 62	5 vs. 5	91 vs. 63
Curley, 2005 <sup>67</sup>	ALI (pediatric study)	51/51	SR	$18\pm4\mathrm{hr}$	28 days	4/50 (8) vs. 4/51 (7.8)	NA	10 vs. 12	16 vs. 20
Mancebo, 2006 <sup>68</sup>	ARDS	60/76	MR	17 hr for 10.1 days	ICU	35/60 (58) vs. 33/76 (43)	15 vs. 18	2 vs. 8	3 vs. NA
Fernandez, 2008 <sup>69</sup>	ARDS	19/21	MRC	Up to 20 hr per day	60 days	10/19 (53) vs. 8/21 (38)	5 vs. 14	10 vs. 5	Very common (prone)

ALI, acute lung injury; C, crossover allowed; ET, endotracheal tube; ICU, intensive care unit; M, multicentric; NA, not applicable; R, randomized; S, single center; VAP, ventilator-assisted pneumonia.

the authors conclude. These conclusions are in line with our own reading of the overall currently available data and our recommendations therefore remain unchanged.

#### **AUTHORS' RECOMMENDATIONS**

- Overall, in the past few decades, significant progress in our understanding of the physiologic effects of positioning on the respiratory system has been made. Judicious use of positioning can improve gas exchange in ventilated critically ill patients. Whether positioning improves outcome in most patients with acute respiratory failure remains unproved and is unlikely.
- Experimental and clinical data, however, suggest that the semirecumbent position and prone positioning may help reduce the risk for ventilator-associated pneumonia in intubated ventilated ICU patients and mortality in patients with severe ARDS, respectively. Further studies are needed, however, to confirm these promising results.
- Pending more definitive data, it appears reasonable to systematically elevate the head of the bed to reduce the risk for aspiration associated with invasive mechanical ventilation and to use prone positioning in patients with severe ARDS, particularly those at high risk for ventilator-induced lung injury (e.g., elevated plateau airway pressure) or failing conventional ventilation, given that positioning is safe when performed carefully.
- There are specific circumstances in which positioning may be helpful and should be considered despite the lack of randomized controlled trials (e.g., lateral position with the "good" lung down in patients with refractory hypoxemia and with the "bad" lung down in patients with massive hemoptysis).

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# 18 What Is the Role of Airway **Pressure Release Ventilation** in ARDS?

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The optimal method of mechanical ventilation in acute respiratory distress syndrome (ARDS) is unknown. To date, large randomized trials have used relatively simple modes of ventilation (such as volume-assist control) to ensure maximal compliance among multiple centers. However, modern intensive care ventilators include an array of technologies that improve patient-ventilator synchrony, to control the work of breathing (proportional assist), or to improve triggering (neurally associated ventilatory assist). Airway pressure release ventilation (APRV) is a ventilator mode that allows unrestricted spontaneous breathing and has been shown to improve gas exchange, in addition to improving patient tolerance to mechanical ventilation in acute lung injury (ALI) and ARDS. It is an extreme version of inverse ratio pressure control ventilation that uses a dynamic expiratory control valve and is variably known as BiLevel, BiVent, Biphasic, and BIPaP.

In the past, the focus of ventilation was to control and adapt the patient to the ventilator. APRV accommodates the patient's breathing pattern and superimposes native ventilation onto a pressure framework that supports spontaneous breathing. APRV differs from other modes of positive-pressure ventilation in that it applies a form of continuous positive airway pressure (CPAP) that is released periodically, augmenting CO<sub>2</sub> clearance. The patient's spontaneous breaths are unrestricted and independent of the ventilator cycle.

#### CURRENT UNDERSTANDING AND APPROACHES

Current strategies in the management of ARDS are based on limiting alveolar stretch, by limiting tidal volumes, airway pressure, or both. There are three major strategies in common use: low tidal volume with low positive endexpiratory pressure (PEEP), low tidal volume with high PEEP (the "open-lung" approach), and full tidal volume ventilation.<sup>1–4</sup> The former modes use the inspiratory limb of the volume-pressure curve; the latter uses the expiratory limb. High-frequency oscillation (HFO) and APRV use the expiratory limb.

ALI creates a heterogeneous distribution of gas within the lung, ranging from atelectasis to hyperinflation.<sup>5,6</sup>

Dependent lung regions, the posterior dorsal segments of the lung, are typically collapsed and consolidated (airless/atelectasis). Conversely, the anterior apical segments of the lung are hyperinflated and become dead space. Sandwiched in between, there is an area of partially injured "recruitable" lung tissue. These lung regions respond differently to the stress (volume/pressure) of mechanical ventilation. Regional variability in lung mechanics with disproportionate air distribution along the dorsal-ventral gradient limits the utility of many clinical approaches.<sup>7,2</sup>

Initially, lung protective strategies focused on limiting tidal hyperinflation. The dependent portion of the injured lung has less aeratable capacity owing to collapse or consolidation. Therefore, low tidal volume strategies limit overdistention in the predominantly nondependent, normally aerated lung regions. Open-lung strategies use elevated mean airway pressures to recruit or re-aerate collapsed lung segments and to maintain recruitment by distributing ventilation over a larger surface.<sup>9–11</sup> Open ventilation approaches also use PEEP to limit those shear forces that may develop from cyclic tidal recruitment and de-recruitment during the respiratory cycle, known as atelectrauma.<sup>7,12</sup> Although limiting shear forces in dependent lung regions may be beneficial, PEEP-induced hyperinflation of the healthy nondependent lung regions results in a significant increase in alveolar dead space and results in hypercarbia.

Interestingly, Borges and colleagues, in a study of lung recruitment, noted a progressive decrease in nondependent hyperinflation with recruitment, suggesting better stress and ventilation distribution within the recruited lung than with nonrecruited lung.13 This would imply that recruitment could be used as a strategy to limit tidal hyperinflation. An alternative explanation suggests that it is the magnitude of atelectasis that drives tidal hyperinflation in the nonatelectatic regions. The atelectatic regions do not appear to sustain cyclic shear stress and alveolar injury.<sup>14</sup> Tsuchida and associates demonstrated that the pattern of lung injury associated with atelectasis produced greater injury to the airways than to the alveolar space in the dependent lung regions.<sup>14</sup> Airways within collapsed airspaces remained open and absorbed the energy of ventilation directly rather than dissipating the force into the airspace. In the nonatelectatic, nondependent regions,

both airway and airspace injury occur because the bulk of the ventilation is directed to that region. In conclusion, this suggests that alveolar injury from shear forces does not occur in the atelectatic areas; rather, atelectasis promotes alveolar hyperinflation injury in nonatelectatic regions of the lung. This is further supported by Terragni and coworkers, who demonstrated that tidal hyperinflation is intensified by the degree of atelectasis and occurs despite tidal volume reduction.<sup>15</sup>

PEEP has been shown to be lung protective in animal studies. The PEEP lung-protective role, whether as a result of limiting shear force or by limiting nondependent hyperinflation, appears to be related to lung recruitment and potential stress redistribution.<sup>16</sup> Low tidal volume strategies may worsen atelectasis and paradoxically increase tidal hyperinflation, especially when inadequate PEEP levels are used.<sup>17</sup> Concurrent PEEP elevation with tidal volume reduction appears to limit de-recruitment.<sup>18</sup> These studies suggest that setting PEEP at the highest level to approach maximal recruitment and a limited plateau pressure does not induce harm, may limit hypoxemic respiratory failure, and is a reasonable method of protective ventilation.<sup>2,3</sup>

In summary, atelectasis may be the main cause of overdistention and alveolar injury in the nonatelectatic regions, and PEEP appears to have a lung-protective effect by limiting atelectasis and improving gas distribution.

#### AIRWAY PRESSURE RELEASE VENTILATION: THE THEORY

The ideal recruitment strategy would be a sustained, noncyclic plateau pressure maintained at a level that minimizes atelectasis and limits tidal hyperinflation (i.e., continuous airway pressure set to the maintain lung aeration much like a recruitment maneuver). CO<sub>2</sub> removal requires cyclic action (ventilation) to exhaust metabolic combustion. A ventilator strategy that achieves these basic concepts may provide a balanced approach of recruitment, limited overdistention, and adequate CO<sub>2</sub> removal. APRV is a form of lung-protective, open-lung ventilation. By setting the P High (upper CPAP level) in APRV, the airway pressure functions as a hybrid combining plateau pressure and PEEP level to maintain nearly complete recruitment pressure. APRV resembles a continuous recruitment maneuver that accommodates ventilation with a brief release of the CPAP phase. Thus, APRV uses the expiratory limb of the volume-pressure cure, and de-recruitment is minimized.<sup>13,19,20</sup> Because ventilation in APRV does not require additional airway pressure above the P High, plateau pressure levels are not exceeded to accommodate tidal volumes. This allows the P High to remain within the pressure limits considered safe (30 to 35 cm  $H_2O$ ). Because  $CO_2$  removal (ventilation) is accomplished during the brief release phase or with spontaneous breathing throughout the P High (CPAP phase), de-recruitment and atelectasis formation are limited. Conventionally, the release time is less than 1 second.

By using a release phase for ventilation, APRV uncouples the association of ventilation with alveolar distention. Rather than producing a tidal volume by elevating airway pressure above the preset PEEP (as in traditional ventilation), tidal volumes during APRV are generated by releasing the airway pressure from P High to P Low (a lower CPAP level). During APRV, release ventilation lowers airway pressure and lung volume, reducing the risk for overdistention. APRV does not require an increase in airway pressure above P High to augment ventilation, allowing the process of ventilation to be directed away from lung inflation and distention. By contrast, conventional ventilation increases airway pressure, elevating lung volumes and potentially increasing the risk for overdistention.

The use of tidal volumes generated during the release phase may have additional advantages in ALI/ARDS. Increased elastic recoil is common to restrictive lung diseases such as ALI/ARDS, resulting in increased expiratory gas flow. With APRV, pressure is interrupted to release tidal volume and is driven by lung recoil stored during the P High period (T High) and gas compression. During traditional ventilation, inspiratory tidal volumes must overcome airway impedance and elastic forces of the restricted lung from its resting volume, increasing the energy or pressure required to distend the lung and chest wall. Furthermore, as compliance decreases, the inspiratory limb of the volume-pressure curve shifts to the right; that is, more pressure is required to deliver a set tidal volume. However, the expiratory limb remains unaffected by the prevailing volume-pressure relation and extends throughout all phases of injury.

#### AIRWAY PRESSURE RELEASE VENTILATION IN PRACTICE

Historically, mechanical ventilation has been used in an attempt to provide total support for the patient until the underlying respiratory failure resolves. Predetermined inspiratory flow rates, respiratory frequencies, tidal volumes, and inspiratory-to-expiratory ratios conform patients to the ventilator. Frequently, mechanical ventilation locks dynamic and metabolically active critically ill patients into predetermined settings that lead to patientventilator dyssynchrony. This has been particularly problematic in pressure-control inverse ratio ventilation, in which prolonged inspiratory times result in expiratory dyssynchrony. As a result, heavy sedation may be necessary to eliminate spontaneous efforts. The development of dynamic expiratory flow valves has allowed for spontaneous breathing during both inspiration and expiration; in effect, the ventilator operated as two distinct circuits: one for mandatory ventilation, and one for spontaneous breathing.

Mandatory breaths during mechanical ventilation preferentially ventilate the anterior apical segments of the lung, and this may lead to progressive de-recruitment of the posterior dorsal segments. Because the latter is the area of greatest blood flow, little is done to improve ventilation-perfusion matching. Animal model studies suggest that even short durations of controlled mechanical ventilation and elimination of spontaneous breathing can cause ventilator-induced diaphragmatic dysfunction and ventilator cachexia.<sup>21</sup> By allowing unrestricted and unassisted spontaneous breathing throughout the respiratory cycle, APRV allows patients to contribute to ventilation. This appears to be beneficial.

Although the data to support the use of APRV are limited and emanate principally from Putensen's group from Bonn, Germany, the following data have significantly advanced our understanding of the relationship between the patient and the ventilator in ALI.

Spontaneous breathing during APRV redistributes ventilation and aeration to dependent, usually well-perfused lung regions close to the diaphragm and may thereby contribute to improved arterial oxygenation.<sup>22</sup> Wrigge and colleagues<sup>23</sup> performed a randomized controlled experiment on 22 pigs, with oleic acid-induced lung injury, that were randomly assigned to receive APRV with or without spontaneous breathing at comparable airway pressures. Four hours after randomization, dynamic computed tomography scans of the lung were obtained in an apical slice and in a juxtadiaphragmatic transverse slice. Whereas no differences were observed in the apical slices, spontaneous breathing resulted in improved tidal ventilation of dependent lung regions (P < .05) and less cyclic collapse (P < .05) in the juxtadiaphragmatic slices. In addition, with spontaneous breathing, the end-expiratory aeration increased and nonaerated tissue decreased in dependent lung regions close to the diaphragm (P < .05 for the interaction ventilator mode and lung region). In a separate although similar study, the same authors<sup>22</sup> demonstrated that 4 hours of APRV with spontaneous breathing resulted in improved oxygenation compared with APRV without spontaneous breathing (arterial oxygen tension, 144  $\pm$ 65 mm Hg versus 91  $\pm$  50 mm Hg; P < .01 for interaction time  $\times$  mode), higher end-expiratory lung volume (786  $\pm$ 320 mL versus  $384 \pm 148$  mL; *P* < .001), and better aeration. End-expiratory lung volume and venous admixture were both correlated with the amount of lung re-aeration [r(2)]= 0.62 and  $r^2 = 0.61$ , respectively].

Hering and colleagues<sup>24</sup> performed a similar experiment on oleic acid–injured pigs and demonstrated that APRV with spontaneous breathing reduced diaphragmatic work and diaphragmatic blood flow to normal, compared with controls that were not breathing spontaneously. APRV appears to improve renal<sup>25</sup> and hepatic<sup>26</sup> function and splanchnic blood flow,<sup>25</sup> probably associated with enhanced cardiac output

Putensen and colleagues studied 30 patients with multiple trauma who were randomly assigned to either breathe spontaneously with APRV (APRV group; n = 15) or to receive pressure-control, time-cycled mechanical ventilation (PCV) for 72 hours followed by weaning with APRV (PCV group; n = 15).<sup>27</sup> Absence of spontaneous breathing (PCV group) was induced with sufentanil and midazolam (Ramsay Sedation Score [RSS] of 5) and neuromuscular blockade. Primary use of APRV was associated with increases (P < .05) in respiratory system compliance (CRS), arterial oxygen tension (Pao<sub>2</sub>), cardiac index (CI), and oxygen delivery (Do<sub>2</sub>), and with reductions (P < .05) in venous admixture (QVA/QT), and oxygen extraction. In contrast, patients who received 72 hours of PCV had lower CRS, Pao<sub>2</sub>, CI, Do<sub>2</sub>, and QVA/QT values (P < .05) and required higher doses of sufentanil (P < .05), midazolam (P < .05), noradrenaline (P < .05), and dobutamine (P < .05). CRS, Pao<sub>2</sub>), CI, and Do<sub>2</sub> were lowest (P < 0.05), and

QVA/QT was highest (P < .05) during PCV. Primary use of APRV was consistently associated with a shorter duration of ventilatory support (APRV group: 15 ± 2 days [mean ± standard error of the mean]; PCV group: 21 ± 2 days) (P < .05) and length of intensive care unit (ICU) stay (APRV group: 23 ± 2 days; PCV group: 30 ± 2 days) (P < .05). These data suggested that maintaining spontaneous breathing during APRV improves gas exchange and cardiopulmonary function, presumably by recruiting nonventilated lung units. In addition, the patients were given significantly less sedation, and this translated to a shorter duration of ventilatory support and ICU stay.

Putensen and colleagues randomized 24 patients to receive APRV and pressure-support ventilation (PSV) with equal airway pressure limits (Paw) (n = 12) or minute ventilation (VE) (n = 12).<sup>97</sup> In both groups, spontaneous breathing during APRV was associated with increases (P < .05) in right ventricular end-diastolic volume, stroke volume, CI, Pao<sub>2</sub>, oxygen delivery, and mixed venous oxygen tension ( $Pvo_2$ ) and with reductions (P < .05) in pulmonary vascular resistance and oxygen extraction. PSV did not consistently improve CI and Pao<sub>2</sub> when compared with APRV without spontaneous breathing. Improved ventilation-perfusion matching during spontaneous breathing with APRV was evidenced by decreases in intrapulmonary shunt (equal Paw:  $33\% \pm 4\%$  to 24% $\pm$  4%; equal VE: 32%  $\pm$  4% to 25%  $\pm$  2%) (P < .05), dead space (equal Paw: 44%  $\pm$  9% to 38%  $\pm$  6%; equal VE:  $44\% \pm 9\%$  to  $38\% \pm 6\%$ ) (*P* < 0.05), and the dispersions of ventilation (equal Paw:  $0.96 \pm 0.23$  to  $0.78 \pm 0.22$ ; equal VE:  $0.92 \pm 0.23$  to  $0.79 \pm 0.22$ ) (P < .05), and pulmonary blood flow distribution (equal Paw: 0.89  $\pm$  0.12 to 0.72  $\pm$ 0.10; equal VE: 0.94  $\pm$  0.19 to 0.78  $\pm$  0.22) (P < .05). PSV did not improve ventilation-perfusion distributions when compared with APRV without spontaneous breathing. These data suggest that uncoupling of spontaneous and mechanical ventilation during APRV improves ventilation-perfusion matching in ARDS. Further, PSV is not sufficient to counteract the ventilation-perfusion maldistribution caused by alveolar collapse in patients with ARDS.

In summary, in APRV, there is significantly better ventilation of the juxtadiaphragmatic area of the lung and improved gas exchange<sup>27,28</sup> (Table 18-1). Enhanced diaphragmatic activity improves dependent ventilation and

Table 18-1 Potential Benefits of Airway PressureRelease Ventilation (with SpontaneousBreathing) versus Conventional Modes

- Improved ventilation of juxtadiaphragmatic lung tissue
- Improved ventilation-perfusion matching: reduced hypoxemia
- Reduced atrophy of diaphragm during critical illness
- Increased cardiac output
- Increased oxygen delivery
- Improved splanchnic perfusion
- Improved renal function
- Improved hepatic function
- Fewer days on mechanical ventilation
- · Fewer days in the intensive care unit
- Fewer days in the hospital

lung recruitment without increasing applied airway pressure.<sup>24,25</sup> Unassisted spontaneous breathing (during APRV) results in cardiopulmonary benefits such as improved venous return and cardiac output, renal and gut perfusion, and dependent lung ventilation.<sup>24,25,29</sup> Spontaneous breathing can maintain dependent aeration and may reduce reactive rescue therapies such as intermittent recruitment maneuvers and increased airway pressure requirements (see Table 18-1).

A secondary benefit of spontaneous ventilation is a significant reduction in the use of sedatives and neuromuscular blockers. Excessive sedation has been linked to delirium. One study of 275 patients on mechanical ventilation in the ICU documented that delirium developed in more than 80% of patients.<sup>30</sup> Nonpulmonary organ dysfunction such as delirium contributes significantly to mortality in mechanically ventilated patients in the ICU and is an independent risk factor associated with increased mortality.<sup>30</sup>

APRV may be associated with a decrease in ICU and hospital length of stay.<sup>31</sup> These data suggest that use of modes of mechanical ventilation that increase patient comfort, adapt to the patient, and promote spontaneous breathing may reduce ventilator days. Several studies show that sedation requirements are typically reduced 30% to 40% and that Neuromuscular Blocking Agents (NMBAs) are reduced up to 70% when using APRV compared with conventional ventilation.<sup>31–34</sup>

#### **AUTHORS' RECOMMENDATIONS**

- When considered as a whole, critically ill patients with ARDS require attention to detail beyond optimal mechanical ventilation for the best outcome.
- Mechanical ventilation is associated with many therapeutic interventions that are harmful and may contribute to morbidity and mortality.
- Ultimately, clinicians strive to return patients to unassisted spontaneous breathing without which they would remain dependent on mechanical ventilation. In general, the sooner patients can be liberated from mechanical ventilation and its linked therapies, the better.
- Ventilation strategies that require sedation and NMBAs can prolong restoration of spontaneous breathing and lead to increased ventilator days, resulting in ventilator-associated complications.
- APRV with spontaneous breathing appears to be associated with better gas distribution and exchange than equivalent modes of ventilation, such as pressure control and pressure support.
- APRV with spontaneous breathing appears to improve cardiac output and oxygen delivery, compared with equivalent modes of ventilation. This results in better gut and splanchnic blood flow.
- APRV appears to be associated with reduced sedation in the ICU, and this may reduce length of stay in both the ICU and the hospital.
- To date, no multicenter prospective randomized double-blind controlled trials have evaluated APRV against alternative modes of ventilation, and it is unknown whether APRV improves outcomes in terms of morbidity or mortality over the medium and long term.
- Ventilator strategies using APRV are entirely compatible with current best practices for the management of the mechanically ventilated patient with ARDS.

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# What Is the Role of Alveolar Recruitment Maneuvers in the Management of ARDS?

Chirag V. Shah

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Acute lung injury (ALI) and its more severe manifestation, the acute respiratory distress syndrome (ARDS), are among the most common causes of acute hypoxemic respiratory failure in the intensive care unit (ICU). ALI complicates many medical and surgical conditions and represents a complex pathophysiologic sequela to a variety of different pulmonary and extrapulmonary insults. Initially described in the 1960s, ARDS is characterized by refractory hypoxemia, diffuse pulmonary infiltrates, and decreased lung compliance.<sup>1</sup> ALI and ARDS are characterized by acute pulmonary inflammation with increased vascular permeability in response to a systemic insult. The two syndromes differ only by their degree of hypoxemia and represent stages along a disease continuum. Because this differentiation is arbitrary, this chapter uses the term *ALI* to refer to the entire spectrum of lung injury.

Increased physiologic shunt and worsening ventilationperfusion mismatch necessitate mechanical ventilation in nearly all patients with ALI. This approach aids in preserving adequate gas exchange and reduces the work of breathing. During the past two decades, the intersection of basic science and clinical research has culminated in strategies best defined as lung-protective ventilation (LPV).<sup>2-4</sup> To this core ventilator management strategy of lower tidal volumes and end-inspiratory pressure limits, many physicians add the adjunctive intervention of alveolar recruitment maneuvers (RMs) in patients with ALI. However, ALI is a syndrome based on nonspecific physiologic and radiographic criteria, and affected patients have varying underlying pathologic disease processes, morphologic abnormalities, and respiratory mechanics. Thus, investigators face challenges in developing universal management strategies other than LPV that are safe and effective for all patients with ALI. Specifically, the role of RMs in the management of ALI remains an area of controversy.

### DEFINITION

The alveolar RM can be defined as a high-pressure inflation maneuver aimed at temporarily raising the transpulmonary pressure above levels typically obtained with mechanical ventilation. The purpose is to overcome the high-threshold opening pressures of diseased and closed alveoli, thereby "recruiting" lung units. Because of the complex elastic properties of alveoli, the magnitude and extent of recruitment are functions of the absolute pressure and duration of application of RMs.<sup>5</sup> Clinically, alveolar RMs can be delivered as elevated sustained pressures, intermittent augmented pressures, large tidal volumes (e.g., sighs), or a combination of these.

#### VENTILATOR-INDUCED LUNG INJURY AND RECRUITMENT

Despite its life-saving potential in ALI, the application of mechanical ventilation can retard lung recovery and even potentiate lung injury.<sup>4</sup> Even though chest radiographs often reveal a homogeneous pattern of injury in ALI, other imaging modalities (e.g., computed tomography) and autopsy studies indicate that the diseased lung is mechanically and histopathologically heterogeneous. Populations of consolidated, collapsed (compression and resorption atelectasis), aerated, and overinflated lung units exist next to one another, but the extent and magnitude of these populations change over time. The threshold opening pressure (TOP) refers to the airway tension that must be generated so that a gasless, collapsed alveolus will yield and expand ("recruit"). The closing pressure, which is often less than the TOP for a given alveolus, refers to the tension that must remain in the alveolus to overcome its tendency to collapse when gas is emptied ("de-recruit"). Because of the wide spectrum of TOP (0 to  $\omega$  cm H<sub>2</sub>O) for the heterogeneous lung units in ALI, coupled with the varying generated regional transpulmonary pressures, mechanically delivered tidal volumes are not uniformly distributed in ALI, leading to ventilator-induced lung injury (VILI).<sup>3,4,6,7</sup>

VILI is a result of a complex interaction between the excessive stress of transpulmonary pressures and the subsequent strain placed on the lung epithelial and endothelial cells from nonphysiologic alveolar overdistention (*volutrauma*).<sup>34,6,8</sup> Mechanical stress leads to cellular changes, including complex intracellular signaling and release of inflammatory mediators that can augment ongoing lung injury (*mechanotransduction*).<sup>3,8,9</sup> Furthermore, VILI

may occur from the repetitive opening and closing of unstable alveolar units during tidal cycling (atelectrauma). VILI may also be potentiated by the amplification of local transpulmonary pressures at junctions between healthy, aerated alveoli and diseased, atelectatic alveoli (amplification stress).<sup>6,10</sup> Because of the interdependence of juxtaposed alveoli, mechanical shearing forces at the interface of heterogeneous alveoli may be amplified to nearly 5 times the actual applied levels (i.e., 30 cm H<sub>2</sub>O applied pressure can translate into 140 cm H<sub>2</sub>O of tension).<sup>5,10</sup> Therefore, there is theoretical appeal in reducing the number of such juxtaposed alveoli with different mechanical characteristics. Transitioning the ALI lung into a more homogeneous structure by recruiting collapsed alveoli may improve overall lung compliance, ventilation-perfusion matching, and shunt fraction. Most important, it may minimize VILI. Theoretically, by "opening" the lung with alveolar recruitment, a given tidal volume or inspiratory pressure should cause less strain (volutrauma), and by keeping the lung open, cyclical recruitment and de-recruitment injury (atelectrauma) should be minimized.<sup>4,11–13</sup> Therefore, the prime motive for implementing alveolar recruitment maneuvers has been for lung protection. However, despite these basic principles, it remains unclear what priority recruitment of atelectatic or partially fluid-filled alveoli should be given in the overall scheme of ALI management. Clinical trials comparing an open-lung approach to the Acute Respiratory Distress Syndrome Clinical Trials Network (ARDSNet) low tidal volume strategy have failed to show a mortality difference.<sup>2,12–17</sup> Furthermore, tidal recruitment and de-recruitment cannot be completely avoided, nor can all diseased alveoli be recruited because some are fully consolidated, and others may require extraordinarily high inflating pressures beyond what would be considered safe in clinical practice.<sup>6,12,14</sup>

#### MECHANISM OF ACTION

The goal of alveolar recruitment maneuvers is to open refractory lung units with elevated transpulmonary pressures without causing hemodynamic instability or barotrauma. In early ALI, the weight of the edematous lung and mediastinal structures causes increasingly dependent compressive atelectasis across the sternovertebral axis. These gravitational forces may be attenuated with positive end-expiratory pressure (PEEP) and alveolar RMs. However, the actual opening of unstable alveoli is a function of sustained elevated inflation pressures and not PEEP. PEEP can keep recruited alveoli open but cannot open alveoli that were not already open during the prior tidal volume. Conceptually, diseased lung units exhibit much higher threshold opening pressures than closing pressures.<sup>12</sup> As the disease process unfolds, the fibrotic changes characteristic of latestage ARDS may not be amenable to recruitment.<sup>18</sup>

The immediate success of alveolar RMs depends on a number of factors. The most important is the pressuretime product. In addition, other variables that influence the effectiveness of recruitment include the morphology of ALI, the stage of ALI, pre-RM PEEP and tidal volume levels, post-RM PEEP level, and the occurrence of adverse events (Table 19-1).<sup>19–35</sup> The degree of elevation of

### Table 19-1 Factors Influencing the Effectivenessof Alveolar Recruitment Maneuvers

Factor	Comment			
Pressure	Direct determinant of transpulmonary pressure achieved			
Time	Increased duration of application increases recruitment of alveoli with long time constants <sup>35,49</sup>			
Morphology	Radiographic evidence of ALI with predominant atelectasis is more recruitable than predominant consolidative ALI <sup>20,22,45,46</sup>			
Stage	Recruitability may decrease in late ALI <sup>23</sup>			
Positive	Recruitability may be increased in the prone position <sup>31</sup>			
Pre-RM PEEP and VT	Lung already maximally recruited with high Pplat and PEEP may not benefit from RM <sup>21,30</sup>			
Post-RM PEEP	Increasing post-RM PEEP may prevent recollapse of recently recruited lung units <sup>33</sup>			
Adverse events	Hypotension, barotraumas, and increased intracranial pressure; common practice is to avoid RMs in patients with hemodynamic instability, hypovolemia, blebs or bullae radiographically, existing barotrauma, or elevated intracranial pressure <sup>19,21,23,34,39,40,42</sup>			

ALI, acute lung injury; PEEP, positive end-expiratory pressure; Pplat, plateau pressure; RM, recruitment maneuver; VT, tidal volume.

transpulmonary pressure needed to overcome the TOP of diseased alveoli in ALI is unclear. Undoubtedly, pressure levels needed to recruit the most unyielding alveoli in ALI may result in overdistention of healthy, compliant lung units.

#### SYSTEMATIC REVIEW OF THE LITERATURE AND INTERPRETATION OF DATA

The role of recruitment maneuvers in the management of ALI remains controversial. Proponents of the technique argue that RMs minimize VILI, improve lung mechanics and gas exchange, and are well tolerated clinically. Opponents question the importance of recruiting lung units that would otherwise remain atelectatic, citing that atelectasis may not be harmful in the absence of refractory hypoxemia. Furthermore, they argue that RMs (1) provide only transient improvements in gas exchange and respiratory mechanics; (2) have not been standardized in terms of pressure, duration, or frequency; (3) carry significant clinical risks for hypotension and barotrauma; and (4) may contribute to cellular mechanisms of injury by overdistending healthy lung units. Table 19-2 summarizes the methodology, outcomes, and significance of human clinical trials using alveolar RMs in patients with ALI.

## Table 19-2 Summary of Clinical Trials Using Alveolar Recruitment Maneuvers in Acute Respiratory Distress Syndrome

Study	No. of Subjects (Intervention/ No Intervention)	Study Design*	Intervention(s)	Control	Outcomes	Comments
Novak, 1987 <sup>36</sup>	16 (16/0)	NR, C	RM using CPAP 40 cm H <sub>2</sub> O for 15-30 sec and bag-sighs	Crossover design	No change in $Pao_2$ or $C_s$ at 5 min in either group	AHRF patients (before AECC ARDS definition)
Amato, 1995 <sup>41</sup>	53 (29/24)	R	RM using CPAP 35-40 cm H <sub>2</sub> O for 40 sec with LPV (low VT, high PEEP)	12 mL/kg Vt, low PEEP, no RM	↓Mortality (38% vs. 71%) ↑Wean from ventilator (66% vs. 29%)	Improved outcomes due to LVP; benefit of RM unknown
Pelosi, 1999 <sup>37</sup>	10 (10/0)	NR	3 Sighs/min for 1 hr using Pplat = 45 cm H <sub>2</sub> O	None	Improved PaO <sub>2</sub> and EELV; effect lost at 1 hr	More effective in ARDSexp; LPV used
Lapinsky, 1999 <sup>25</sup>	14 (14/0)	NR	RM using CPAP 30-45 cm H <sub>2</sub> O for 20 sec	None	70% had better Pao <sub>2</sub> at 4 hr; no adverse events	Early AHRF; LPV not used
Foti, 2000 <sup>21</sup>	15 (15/0)	R, C	$\begin{array}{l} 3 \text{ Groups: VC} \\ \text{low-PEEP vs.} \\ \text{VC high-PEEP} \\ \text{vs. VC low-PEEP} \\ \text{with RM (PEEP} \\ \leq 20 \text{ cm } H_2 \text{O} \\ \text{every 30 sec)} \end{array}$	Triple crossover design	Group with RM had improved Pao <sub>2</sub> , shunt fraction, C <sub>s</sub> vs. VC low-PEEP but worse Pao <sub>2</sub> and shunt fraction vs. VC high-PEEP	PEEP-responsive ARDS only; mixed ARDSp/ exp; variable ARDS duration
Crotti, 2001 <sup>20</sup>	5 (5/0)	NR	RM using PCV with varying Pplat (30-45 cm H <sub>2</sub> O) and PEEP (5-20 cm H <sub>2</sub> O) with CT	None	Recruitment is pan-inspiratory; improved gas exchange; no adverse events	Early ARDS; ARDSp/exp; LPV not used; variable ARDS duration
Lim, 2001 <sup>27</sup>	20 (20/0)	NR	Two 90-sec sighs with stepwise increase in PEEP and decrease in VT (Pplat ≤ 40 cm H <sub>2</sub> O)	None	Improved Pao <sub>2</sub> and C <sub>s</sub> at 1 hr; no adverse events	Mixed ARDSp/ exp; early ARDS
Richard, 2001 <sup>33</sup>	10 (10/0)	NR	RM using CPAP 45 cm H <sub>2</sub> O for 15 sec in 6 mL/ kg Vt and 10 mL/kg Vt groups	None	Improved short- term Pao <sub>2</sub> and EELV in 6 mL/ kg VT group only	Mixed ARDSp/ exp; increasing PEEP has same effect as RM
Villagra, 2002 <sup>34</sup>	17 (17/0)	NR	$\begin{array}{l} \text{RM using 2 min} \\ \text{PCV of } P_{\text{PK}} \\ \text{50 cm } H_2\text{O with} \\ \text{PEEP} > \text{UIP for} \\ \text{2 min} \end{array}$	None	No change in Pao <sub>2</sub> for late or early ARDS; possible overdistention and worsening shunt	LPV used; mixed ARDSp/exp; effect on ARDS duration studied
Patroniti, 2002 <sup>30</sup>	13 (13/0)	NR	"Sigh ventilation" for 1 hr (1 sigh/ min with 3-5 sec of CPAP $\ge$ 35 cm H <sub>2</sub> O)	None	Improved Pao <sub>2</sub> , EELV, and C <sub>s</sub> ; effect lost after cessation of sighs	Early ARDS; mixed ARDSp/ exp; PSV used

## Table 19-2 Summary of Clinical Trials Using Alveolar Recruitment Maneuvers in Acute Respiratory Distress Syndrome—Cont'd

Study	No. of Subjects (Intervention/ No Intervention)	Study Design	Intervention(s)	Control	Outcomes	Comments
Grasso, 2002 <sup>23</sup>	22 (22/0)	NR	RM using 40 cm H <sub>2</sub> O for 40 sec	None	Improved Pao <sub>2</sub> at 20 min in early ARDS only; ~25% ↓MAP and CO in late ARDS group	Effect on ARDS duration studied; mixed ARDSp/exp; LPV used
Bien, 2002 <sup>40</sup>	11 (11/0)	NR	RM using PCV with Pplat = 60 cm H <sub>2</sub> O for 30 sec	None	Decrease in MAP and CPP	All patients with cerebral injury
Pelosi, 2003 <sup>31</sup>	10 (10/0)	NR	3 Sighs/min for 1 hr using Pplat = 45 cm H <sub>2</sub> O in prone/supine	None	Increase in Pao <sub>2</sub> , EELV, and C <sub>s</sub> better in prone, but effect gone at 1 hr	LPV used; early ARDS
Lim, 2003 <sup>26</sup>	47 (47/0)	NR	RM as above (Lim, 2001); 3 groups: RM followed by †PEEP vs. RM followed by no change in PEEP vs. †PEEP alone	None	Improved Pao <sub>2</sub> in all (best in ARDSexp); effect lost immediately unless ↑PEEP after RM; ARM + ↑PEEP better than ↑PEEP alone	LVP used; early ARDS
Tugrul, 2003 <sup>38</sup>	24 (24/0)	NR	RM using CPAP 45 cm H₂O for 30 sec with ↑PEEP post-RM	None	Improved Pao <sub>2</sub> 6 hr post-RM (ARDSexp > ARDSp); improved C <sub>s</sub> in ARDSexp	LPV used; no adverse events
ARDSNet, 2003 <sup>2</sup>	72 (72/0)	R, C, P, MC	RM using CPAP 35-40 cm H <sub>2</sub> O for 5-10 sec every 48 hr (on days 1/3 or 2/4)	Crossover design with sham RM;	Improved Pao <sub>2</sub> at 10 min (transient), but no change in FiO <sub>2</sub> /PEEP; no difference by ARDS phenotype; transient ↓BP with RM	LPV with high PEEP used; protocol for changes in FIo <sub>2</sub> /PEEP after RM
Oczenski, 2004 <sup>29</sup>	30 (15/15)	R	Single RM using CPAP 50 cm H <sub>2</sub> O for 30 sec with LPV	LPV without RM	Improved Pao <sub>2</sub> and shunt fraction at 3 min, effect lost at 30 min; no adverse events	Early ARDSexp; PEEP trial before RM
Povoa, 2004 <sup>32</sup>	8 (8/0)	NR	RM using PCV with stepwise increase in Pplat/PEEP (max of 60/45) over 30 min	None	Improved Pao <sub>2</sub> and C <sub>s</sub> at 30 min	Early ARDS; LPV with high PEEP used; mixed ARDSp/exp
Borges, 2006 <sup>39</sup>	26 (26/0)	NR	RM using PCV with stepwise increase in Pplat/PEEP to 60/45 followed by PEEP decremental trial	None	24/26 were recruitable; Improved Pao <sub>2</sub> at 6 hr; transient hypotension and hypercarbia	Early ARDS; mixed ARDSp/ exp; LPV with low PEEP pre-RM

Distress Syndrome—Cont'd						
Study	No. of Subjects (Intervention/ No Intervention)	Study Design	Intervention(s)	Control	Outcomes	Comments
Constantin, 2008 <sup>19</sup>	19 (19/0)	R, C	2 RM groups: CPAP 40 cm H <sub>2</sub> O for 40 sec vs. 15 min sigh (VCV with PEEP 10 cm H <sub>2</sub> O above LIP)	Crossover design	Both RM improved PaO <sub>2</sub> (better with sigh); only sigh increased EELV	LPV used; CPAP RM stopped in 2 patients due to hypotension
LOVS, 2008 <sup>15</sup>	983 (475/508)	R, MC	LOV: PCV with goal VT 6 mL/kg, Pplat $\leq$ 40 cm H <sub>2</sub> O, high PEEP, RM using CPAP 40 cm H <sub>2</sub> O for 40 sec	ARDSNet LPV with no RM	LOV with less refractory hypoxemia (5% vs. 10%), but no difference in mortality or barotrauma	Protocolized ventilation strategy

Table 19-2 Summary of Clinical Trials Using Alveolar Recruitment Maneuvers in Acute Respiratory Distress Syndrome—Cont'd

\*C, crossover; MC, multicenter; NR, nonrandomized; R, randomized.

AECC, American-European Consensus Conference; AHRF, acute hypoxemic respiratory failure; ARDS<sub>EXP</sub>, extrapulmonary ARDS; ARDS<sub>P</sub>, pulmonary ARDS; CO, cardiac output; CPAP, continuous positive airway pressure; CPP, cerebral perfusion pressure; C<sub>s</sub>, static respiratory system compliance; CT, computed tomography; EELV, end-expiratory lung volume; LIP, lower inflection point on pressure-volume curve; LOV, "lung open" ventilation strategy; LPV, lung protective ventilation; MAP, mean arterial pressure; Pao<sub>2</sub>, partial pressure of arterial oxygen; PCV, pressure-control ventilation; PEEP, positive end-expiratory pressure; Psv, peak pressure; Plat, plateau pressure; PSV, pressure-support ventilation; RM, recruitment maneuver; VC, volume control; VT, tidal volume; UIP, upper inflection point on pressure-volume curve.

Despite the number of studies, most have been small (n < 50), uncontrolled, nonrandomized clinical trials using varied RM strategies to evaluate surrogate outcome measures.<sup>20,23,25–27,29–34,36–40</sup> Strategies used have included single or repeated sustained inflations with continuous positive airway pressure (CPAP), pressure-control ventilation (PCV) with incremental increases in PEEP and decreases in tidal volume, traditional sighs with large tidal volumes titrated to plateau pressure (Pplat), "extended" sigh maneuvers, and other approaches (see Table 19-2 for details). Amato and colleagues, using a low tidal volume strategy that included alveolar RMs and high PEEP, showed a significant decrease in mortality compared with the then traditional 12 mL/kg tidal volume ventilation.41 However, the independent benefit of RMs in ALI could not be elicited. It is likely that the mortality benefit was related to the use of low tidal volumes and not RMs. Nonetheless, this study spurred a large number of subsequent clinical trials that attempted to evaluate the independent benefit and risk of RMs when included as adjunctive therapy in the management of ALI.

Drawing concrete conclusions after comprehensive review of these clinical studies is difficult. Many investigators have shown improvements in varying surrogate end points in ALI patients when RMs were added to core mechanical ventilation.<sup>15,19–21,23,25–27,29–32,38,39,42</sup> These have included gas exchange, respiratory system mechanics (compliance, elastance, end-expiratory lung volume) and shunt fraction. Others, however, have been unable to duplicate these results.<sup>21,34,36</sup> More important, surrogates do not always translate into long-term outcomes (e.g., mortality), and in ALI, improved oxygenation has never consistently predicted survival. Specifically, in the landmark ARDSNet study comparing lower tidal volumes with higher tidal volumes, the lower tidal volume group had worse day 1 oxygenation indices despite an overall superior hospital survival rate.<sup>2</sup> In addition, studies using nitric oxide and prone positioning in ALI have reported improved oxygenation without survival advantage.<sup>43,44</sup> Nonetheless, these studies have taught us much, and several key observations can be made. Improvements in physiologic parameters were never sustained beyond 6 hours, and most investigators report gas exchange and respiratory function improvements returning to baseline after 1 hour. Studies that included only PEEP-responsive patients or used low levels of PEEP (<10 cm H<sub>2</sub>O) before implementing RMs were likely investigating ALI patients who were "under-recruited" to begin with.21,27,30 It is unclear whether RMs have significant benefit on gas exchange or respiratory mechanics in patients already ventilated with moderate to high levels of PEEP. In these patients, high levels of PEEP may have already maintained lung units recruited during tidal ventilation. The application of sustained elevated inflation pressures in these patients may result in excessive overdistention of healthy alveoli, negating the perceived benefit of further recruitment of unstable alveoli.21,23,34,42 Several studies have shown greater gas exchange improvements in patients with extrapulmonary ALI (ALIexp), suggesting that the precipitating insult in ALI may influence response to RMs.<sup>23,26,29,37,38</sup> However, the actual ALI morphology by computed tomography (predominantly atelectatic versus predominant consolidative) is likely more important.<sup>42,45,46</sup> In general, RMs are typically well tolerated by nonhypotensive, well-resuscitated ALI patients. In those with increased intracranial pressure, RMs may result in decreased cerebral perfusion, but there are limited data in this subgroup of patients.<sup>40</sup>

A few investigations deserve further attention given their superior study methodologies. Foti and colleagues

conducted a randomized crossover trial in which patients received each of three interventions in succession: volume control ventilation (VCV) with low PEEP, VCV with low PEEP and RMs, and VCV with high PEEP.<sup>21</sup> The investigators found that RMs only improved oxygenation, compliance, and shunt fraction when added to ventilation using low PEEP and were less effective in improving these parameters compared with VCV with a continuous high PEEP level. The ARDSNet investigators conducted a multicenter, randomized, sham-controlled, crossover study to assess the effects of adjunctive RMs to LPV with high PEEP.42 This study was done using a subset of patients from the "high" PEEP arm of the parent ALVEOLI study.<sup>17</sup> Using an explicit protocol to wean oxygen after RMs, the authors concluded that RMs have transient effects on oxygenation but do not affect the eventual titration of FIO<sub>2</sub>/ PEEP requirements. In addition, RMs were not influenced by ALI subtype (e.g., pulmonary versus extrapulmonary). Oczenski and colleagues randomized ALIexp patients receiving LPV to a single RM with CPAP of 50 cm H<sub>2</sub>O for 30 seconds.<sup>29</sup> Importantly, all patients had their pre-RM PEEP optimized using a PEEP trial. 37,47,48 RMs failed to induce any sustained improvement in gas exchange or shunt fraction. Finally, the Lung Open Ventilation Study (LOVS) investigators conducted a multicenter, randomized controlled trial comparing an established low tidal volume strategy to a strategy that employed low tidal volumes, RMs, and high PEEP.<sup>15</sup> Although the experimental arm had less refractory hypoxemia (4.6% versus 10.2%; P =.01) and fewer deaths with refractory hypoxemia (4.2% versus 8.9%; P = .03), overall hospital mortality was not significantly altered (36.4% versus 40.4%; P = .19).

Thus, a critical appraisal of the current literature does not support the *routine* use of RMs in the management of ALI. However, each individual patient, especially those with life-threatening hypoxemia, should be assessed independently. If employed, there are several matters that require careful attention. It is essential that patients be adequately volume-resuscitated to avoid hemodynamic compromise. In general, post-RM PEEP should be increased to levels higher than pre-RM PEEP to prevent de-recruitment and avoid repeated maneuvers. Finally, RMs are likely more effective in early ALI and in patients with more homogeneous disease (i.e., with predominantly atelectatic lung and ground-glass opacities on imaging). Further studies are needed to better define the optimal method of alveolar RMs (i.e., method of pressure delivery, duration, periodicity, post-RM PEEP level), and welldesigned randomized controlled trials are needed to better define the role of RMs in ALI management.

#### CONCLUSION

ALI is a heterogeneous process consisting of aerated, atelectatic, and consolidated lung units. Lung-protective ventilation strategies using lower tidal volumes and limiting end-inflationary pressures are recommended to decrease VILI. The pathophysiologic basis of recruiting collapsed lung units to participate in gas exchange comes from a body of experimental evidence suggesting that homogenizing the lung could limit VILI. In clinical trials, RMs can have transient improvements on oxygenation and respiratory mechanics but have not been shown to independently improve long-term outcomes in ALI.

#### **AUTHOR'S RECOMMENDATIONS**

- The alveolar RM can be defined as a high-pressure inflation maneuver aimed at temporarily raising the transpulmonary pressure above levels typically obtained with mechanical ventilation to aerate previously collapsed lung units.
- Clinically, alveolar RMs can be delivered as elevated sustained pressures, intermittent augmented pressures, large tidal volumes (e.g., sighs), or a combination of these.
- The goal of RMs is to convert the ALI lung into a more homogeneous structure and thereby decrease the potential for VILI.
- RMs may be associated with hypotension and barotrauma.
- Most clinical trials of RMs have reported transient improvement (<4 hours) in physiologic end points such as gas exchange and respiratory mechanics.
- Given the lack of demonstrated efficacy in clinically relevant outcomes (e.g., mortality, length of ventilation), the routine use of RMs remains controversial and not is recommended.

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# 20 What Is the Role of High-Frequency Oscillation in ARDS?

Chuin Siau, Thomas E. Stewart

#### PROLOGUE OF CLINICAL CONTEXT

A 39-year-old, previously healthy man was recently hospitalized with severe, likely bacterial, community-acquired pneumonia several days after having flu-like symptoms. Nasal swabs subsequently proved positive for influenza A (Fig. 20-1A). He rapidly deteriorated, developing hypoxic respiratory failure with a Pao<sub>2</sub> of 61 mm Hg at an FIO<sub>2</sub> of 1.0 while on a non-rebreathing mask. He was transferred to our intensive care unit (ICU), intubated, and conventionally ventilated with a pressure- and volume-limited lung-protective strategy incorporating lung recruitment maneuvers (RMs). A repeat chest radiograph (Fig. 20-1B) showed bilateral diffuse alveolar infiltrates. The Pao<sub>2</sub>/ FIO2 ratio was 79 while on an FIO2 of 1. He had an oxygenation index (OI = mean airway pressure [mPaw]  $\times$  Fio<sub>2</sub>  $\times$  $100 \div Pao_2$ ) of 29. His respiratory failure was complicated by septic shock and acute renal failure. Despite efforts to maintain an open-lung and lung-protective ventilation strategy (pressure-control ventilation [PCV] mode with a driving pressure of 16 cm H<sub>2</sub>O, positive end-expiratory pressure [PEEP] of 18 cm H<sub>2</sub>O, mPaw of 25 cm H<sub>2</sub>O, and a target tidal volume [VT] of 462 mL [6 mL/ kg]), the patient's oxygenation and ventilation continued to deteriorate to a life-threatening level. The decision was made to switch patient to high-frequency oscillatory ventilation (HFOV) as "rescue" therapy. After an initial inflation RM, our patient's Pao<sub>2</sub>/Fio<sub>2</sub> ratio and OI improved (146 and 22, respectively) when he was placed on HFOV. This improvement was maintained over the next 4 days, after which he was transitioned back to conventional mechanical ventilation. During the following month, he was weaned to supplemental oxygen through tracheostomy and was subsequently discharged from hospital. There was no evidence that he developed any complications related to mechanical ventilation. Importantly, we recognize that an anecdote such as this, regarding the apparent success of HFOV, should not necessarily change clinical practice. Nonetheless, it should cause us to pause and ask: What is the role of HFOV in adults with ARDS?

#### INTRODUCTION

Injurious mechanical ventilatory strategies can cause ventilator-induced lung injury (VILI).<sup>1,2</sup> This exacerbates preexisting lung damage in patients with acute lung

injury (ALI) and acute respiratory distress syndrome (ARDS) and may itself be the cause of ALI/ARDS in patients with uninjured lungs. Physical injuries to the alveoli trigger the release of inflammatory mediators, which leak into the systemic circulation, potentially causing multiorgan dysfunction and failure.<sup>3,4</sup>

Reduction of mortality and nonpulmonary organ failure have been demonstrated by adopting lung protective strategies.<sup>5,6</sup> In recent years, conventional mechanical ventilation, emphasizing pressure and volume limitation, has become the standard of care for patients with ALI/ARDS. A recent study by Terragni and colleagues,<sup>7</sup> however, showed that, despite adoption of the Acute Respiratory Distress Syndrome Network (ARDSNet) protocol,<sup>6</sup> aerated lungs are at risk for tidal hyperinflation in ARDS patients with large, dependent, nonaerated compartments. This is associated with increased pulmonary cytokines and fewer ventilator-free days. These results suggest that rather than adopting a universal approach to mechanical ventilation, ventilatory strategies should be individualized, attending to the specific needs of patients and their disease process.

HFOV is an alternative mode of ventilation that uses a higher mPaw to achieve many of the goals of lung protection. In this chapter, we review the physiology as well as the data defining the role of HFOV in adult patients with ARDS.

#### OVERVIEW AND PHYSIOLOGIC EFFECTS

Most clinical trials on HFOV have been performed in the neonatal population.<sup>8</sup> Recently, a better understanding of the injurious effects of mechanical ventilation has led to renewed interest and advances in the application of HFOV in adult patients with ALI/ARDS.

HFOV is characterized by rapid oscillations of a diaphragm (at frequencies of 3 to 10 Hz, i.e., 180 to 600 breaths/minute) (Fig. 20-2) driven by a piston pump. The pressure swings become significantly attenuated as they move distally from the airways to the alveoli, resulting in small tidal volumes. An inspiratory bias flow (30 to 60 L/minute) and a resistance valve determine the mPaw in the circuit.

The forward and backward excursions of the diaphragm result in active inspiration and expiration, respectively. Because exhalation is an active process, the risk for air



Figure 20-1. A, Chest radiograph at time of admission. B, Chest radiograph at time of intubation.



**Figure 20-2.** Pressure-time tracing for high-frequency oscillatory ventilation (HFOV, *solid line*) as compared with conventional mechanical ventilation (CMV, *dotted line*). Note that the frequency is not to scale. In addition, note that the exact positioning of the waveforms will vary based on a variety of factors. (*From Fan E, Stewart TE. New modalities of mechanical ventilation: High frequency oscillatory ventilation and airway pressure release ventilation.* Clin Chest Med. 2006;27:615-625.)

trapping and dynamic hyperinflation, at least when compared with other forms of high-frequency ventilation, is reduced.<sup>9</sup>

A unique feature of HFOV is the ability to decouple oxygenation and ventilation. Oxygenation is dependent on the mPaw and the fraction of inspired oxygen (FIO<sub>2</sub>), whereas ventilation is inversely related to the frequency and is directly related to the excursion of the diaphragm of the oscillator (pressure amplitude,  $\Delta P$ ).

Gas transport is believed to occur through several mechanisms. Direct bulk flow delivers air into alveoli situated near the proximal tracheobronchial tree. Cardiogenic oscillation and molecular diffusion aid in gas mixing. Taylor dispersion, the Pendelluft effect, and asymmetrical velocity profiles are the other mechanisms postulated to be involved. Detailed description of these mechanisms can be found elsewhere.<sup>9,10</sup>

In animal studies, many of the goals of lung protective strategy have been achieved with HFOV. A constant, higher mPaw aids in lung recruitment, maintains an "open lung,"<sup>11</sup> and likely mitigates atelectrauma. A higher mPaw reduces the risk for oxygen toxicity by improving oxygenation, particularly if adequate intravascular volume and cardiac output are maintained. In addition, the risk for alveolar overdistention probably is minimized because the tidal volumes delivered by HFOV are significantly lower than those observed during conventional mechanical ventilation. These serve to attenuate VILI, reducing the amount of histologic damage and lung inflammation.<sup>12–14</sup>

#### CLINICAL STUDIES IN ACUTE LUNG INJURY AND ARDS

Current published clinical studies on the application of HFOV in adults have mainly been case series in "rescue" situations in which conventional ventilation arguably has failed. The clinical anecdote at the beginning of this chapter would be an example of a rescue situation in which the clinicians believe they are at the limits of conventional ventilation. Table 20-1 summarizes the clinical trials on HFOV in adult ALI/ARDS patients.<sup>15–30</sup> There have only been two published randomized controlled trials (RCTs) that compared HFOV with conventional mechanical ventilation in adult ALI/ARDS. It is important to understand that the RCTs investigated use of HFOV earlier in the course of ARDS (i.e., before the patient was in a rescue situation).

Derdak and associates<sup>15</sup> set out to compare equivalency between HFOV and conventional ventilation (CV). In 148 patients, there was no significant difference in key Table 20-1 Clinical Studies Evaluating High-Frequency Oscillatory Ventilation in Adult Patients with Acute Lung Injury and ARDS

Study	Study Design	No. of Patients	Patient Population	Mortality	Comments
Fort et al, 1997 <sup>18</sup>	Prospective observational	17	Age: 38 yr Pa0 <sub>2</sub> /Fi0 <sub>2</sub> : 69 OI: 49 APACHE II: 23	30-day: 53%	A greater number of pretreatment days on CMV and an OI > 47 are associated with mortality. No significant compromise on cardiac output, but 3 patients withdrawn from HFOV because of hypotension
Claridge et al, 1999 <sup>25</sup>	Prospective observational	5	Trauma patients Age: 37 yr Pao <sub>2</sub> /Fio <sub>2</sub> : 52 APACHE II: 29	In-hospital: 20%	HFOV used as rescue therapy for refractory hypoxemia with improvement in Pao <sub>2</sub> /Fio <sub>2</sub> ratios
Mehta et al, 2001 <sup>19</sup>	Prospective observational	24	Age: 49 yr Pao <sub>2</sub> /Fio <sub>2</sub> : 99 OI: 33 APACHE II: 22	30-day: 66%	No significant change in systemic BP, although increases in PAOP and CVP with decrease in CO noted. Pneumothoraces reported in 2 patients
Derdak et al, 2002 <sup>15</sup>	RCT	148	Age: 50 yr Pao <sub>2</sub> /Fio <sub>2</sub> : 113 OI: 25 APACHE II: 22	30-day: HFOV: 37% CMV: 52% ( <i>P</i> = .102)	No differences in hemodynamic variables, oxygenation, or ventilation failures between treatment groups. Both groups had similar complication rates.
Andersen et al, 2002 <sup>26</sup>	Retrospective	16	Age: 38 yr Pao <sub>2</sub> /Fio <sub>2</sub> : 92 OI: 28 SAPS II: 40	90-day: 31%	1 patient had pneumothorax.
Mehta et al, 2003 <sup>22</sup>	Prospective	23	Age: 45 yr Pa0 <sub>2</sub> /F10 <sub>2</sub> : 75 APACHE II: 29	ICU: 61%	iNO was used successfully as a viable rescue therapy in ARDS patients on HFOV with high oxygen requirements
David et al, 2003 <sup>27</sup>	Prospective observational	42	(Median) Age: 49 yr Pao <sub>2</sub> /Fio <sub>2</sub> : 94 OI: 23 APACHE II: 28	30-day: 43%	Subset analysis showed patients without oxygenation improvement after 24 hr of HFOV had higher 30-day mortality. 1 patient had pneumothorax.
Mehta et al, 2004 <sup>17</sup>	Retrospective	156	(Median) Age: 48 yr Pao <sub>2</sub> /Fio <sub>2</sub> : 91 OI: 31 APACHE II: 24	30-day: 62%	34 patients had pneumothorax.
Ferguson et al, 2005 <sup>21</sup>	Prospective observational	25	(Median) Age: 50 yr Pao <sub>2</sub> /Fio <sub>2</sub> : 96 OI: 23 APACHE II: 24	ICU: 44%	This study demonstrated the safety and efficacy of combining lung RMs with HFOV.
Papazian et al, 2005 <sup>28</sup>	RCT	39	Age: 52 yr Pao <sub>2</sub> /Fio <sub>2</sub> : 103 SOFA: 10	ICU: supine HFOV: 38% prone CV: 31% prone HFOV: 23%	The study compared prone positioning, HFOV, or their combination in ARDS patients. Gas exchange did not improve in patients in the supine-HFOV group. Prone position appeared superior to HFOV for oxygenation.
Bollen et al, 2005 <sup>16</sup>	RCT	61	Age: 81 yr Pa0 <sub>2</sub> /F10 <sub>2</sub> : 109 OI: 22 APACHE II: 21	30-day: HFOV: 43% CMV: 33% (P = .59)	Post hoc analysis showed that a subgroup of patients with the most severe hypoxemia tended to benefit from HFOV.
Pachl et al, 2006 <sup>29</sup>	Prospective observational	30	Age: 55 yr Рао <sub>2</sub> /Fю <sub>2</sub> : 121 SOFA: 10	46%	The study suggested that HFOV may benefit patients with extrapulmonary ARDS more than those with pulmonary ARDS.
Finkielman et al, 2006 <sup>30</sup>	Retrospective	14	Age: 56 yr Pao <sub>2</sub> /Fio <sub>2</sub> : 73 APACHE II: 35 SOFA: 15	ICU: 57%	Although no change in mean arterial pressure or vasopressor requirements, 1 patient had HFOV withdrawn for refractory hypotension.

\*All results reported are mean unless otherwise specified.

APACHE, acute physiology and chronic health evaluation; BP, blood pressure; CMV, conventional mechanical ventilation; CVP, central venous pressure; HFOV, high-frequency oscillatory ventilation; ICU, intensive care unit; iNO, inhaled nitric oxide; OI, oxygenation index; PAOP, pulmonary artery occlusion pressure; RCT, randomized controlled trial; SAPS, simplified acute physiology score; SOFA, sequential organ failure assessment. adverse events such as oxygenation or ventilatory failure, new air leaks, intractable hypotension, or mucous plugging requiring endotracheal tube exchanges between the two arms. Interestingly, although the trial was inadequately powered, a nonsignificant trend toward improved 30-day mortality was noted in those who received HFOV compared with CV (37% versus 52%; P = .102). Of note, however, is that the control arm was not necessarily managed under current standards. For example, patients were ventilated with tidal volumes of up to 10 mL/kg. Notably, the study was designed before the publication of the ARDSNet trial using smaller target tidal volumes. As a result, an adequately powered comparison to the current standard of CV is something clinicians require.

A subsequent RCT involving 61 patients<sup>16</sup> showed no significant difference in survival without ventilatory support or supplemental oxygen at 30 days between HFOV and CV. Methodologic problems included a need to stop the trial early because of difficulties encountered in patient recruitment, significant baseline differences in the two arms, and unequal randomization (37 patients in the HFOV group versus 24 in the conventional ventilation group). In addition, 11% of the patients had incomplete follow-up for the primary end point, and 18% crossed over treatment arms during the study. The interpretation and comparison of the study results are further complicated by a lack of an explicit ventilator protocol. Despite its limitations, a post hoc analysis revealed that a subgroup of patients, with the most severe hypoxemia (high oxygenation indices) tended to benefit from HFOV compared with CV. Certainly, this latter group is the type of patients encountered when HFOV is used in rescue situations. Thus, despite the obvious limitations of post hoc analysis, this study may provide additional support for the use of HFOV in the most severely hypoxemic patients.

Mehta and colleagues performed a retrospective chart review of 156 adult patients with ARDS ventilated on HFOV, primarily in rescue situations.<sup>17</sup> This case series report detailed patients' characteristics, HFOV strategies, predictors of mortality, and outcomes. These patients had a mean age of  $48 \pm 18$  years, mean acute physiology and chronic health evaluation (APACHE) II score of 23  $\pm$  7.5, and severe ARDS (mean Pao<sub>2</sub>/Fio<sub>2</sub>, 91  $\pm$  48 mm Hg; OI,  $31 \pm 14$ ). A significant improvement in oxygenation (PaO<sub>2</sub>/FIO<sub>2</sub> and OI) was observed and sustained for a 72hour period after the application of HFOV, although the mortality rate (61.7%) was arguably high. It should be noted that this population does not represent all patients with ARDS but rather those with the most severe respiratory failure. Thus, a higher than usual mortality rate is, conceivably, expected. In this study, the authors used multivariate analysis and found that older age, higher APACHE II score, lower pH at initiation of HFOV, and greater duration of CV before HFOV all were independent predictors of mortality. Other studies<sup>18,19</sup> also have illustrated that a greater number of pretreatment CV days correlated directly with mortality. This finding, however, was not confirmed in a subsequent systematic review by Bollen and associates.<sup>20</sup>

Improvement in patients' oxygenation on HFOV can be slow, in part owing to low tidal volumes and little tidal recruitment. The role of adjunctive therapies has been explored in several studies with the hypothesis of additive or synergistic effects when used in combination with HFOV.

The safety and efficacy of repeated RMs in conjunction with a more aggressive "open-lung" approach with HFOV were demonstrated by Ferguson and coworkers.<sup>21</sup> Twenty-five patients with ARDS and severe oxygenation failure were transitioned from conventional ventilation to HFOV with an initial cycle of up to three sustained RMs of escalating pressure. RMs were repeated for hypoxemia and at least twice per day if Fio<sub>2</sub> was higher than 0.4. After the initial cycle of recruitment, the mean Pao<sub>2</sub>/Fio<sub>2</sub> ratio increased dramatically compared with standardized conventional ventilation (200 ± 117 versus 92 ± 36 mm Hg; *P* < .001). Twelve hours after initiation of HFOV, the mean Fio<sub>2</sub> was significantly reduced compared with prestudy levels (0.5 ± 0.2 versus 0.9 ± 0.1; *P* < .001).

The effects of inhaled nitric oxide (iNO) were prospectively explored in 23 adult patients with continued oxygenation failure despite HFOV.<sup>22</sup> Using doses of iNO between 5 and 20 ppm that best acutely improved oxygenation, the authors found an improvement in oxygenation ( $\geq$ 20% increase in PaO<sub>2</sub>/FiO<sub>2</sub> ratio) in most patients (83%) at the 8- to 12-hour mark. This allowed for a marked reduction of FiO<sub>2</sub>. Similarly, combining prone positioning with HFOV has been shown to improve gas exchange (PaO<sub>2</sub>/FiO<sub>2</sub>) and FiO<sub>2</sub> requirements,<sup>23</sup> although the extent to which the HFOV effect was independent of prone positioning is debatable.

Despite these encouraging results, it remains unclear what effects these adjunctive therapies may have when used simultaneously, although the successful use of combined HFOV, iNO, and prone positioning has been reported.<sup>24</sup>

#### POTENTIAL LIMITATIONS AND PITFALLS

The higher applied mPaws have, invariably, led to concerns about barotrauma and hemodynamic compromise. Mehta and colleagues<sup>17</sup> reported the incidence of pneumothorax in HFOV to be 21.8%. Of 156 patients, 26% needed to have HFOV discontinued because of problems with oxygenation and ventilation or hemodynamics. In contrast, the incidences of pneumothorax and hemodynamic instability were found to be similar in the two trials<sup>15,16</sup> that compared HFOV with CV. Furthermore, in 25 patients on HFOV with an aggressive open-lung strategy,<sup>21</sup> only 8% (2 patients) required a chest tube insertion for barotrauma and 3.3% (8 of 244) RMs had to be aborted because of hypotension. Nonethless, it is prudent for clinicians to be aware and watchful that both barotraumas and hemodynamic compromise may occur during the higher mPaw with HFOV. In addition, it is important to re-emphasize that adequate intravascular volume and cardiac output support are frequently important to optimize oxygenation and ventilation.

Recent work by Hager and coworkers<sup>31</sup> suggests that the tidal volumes delivered by HFOV may be higher than previously thought. Data collected from seven ARDS patients showed that tidal volumes were in the range of 44 to 210 mL. Of particular interest, the tidal volumes delivered can approach values similar to those delivered by a conventional ventilator. This is especially so when HFOV is set at low frequency with a high  $\Delta P$ , both of which are commonly used in adult patients. By delivering tidal volumes that are larger than expected, barotrauma is understandably a concern. Further studies are necessary to verify this finding and what affect this has on the overall goal of lung protection. For now, it may be prudent to avoid low frequencies, particularly with high  $\Delta P$  settings, in adult patients on HFOV. In addition, the extent to which the higher mPaws are damaging needs to be determined.

Another concern is the heavy sedation and, frequently, paralysis that patients may require during HFOV. These agents can prolong duration of mechanical ventilation, lengthen ICU and hospital length of stay, and lead to complications like critical illness polyneuropathy.<sup>32,33</sup> The need for these agents is much different than the approach in the neonatal or small pediatric setting. In adults, the bias flow rate provided by the machine generally is not sufficient to meet minute ventilation demands. As a result, mPaws may drop, patient agitation escalates, and lung derecruitment may occur as spontaneous breathing resumes.

Another issue is the different approach caregivers must take to physical examination and patient assessment. With the rapid tiny breaths delivered, there will be few to no breath sounds heard. Clinicians need to be aware that situations such as pneumothorax, endotracheal tube malposition, or lung collapse will not be associated with the classic clinical findings of diminished breath sounds. Rather, the degree to which the patient wiggles or moves with each oscillation will decrease or  $\Delta P$  will rise, or both.

Finally, de-recruitment that occurs when there is a decrease in mPaw is a concern. This becomes an issue when there is consideration of transporting a patient because currently we know of no transport oscillators for adults. In addition, the same concerns apply to procedures that require disconnecting the patient from the ventilator, such as direct bronchoscopy. Although these issues appear rather important, they are not dramatically different from the patient with severe ARDS on CV, where transport and procedures are often associated with morbidity.

#### **AUTHORS' RECOMMENDATIONS**

- HFOV is a unique open-lung ventilatory strategy that may offer improved gas exchange and lung protection. These favorable physiologic effects, however, have not been translated into demonstrable survival benefits in clinical trials when compared with CV.
- Better short-term oxygenation does not necessarily lead to improved survival, and most ALI/ARDS patients succumb to multisystem organ failure rather than hypoxemia.
- In the absence of clinical trials demonstrating superiority of HFOV over optimal lung-protective conventional ventilation, the widespread early use of HFOV in adult ALI/ARDS patients cannot be recommended. For now, its role remains in the rescue situation, in which patients have failed conventional ventilation and clinicians believe there are few alternate options.

- The challenges facing the proponents of HFOV include identifying the ideal patient population that may derive a survival benefit and the timing as well as the optimal way to ventilate patients while on HFOV.
- At this point, we are aware of an ongoing large international multicenter RCT comparing HFOV with optimal lungprotective CV (personal communication, Drs. M. Meade and N. Ferguson), which we anticipate will help clarify the role of HFOV and provide further directions in its clinical application.

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# 21 Inhaled Vasodilators in ARDS: Do They Make a Difference?

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Inhaled vasodilators have a compelling physiologic rationale in the management of critically ill patients with ARDS. A 20-year accumulation of rigorous research has helped to clarify their role in this setting, which is significantly more limited than original reports suggested.

#### PHYSIOLOGIC RATIONALE

Imaging studies show that alveoli that are poorly aerated due to exudative edema, hyaline membranes, and microatelectasis are not homogeneously distributed throughout the lung parenchyma. Instead, certain zones are preserved and remain compliant, allowing them to receive disproportionately large fractions of the minute ventilation.<sup>1,2</sup> The more diseased lung regions, located predominantly in the dependent areas of the lungs, may be poorly ventilated and yet receive much of the right ventricular cardiac output resulting in a significant mismatch. Meanwhile, laboratory research shows that pulmonary hypertension in acute respiratory distress syndrome (ARDS)<sup>3,4</sup> is not solely the consequence of hypoxia-induced vasoconstriction. Rather, the dysregulation of constricting and dilating mediators contributes to a pathologic and counterproductive increase in the pulmonary vascular resistance.<sup>5</sup> Theoretically, selective vasodilation of vessels perfusing aerated lung tissue would redistribute blood from poorly ventilated regions, reducing the shunt fraction and at the same time correcting pulmonary hypertension. Improved oxygenation would reduce mortality directly attributable to respiratory failure, and quicker resolution of ARDS would reduce the complications and morbidities associated with prolonged mechanical ventilation. Unfortunately, these are not the effects that investigators have observed in randomized clinical trials.

Our discussion will focus mainly on inhaled nitric oxide (NO), which is by far the most extensively studied inhaled vasodilator in the context of ARDS. Much less data are available for nebulized prostaglandins, specifically prostaglandin I2 (PGI2; prostacyclin), and prostaglandin E2 (PGE2).

#### NITRIC OXIDE

In 1993, Rossaint and colleagues demonstrated in a prospective cohort of 10 patients who inhaled NO as opposed to intravenous prostacyclin improved oxygenation in cases of ARDS.<sup>6</sup> This report supported the potential benefit of selective vasodilation. Other preclinical and clinical observational studies confirmed the effects of inhaled NO on arterial oxygenation.<sup>7–9</sup> Added to further laboratory investigations finding additional benefits of NO on platelet and leukocyte function,<sup>10</sup> these results inspired the conduct of several randomized clinical trials (RCTs).

A systematic review by Adhikari and associates provides a current synthesis of the literature weighing in on the role for inhaled NO in ARDS.<sup>11</sup> Among the 12 randomized trials published between 1997 and 2004, the study populations varied to some extent. Most included adults with ARDS; however, some included children,<sup>12,13</sup> patients with less severe acute lung injury,<sup>14,15</sup> or patients with a demonstrated favorable physiologic response to inhaled NO.<sup>16</sup> Protocols for the dose and duration of therapy also varied from 1 to 80 ppm and less than 1 day to 28 days, respectively. One trial was a dose-finding study.<sup>16</sup> Finally, efforts to minimize bias ranged across the studies: 10 had concealed allocation,<sup>12–21</sup> 5 studies blinded care-givers,<sup>13,15,17,20,21</sup> 6 reported on the use of alternative experimental therapies for ARDS,<sup>14,15,17–19,22</sup> and all trials reported results according to the intention-to-treat principle. Despite the nuances of study populations, therapeutic protocols and methodologic rigor, the results related to mortality were strikingly similar across the 9 trials that reported these data. Seven studies showed small, nonstatistically significant increases in mortality<sup>14-16,19,20,22,23</sup>; one observed virtually no survival effect<sup>17</sup>; and one (N = 40) reported a small, nonstatistically significant reduction in mortality.<sup>18</sup> The relative similarity of patients, methods, and results supports the decision to statistically aggregate results from across these 9 studies. With or without statistical pooling, a visual review of the study results provides a strong impression (Fig. 21-1). The aggregate results suggest that inhaled NO does not improve survival despite a demonstration of improved oxygenation with inhaled NO therapy. The trend was rather one of increased mortality (relative risk, 1.10; 95% confidence interval, 0.94 to 1.30). Similarly, the pooled results suggest that inhaled NO is not beneficial in terms of duration of mechanical ventilation (ratio of means, 1.17 days; 95% confidence interval, 0.80 to 1.70) nor ventilator-free days (ratio of means, 0.94; 95% confidence interval, 0.84 to 1.06). An unanticipated finding of the review was a statistically significant increase in the risk



Figure 21-1. Effect of nitric oxide on mortality. (From Adhikari NK, Burns KE, Friedrich JO, et al. Effect of nitric oxide on oxygenation and mortality in acute lung injury: Systematic review and meta-analysis. BMJ. 2007;334:779-787.)

for renal dysfunction with inhaled NO therapy (relative risk, 1.50; 95% confidence interval, 1.11 to 2.02). One unblinded and three blinded trials observed this effect.  $^{15-17,20}$ 

The generalizability of these results to clinical practice is high. These studies included patients across the spectrum of acute lung injury and ARDS that clinicians commonly considered (before the publication of these studies) for inhaled NO therapy. Moreover, the treatment effects were strikingly similar across studies, notwithstanding the variations in populations, drug administration protocols, and methodologic quality. In summary, current clinical trials do not support a role for inhaled nitric oxide in the routine management of patients with acute lung injury and ARDS; in fact, this approach to patient care is more likely to cause harm.

This discordance between physiologic outcomes and mortality is not without precedent in critical care. In a landmark study of low tidal volume ventilation conducted by the Acute Respiratory Distress Syndrome Network, patients ventilated with low tidal volumes had lower oxygen levels but an increased survival rate compared with those patients receiving traditionally larger tidal volumes.<sup>24</sup> This disconnect between effects on physiologic outcomes and survival agrees with the concept that ARDS patients seldom die of respiratory failure.<sup>25</sup> Yet for the minority of patients with profound and refractory hypoxemia threatening immediate survival, the question remains unanswered. There are insufficient research data in this specific subgroup to conclude that inhaled NO is on balance more likely to benefit or to harm.

There are a number of plausible explanations for the lack of benefit in most patients with ARDS. It is conceivable that the purported physiologic benefits of inhaled NO are offset by the deleterious effects on other organ systems. Contrary to a common belief, recent experiments have shown that inhaled NO does not act strictly within the pulmonary vasculature. Rather, it reacts with various molecules to produce nitrosothiol compounds that share many properties of NO donors but have longer half-lives.<sup>26–29</sup> This evidence, in keeping with the unexpected association between inhaled NO administration and renal dysfunction, suggests that the pharmacodynamic effects of inhaled NO are likely more complex than originally understood.

#### PROSTAGLANDINS

Bearing the same physiologic rationale as inhaled NO in ARDS, two vasodilating prostaglandin molecules are a focus of interest in ARDS research: PGI2 and PGE2. Additionally, PGI2 blocks platelet aggregation and neutrophil migration, and PGE2 has anti-inflammatory effects. For those reasons, many hypothesized that nebulized PGI2 and PGE2 would act as selective vasodilators and be useful adjuncts in the context of ARDS. The available body of literature, however, is limited. Dahlem and associates reported that, in 14 children with ARDS randomized to nebulized prostacyclin or placebo, oxygenation improved with prostacyclin.<sup>30</sup> Other uncontrolled trials led to the same results,  $^{31,32}$  but these investigators disagree with the results obtained by Camamo and colleagues in a retrospective chart review and with Domenighetti and coworkers in a prospective uncontrolled trial, in which the prostaglandins were not found to have an effect on oxygenation.<sup>33,34</sup> Other studies of various design directly compared the effects of nebulized prostaglandins to inhaled NO.<sup>35,36</sup> The lack of a placebo arm precludes any conclusion in respect to the efficacy of inhaled prostaglandin therapy.

#### CONCLUSION

The use of inhaled vasodilators appeals to our current understanding of ARDS physiopathology. Caregivers expect that by limiting ventilation-perfusion mismatch, these medications will improve survival. Also, there are the hopes related to pleiotropic effects on leukocyte migration, platelet adhesion, and overall inflammation. Inhaled vasodilator therapies therefore have be subjected to wide and rapid dissemination.<sup>37</sup> A careful examination of randomized trials, however, reveals disappointing results. In the case of NO, where the overall trend is indicative of harm, there are enough data, in quantity and quality, to suggest that inhaled NO should not be used in the routine management of patients with ARDS. Whether inhaled NO can make a difference in the setting of severe refractory hypoxemia is uncertain, but we now know that any potential benefit needs to be weighed against the risk for extrapulmonary side effects such as renal failure. Less data are available to address the potential role for nebulized prostaglandin therapy, but the learnings from NO research warrant caution.

#### **AUTHORS' RECOMMENDATIONS**

- Current evidence does not support inhaled NO therapy for routine management of patients with acute lung injury and ARDS; this approach is likely to cause more harm than good.
- For patients with profound and refractory hypoxemia, there are insufficient research data to elucidate the value of inhaled NO therapy.
- Extremely limited clinical research data address the role for nebulized prostaglandin therapy.

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## 22 Are Anti-Inflammatory Therapies in ARDS Effective?

Ben Messer, Simon V. Baudouin

The adult respiratory distress syndrome (ARDS) is a common syndrome of acute lung injury (ALI) caused by direct or indirect damage to the lung parenchyma. It is characterized clinically by hypoxemic respiratory failure and bilateral infiltrative changes on chest radiograph in the absence of clinical or other signs of left atrial hypertension. Pathologically, the findings include diffuse alveolar damage with neutrophil and macrophage infiltration and protein-rich edema fluid in the alveolar spaces. This is associated with both capillary injury and disruption of the alveolar epithelium.

ARDS is an inflammatory condition. Lung biopsy demonstrates an intense granulocytic and mononuclear cell infiltrate in the airspaces. Bronchoalveolar lavage (BAL) confirms the inflammatory nature of the lung injury with the presence of neutrophils, monocytes, and several proinflammatory and anti-inflammatory mediators detected in lavage fluid. In addition, reactive oxygen species (ROS), their byproducts, and changes in oxidantantioxidant balance also have been reported. Proinflammatory and anti-inflammatory changes that mirror those found in the lung can be found systemically in patients with ARDS. In parallel with these inflammatory changes, a potentially fibrotic healing process is initiated at an early stage of lung injury. Ultimately, ARDS may completely resolve with little evidence of permanent lung damage or evolve into a stage of irreversible lung fibrosis. The factors that govern these transitions are poorly understood.

The basic science of ARDS, therefore, suggests that anti-inflammatory agents should be effective in preventing the initiation and progression of lung injury. In this chapter, we review the evidence for the use of antiinflammatory therapies in ARDS. In particular, we concentrate on the role of corticosteroids in the treatment of ARDS because these have been widely studied and have generated much debate. We limit the review to anti-inflammatory therapies and exclude other pharmacologic strategies such as the use of anticoagulants or physiologic antagonists of other parts of the pathologic process such as nitric oxide,  $\beta_2$ -receptor agonists, and surfactant administration. However, it should be acknowledged that all these agents have multiple actions that, in many cases, significantly effect the inflammatory process.

#### STEROIDS

#### Steroids in Early ARDS

The long-established anti-inflammatory actions of corticosteroids have made these drugs the most well-studied potential therapy for ARDS. Initial investigations examined the use of high-dose methylprednisolone in early ARDS. In 1987, Bernard and colleagues published a placebo-controlled trial of four doses of 30 mg/kg of methylprednisolone.<sup>2</sup> Ninety-nine patients were randomized within 3 days of developing ARDS. At 45 days, there were no differences in mortality, pulmonary compliance, or severity of ARDS as determined by arterial blood gas analysis or chest radiographic appearance. Similar results had been observed using high-dose steroids in patients with septic shock who commonly develop ARDS.<sup>3</sup>

The use of steroids in early ARDS recently has been revisited. These studies have used lower steroid doses than the original trials, but levels remain significantly greater than normal physiologic levels even under stress. In 2006, a retrospective subgroup analysis of patients with ARDS in a study of corticosteroids in sepsis found that early ARDS patients treated with 7 days of low-dose corticosteroids and mineralosteroids demonstrated a reduction in mortality.<sup>4</sup> This effect was seen only in the patients who did not show a response to a short Synacthen test.<sup>5</sup>

In 2007, Meduri and colleagues re-examined the use of corticosteroids in early ARDS. They enrolled patients recruited within 72 hours of the onset of ARDS.<sup>6</sup> Ninety-one patients were randomized with a ratio of two patients in the treatment group for each patient in the placebo group. The dose of methylprednisolone was 1 mg/kg per day for 2 weeks. This was tapered over the next 2 weeks. Compared with placebo, there was a significant improvement in intensive care unit (ICU) survival and a trend toward increased hospital survival in the steroid group. At day 7, there were also improvements in length of ICU stay, ventilator-free days, PaO<sub>2</sub>/FIO<sub>2</sub> ratio, lung injury score, and multiorgan dysfunction score in the treatment arm of the study compared with placebo.

At longer-term follow-up (up to 12 months), there was no significant mortality benefit, but a trend to improved survival was noted in the steroid-treated patients. The significantly higher baseline incidence of shock in the placebo group may have contributed to this trend. There were significantly fewer infectious complications in the methylprednisolone group but also a nonsignificant trend toward more ventilator-associated pneumonia in this group.

#### Steroids in Late ARDS

The lack of efficacy of steroid therapy in preventing the development of ARDS prompted researchers to investigate their potential in the later, so-called fibroproliferative stage of lung injury. Steroid therapy has an established, if somewhat controversial, role in the treatment of interstitial fibrosis. Meduri and colleagues reported a case series of nine patients with ARDS and fibrotic changes on open-lung biopsy.<sup>7</sup> The use of 2 to 3 mg/kg per day of methylprednisolone resulted in improved lung injury scores, chest radiographic appearance, and oxygenation in all patients. A reduction in neutrophil levels in BAL specimens was also noted. In 1994, the same author published a larger case series of 25 patients using similar doses of methylprednisolone followed by a tapering dose over 6 weeks. This regimen resulted in marked improvement in most indices of lung function.8

In a further randomized placebo-controlled trial of 24 patients (with 2:1 randomization to the methylprednisolone group), low-dose methylprednisolone, of at least 7 days' duration improved hospital mortality and indices of lung function.<sup>9</sup> Mortality in the control group was due to unresolved ARDS, with four of five deaths associated with hypercapnic respiratory failure. There was, however, a nonsignificant trend toward increased ventilator-associated pneumonia in the treatment group.

These small studies and case series prompted a larger trial into the use of steroids in late, nonresolving ARDS. This was conducted by the Acute Respiratory Distress Syndrome Clinical Trials Network (ARDSNet) and published in 2006.<sup>10</sup> It involved a 25-center trial of methylprednisolone in patients recruited 7 to 28 days after the diagnosis of ARDS. ARDS was due to direct causes of lung injury in 55% of patients. Patients were followed until death, discharge, or 180 days. Of 4123 patients screened for the trial, only 180 patients were randomized to receive 2 mg/kg per day of methylprednisolone or placebo. Major causes of exclusion were previous use of steroids or immunosuppression (22%), chronic lung disease (15%), and physician refusal (8%). The steroids were tapered over a 3-week period unless the patient remained ventilated at 21 days, in which case steroids were tapered over 4 days.

At 60 days, the mortality rates were 28.6% in the placebo group and 29.2% in the treatment group (nonsignificant difference in a significantly underpowered study). Patients who had had ARDS for more than 13 days and received steroids had a statistically significant increased 60-day mortality rate compared with placebo. Patients with a raised procollagen type III in BAL specimens (a biologic marker of collagen synthesis and thus pulmonary fibrosis) showed an improvement in mortality in the treatment group.

A number of secondary end points were significantly better in the treatment group. These included ventilatorfree days during the first 28 days as well as at 180 days. Patients in the treatment group were able to breathe without assistance earlier than patients given placebo. Compared with the placebo group, the methylprednisolone group had significantly fewer days in the ICU during the first 28 days. Indices of oxygenation and respiratory mechanics were improved in the patients receiving steroids. However, more patients in the treatment group required resumption of ventilatory support, and these patients were more likely to develop shock. There was no increase in infectious complications in the steroid group; in fact, there were fewer cases of pneumonia and fewer incidences of septic shock.

The main conclusions drawn from this trial were that administration of methylprednisolone in late ARDS did not result in any survival improvement, and when patients were treated with steroids later than 13 days into their illness, there was an increase in mortality. However, there was a high exclusion rate for patients, raising the question of the wider applicability of these data to clinical practice. Further, the rapid tapering of steroids after extubation may have been a factor in causing the higher levels of reintubation in the steroid group.

#### **Steroid Trials' Appraisal**

The use of steroids in ARDS remains controversial, with some polarization of views occurring.<sup>11,12</sup> A key to understanding these differences is a critical examination of several aspects of the trial designs (Table 22-1). These include the timing of the administration of steroids, the length of the course of steroids, the dose of steroids, the patients to whom steroids are administered, and the cause of ARDS. Each is discussed individually below.

#### Timing of Doses

Experimental studies of anti-inflammatory agents in lung injury emphasize that the timing of the intervention is important. Anti-inflammatories most often are effective if given before or during the initiation of the injury-inducing agent. Given at a later period, they are commonly ineffective. Studies suggest that earlier intervention is more likely to prevent the progression of ALI. Evidence that lung fibrosis begins at a very early stage of ALI also would support the earliest possible use of anti-inflammatory agents. Clinical data in ARDS support this conclusion. Inflammatory cytokines are present in the plasma and in the BAL specimens of patients with ARDS from the outset of their illness,<sup>13</sup> and their presence may predate the clinical manifestation of ALI. For example, Park and coworkers found that in patients at risk for ARDS (patients with sepsis or trauma), levels of tumor necrosis factor- $\alpha$  and interleukin-1 were elevated in BAL specimens before the onset of clinical lung injury.<sup>14</sup>

The timing of steroid dose differed significantly in the two recent major studies.<sup>6,10</sup> The ARDSNet study recruited patients at least 7 days into the course of their disease, whereas Meduri's group recruited patients within 3 days of diagnosis. One interpretation of these trials is that steroids may only be effective if given early in lung injury, before the inflammatory process has caused irreversible damage to the alveoli.

Table 22-1 Summary of Major Clinical Trials of Steroid Therapy in ARDS							
Trial	Design	No. of Patients	Timing of Steroids	Duration of Therapy (days)	Dose of Steroids	Taper (Yes/No)	Results
Bernard et al, 1987 <sup>2</sup>	Randomized, placebo- controlled	99	Early (3 days)	1	120 mg/kg/day methylprednisolone	No	No mortality difference
Meduri et al, 1991 <sup>7</sup>	Case series	9	Medium (>3 days)	Variable	2-3 mg/kg/day methylprednisolone	Yes	Improved indices of lung function
Meduri et al, 1994 <sup>8</sup>	Case series	25	Late	Until extubation	2-3 mg/kg/day methylprednisolone	Yes	Improved indices of lung function
Meduri et al, 1998 <sup>9</sup>	Randomized, placebo- controlled with crossover	24	Late	14	2 mg/kg/day methylprednisolone	Yes	Improved ITU and hospital mortality
Annane et al, 2006 <sup>5</sup>	Post hoc analysis of randomized, placebo- controlled	177	Early	7	200 mg/day hydrocortisone 50 μg/day fludrocortisone	No	Improved mortality in nonresponders to short Synacthen test
ARDSNet, 2006 <sup>10</sup>	Randomized, placebo- controlled	180	Late	14	2 mg/kg/day methylprednisolone	Yes	No mortality difference
Meduri, 2007 <sup>6</sup>	Randomized, placebo- controlled	91	Early (within 72 hr)	14	1 mg/kg/day methylprednisolone	Yes	Improved ITU survival

#### **Duration of Treatment**

Proinflammatory and anti-inflammatory cytokines are present at raised levels in BAL specimens until at least 21 days into the course of ARDS.<sup>14</sup> If the rationale for treatment is to reduce inflammation in the lungs, a prolonged course is more likely to be of benefit. However, steroid-related side effects increase with duration of therapy and could negate any potential benefits.

#### Steroid Dose

Little is known about steroid dose-response relationships in critically ill patients. Metabolism and tissue distribution of steroids will change in this population. In addition, the principal target of anti-inflammatories remains uncertain, with both local (lung) and systemic actions of possible importance. Further, the inflammatory response is extremely complex and multifaceted. Overlapping and redundant pathways are common, and it may be naïve to presume that a one-dose-fits-all strategy of anti-inflammatory treatment will be successful.

#### **Physiologic Response**

In the retrospective analysis of ARDS patients from the sepsis trial conducted by Annane and coworkers in 2002,<sup>4</sup> there was a difference in outcome from steroid treatment in subgroups depending on their response to a corticotrophin test.<sup>5</sup> Furthermore, the ARDSNet study found different results depending on whether patients had greater than or less than median levels of procollagen type III in BAL specimens.<sup>10</sup> Selection of patients dependent on inflammatory cytokine levels or other biomarkers of inflammation may in the future help predict response to steroids in ARDS.

#### **Direct versus Indirect Lung Injury**

ARDS is a heterogeneous syndrome with outcome determined by multiple factors, including the nature of the initial insult. The mortality of patients with direct lung injury (e.g., pneumonia) may be different than that of those with indirect injury (e.g., sepsis). This suggests that different inflammatory pathways may be involved in the pathogenesis of lung injury. The trials differ, to some extent, in recruitment in terms of the cause of lung injury. There is a slightly higher proportion of direct lung injury in the recent positive study of steroids in ARDS.<sup>6</sup> It may be that the two causes of lung injury behave differently in their response to steroids and other treatments. For example, there are data to suggest that different patterns of lung injury respond differently to lung recruitment strategies.<sup>15</sup>

#### **OTHER ANTI-INFLAMMATORY AGENTS**

#### **Prostaglandin E1**

Experimental trials indicate that prostaglandin E1 (PGE1) modulates neutrophil function (Table 22-2).<sup>1617</sup> The neutrophil previously has been implicated in the pathogenesis of ARDS, and alteration of neutrophil function is an attractive therapeutic strategy. In 1989, a multicenter trial of PGE1 versus placebo in ARDS following trauma, sepsis, or surgery was carried out. At 6 months, there was no significant difference in survival between the two groups, although the patients in the PGE1 group were older, had a greater incidence of sepsis, and had more severe derangements of oxygenation than the placebo group.<sup>18</sup>

In 1999, a randomized double-blind trial of liposomal PGE1 versus placebo in ARDS of less than 24 hours' duration was conducted. No difference in mortality was seen at 28 days. No difference in time to cessation of respiratory support and no difference in pulmonary compliance were noted between the groups. The treatment group attained a  $Pao_2/FiO_2$  ratio of greater than 300 in significantly fewer days than the placebo group.<sup>19</sup> This study was well powered, achieving its target of 350 patients randomized (348 analyzed), giving an 80% power to detect a 26% difference in time to discontinuation of mechanical ventilation for 24 hours. It was not powered to detect a mortality difference.

Trial	Design	No. of Patients	Treatment	Early/Late ARDS	Results
Bone et al, 1989 <sup>18</sup>	Randomized, placebo-controlled	100	Prostaglandin E1	Early	No mortality difference
Abraham et al, 1999 <sup>19</sup>	Randomized, placebo-controlled	348	Prostaglandin E1	Early	No mortality difference
ARDSNet, 2000 <sup>21</sup>	Randomized, placebo-controlled	234	Ketoconazole	Early	No mortality difference
Jepsen et al, 1992 <sup>23</sup>	Randomized, placebo-controlled	66	N-acetylcysteine	Early	No mortality difference
Bernard et al, 1997 <sup>24</sup>	Randomized, placebo-controlled	46	N-acetylcysteine Procysteine	Early	No mortality difference
ARDSNet, 2006 <sup>28</sup>	Randomized, placebo-controlled	235	Lisofylline	Early	No mortality difference

#### Table 22-2 Summary of Major Trials of Nonsteroidal Anti-Inflammatory Agents in ARDS

#### Ketoconazole

Ketoconazole has anti-inflammatory actions that include inhibition of thromboxane synthase and lipoxygenase and a decrease in procoagulant activity.<sup>20</sup> In 2000, the ARDSNet group recruited 234 patients with ARDS into a randomized controlled trial in a  $2 \times 2$  trial design that also examined the effect of low tidal volumes in ALI. Patients were recruited early (within 36 hours) in the course of ALI. Treatment, which was double-blinded, was randomized to 400 mg orally of ketoconazole or placebo. Treatment was for 21 days or until patients were no longer ventilator dependent. In-hospital mortality, ventilator-free days, and indices of lung injury were not significantly different between the two groups. In terms of adverse effects, there was a nonsignificant trend toward an increase in cardiovascular complications in the treatment group.<sup>21</sup>

#### Antioxidants

The proposed role of oxygen free radical species in the pathogenesis of  $ARDS^{22}$  prompted interest in the use of *N*-acetylcysteine and procysteine. These agents should increase intracellular glutathione and reduce the load of free radicals. A placebo-controlled trial of *N*-acetylcysteine in 1992 recruited 66 patients. The investigators found no 60-day mortality benefit.<sup>23</sup> Similarly, in a 1997 trial, *N*-acetylcysteine was compared with procysteine and placebo. This study also failed to detect an improvement in mortality, although there was a trend toward less organ failure, sepsis, ventilator dependency, and ICU stay in the treatment groups.<sup>24</sup>

#### Lisofylline

Circulating free fatty acids have been shown to cause lung damage and may predict the development of ARDS.<sup>25</sup> Lisofylline reduces levels of free fatty acids and also decreases levels of some inflammatory cytokines.<sup>26,27</sup> A 2002 placebo-controlled trial of 235 patients carried out by the ARDSNet group failed to show any benefit in mortality, organ failure, ventilator-free days, or infections in the lisofylline group. Interestingly, there was no change in free fatty acid levels in the trial, suggesting that the dose of lisofylline used may have been too low. However, the authors stated that higher doses of the study drug could be associated with gastrointestinal and cardiovascular toxicity.<sup>28</sup>

#### **Activated Protein C**

As well as its anticoagulant effect, activated protein C also has anti-inflammatory properties, and its effect in sepsis has been extensively studied.<sup>29–31</sup> It has not been examined specifically in ARDS, nor were ARDS patients subjected to any detailed subgroup analysis in any of the activated protein C trials. However, in the PROWESS study,<sup>29</sup> the absolute risk reduction of death in patients treated with activated protein C who were ventilated was greater than that seen in all patients (7.4% reduction versus 6.1% reduction overall).

#### AUTHORS' RECOMMENDATIONS

- Despite significant experimental evidence that antiinflammatories are effective in ALI, no clinical trial has produced unequivocal evidence for a therapeutic effect in humans. There are several possible explanations for these disappointing results.
- The hypothesis is wrong. Inflammation is not causal in lung injury but rather just an "innocent bystander." An extreme view would emphasize the role of inflammation in lung repair and regeneration and suggest that anti-inflammatories could be harmful in ALI.
- Inflammation is too complex a process to be manipulated successfully by single agents. In this view, there is no final common pathway that can be simply targeted by a single agent.
- ARDS is a syndrome, not a disease. Clinical definitions of ARDS are useful for trial recruitment but may not define a specific disease entity. The comparison with acute myocardial infarction is useful. There, a uniform pathophysiologic process (thrombotic artery occlusion) is easily identified by a simple, reliable test (electrocardiography).
- Interventions are given at an irreversible stage of illness. Inflammation occurs at an early preclinical stage of the disease. Even "early" ARDS trials start treatment at a relatively late stage of disease evolution. In this scenario, better markers of early, subclinical lung injury are needed to guide therapy.
- Side effects of anti-inflammatories outweigh benefits. Most anti-inflammatory agents have immunosuppressive effects. It is possible that any potential benefits in reducing the severity of lung injury are offset by infection and other side effects. Although most studies have not reported excessive infections in the treatment group, more subtle complications cannot be fully excluded.
- The extent of lung injury is not the main determinant of outcome in ARDS. Multiorgan failure is common in ARDS, and outcome is heavily determined by the involvement of other organs. In this situation, a reduction in lung injury may have only minimal effects on survival.
- The inflammatory response appears to be an attractive target in the treatment of ALI. However, the translation of approaches developed in basic science laboratories into better clinical outcomes remains elusive. The possibility that antiinflammatory strategies in ARDS are ineffective need to be seriously considered by the research community.

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## Is Extracorporeal Life Support for Adults with Acute Respiratory Distress Syndrome Useful?

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In fact, if appearance and essence were the same thing, there would be no need for science.

Michio Kaku: Hyperspace. New York, Oxford University Press, 1994

Extracorporeal life support (ECLS) is most commonly used in patients with inadequate oxygen delivery. This can result from either ineffective oxygenation due to severe lung disease or ineffective cardiac output due to severe circulatory failure or both. This review will focus on the evidence for ECLS in adults and will address details of ECLS techniques. We only briefly address ECLS in children and neonates. We will focus on the question Is ECLS useful in critically ill adults with acute respiratory distress syndrome (ARDS)?

## EVIDENCE SUPPORTING THE BENEFIT OF ECLS FOR PATIENTS WITH ARDS

The quote above, by the physicist Michio Kaku, underscores the need for rigorous scientific studies in medicine.<sup>1</sup> Scientifically rigorous clinical experiments provide the best foundation for the evaluation of the efficacy of clinical interventions. Personal clinical experiences, including anecdotal and case reports, provide important information and stimulate thinking but are not as compelling as rigorous clinical experiments. Unfortunately, such experiments are infrequent and the quality of clinical trials, our most credible source of evidence, appears in general to be low.<sup>2–4</sup> A systematic review of ECLS in adults listed 42 reports of case series,<sup>5</sup> but only two randomized clinical trials. Some believe meta-analyses can overcome the low quality of many clinical studies, but the quality of a meta-analytic result is limited by the quality of the clinical studies on which it is based.<sup>6–8</sup> Scientists expect experimental results that properly describe the way the world works to be independently reproduced by other investigators. Such replication of results requires replicable methods.<sup>1,9–11</sup> Unfortunately, the methods of most ECLS studies lack detail and are not replicable, in even the most experienced clinical sites.<sup>12-14</sup>

Random and systematic error can reduce credibility of clinical trial results. Systematic error (bias) is the more challenging and requires careful attention in experimental design. The belief that bias plays little role in clinical trials<sup>15,16</sup> is incorrect for many critical care experiments.<sup>1</sup> Differential (between-group) bias frequently exists because of uneven distribution of confounders but can also exist because of uneven distribution of the experimental intervention, especially in non-blinded (open) clinical trials. Confounders introduced after subject assignment to the clinical trial groups are better termed co-interventions and should be distinguished from confounders that exist before subject allocation to the experimental groups.<sup>17-19</sup> Co-interventions often result from the interaction of the subject with the clinical environment (e.g., mechanical ventilation strategy, drug therapy for hypotension, intravenous fluid therapy, diagnostic strategies for suspected infection, monitoring intervals, laboratory tests, antibiotic therapy, sedation, etc.). Co-interventions in clinical trials are frequently neither controlled nor measured and this deficiency threatens the internal validity of critical care clinical trials. In nonblinded (open) scientifically rigorous critical care clinical trials, all experimental arms require well-defined and detailed protocols that are adequately explicit and standardize clinician decisions about both the experimental intervention and important co-interventions.<sup>1,20</sup> In clinical studies of ECLS, between-group non-uniformity can occur in the management of the ECLS itself (the experimental intervention) because the methods used are commonly not reproducible.<sup>1</sup> The recently published CESAR clinical trial is one such example (see below).<sup>12</sup>

An additional general cause for variability among clinical ECLS study results is the uncertain link between the subjects of a study and the population of interest from which they are derived. The patients who arrive at our institutions constitute a convenience sample. Almost all clinical trials use subjects from these convenience samples, with unknown statistical links to the larger population of interest. This produces questions about generalizability (external validity) with almost all clinical studies. Consequently, clinicians who try to apply study results must always evaluate external validity by asking if their patient under consideration belongs to the subset of subjects from which the study results were obtained.<sup>17,21</sup>

## ARDS PATIENT SURVIVAL AND MANAGEMENT

ARDS therapy is usually only supportive. Mechanical ventilation, positive end-expiratory pressure (PEEP), and O<sub>2</sub> breathing play central roles. ARDS injury, while diffuse, is not uniform, but this was not widely appreciated in early studies. The static thoracic compliance (C<sub>th</sub>) of ARDS patients appears directly proportional to the fraction of aerated lung and only a small fraction of the lung appears to receive the tidal volume.<sup>22</sup> Following this understanding, newer therapeutic approaches have focused on reducing the vigor of mechanical ventilation; these included intravenous oxygenation (IVOX).<sup>23,24</sup>

Reported survival for severe ARDS patients varies from 9% to 84% and is detailed in Chapter 11. From 1974 to 1988 the survivals of severe ARDS patients who met extracorporeal membrane oxygenation (ECMO) criteria, but were supported only with mechanical ventilation, in two of the nine original ECMO centers were  $0\%^{25}$  and  $15\%.^{26}$  Their aggregate 13% average survival is not statistically significantly different from the 9% survival of patients who met similar criteria and were supported with ECMO in the 1974–1977 ECMO clinical trial (P = .15).<sup>27</sup> Other patients with ARDS who were less severely ill appeared to have similar survival rates.<sup>26,28–31</sup> Following 1988, survival of ARDS patients changed.<sup>32–34</sup>

The changes in ARDS survival rates over time will confound the interpretation of results of any ECLS trial using historical controls. Several reported mechanical ventilator management strategies for ARDS were associated with increases in ARDS patient survival.<sup>35–38</sup> None of the mechanical ventilator management strategies were evaluated, however, with controlled clinical trials and therefore lacked well-defined concurrent control data. Without such trials and appropriate concurrent controls much uncertainty remains. The use of historical controls leads to a lack of convincing data that any particular ventilatory support mode was superior. Other mechanical ventilation strategies showed promise but their role has not vet been defined.<sup>39</sup> Clinician prediction of patient survival is often incorrect, further complicating the issue.<sup>40</sup> Patient selection might be enhanced by using defined FIO2 and PEEP conditions for determining PaO2/FIO2 ratio, because they seem to lead to better patient outcome prediction.<sup>41</sup> This selection strategy was, in fact, used in the first ECLS clinical trial, the 1970s ECMO trial.<sup>53</sup> An important conclusion to be drawn from this discussion of variation in survival over time is that the use of historic controls for estimating ECLS efficacy is dangerous. This emphasizes the need for carefully crafted randomized controlled clinical trials.

Technical advances and extensive clinical experience have made it clear that patients with ARDS can be supported successfully with ECLS. Some experienced teams are so accomplished they make this difficult procedure appear easy.<sup>42–47</sup> In spite of the enthusiasm with which some

proponents encourage ECLS, the following questions need resolution:

- 1. Does ECLS have a role, based on scientifically credible evidence, in the routine management of patients with ARDS?
- 2. If so, what are the selection criteria for the patients who will benefit?
- 3. What are the methods for conducting ECLS (the detailed rules and protocols) that would enable interested clinicians or investigators to duplicate the work of ECLS developers and experts?

#### PRINCIPLES AND OBJECTIVES OF ECLS

ECLS can support patient gas exchange (oxygenation and alveolar ventilation) and hemodynamic function with two general strategies of circulatory access, veno-venous (VV) or veno-arterial (VA). With VA cannulation, blood is drained from the right atrium via the central venous system and returned to the proximal arterial system. VA support bypasses both ventricles and the intervening pulmonary system, supporting both the patient's natural heart and lung, providing both gas exchange and hemodynamic support. In most cases partial support is achieved, with some residual pulmonary blood flow present in the natural lung.

With VV cannulation, blood is drained and subsequently returned via the right internal jugular vein or femoral veins. Veno-venous support has its origins in the work of Kolobow, Gattinoni, and others who introduced VV cannulation for extracorporeal CO<sub>2</sub> removal (ECCO<sub>2</sub>R).<sup>48–50</sup> Newer cannulation techniques allow higher blood flows and minimal recirculation and can provide adequate support of oxygenation as well. While VV support does not directly provide hemodynamic support, improved oxygen delivery may improve myocardial performance.

Low-frequency positive-pressure ventilation-extracorporeal CO<sub>2</sub> removal (LFPPV-ECCO<sub>2</sub>R) uses VV extracorporeal circulation. Carbon dioxide can be removed with a low extracorporeal blood flow (initially 20-25% of the patient's baseline cardiac output, Qt). This contrasts with the extracorporeal blood flows of about 90% of the patient's baseline Qt needed for VA oxygenation during the ECMO clinical trial.<sup>51–53</sup> The difference in required extracorporeal blood flow is due to the difference in shape of the blood dissociation curves for CO<sub>2</sub> and O<sub>2</sub>. The approximately linear shape of the CO<sub>2</sub> dissociation curve allows adequate removal of CO<sub>2</sub> from a fraction of venous blood to meet the body's CO<sub>2</sub> production needs. In contrast, the relatively flat shape of the O<sub>2</sub> dissociation curve at  $Pao_2 > 60 \text{ mm}$  Hg prevents the loading of extra  $O_2$ . Thus almost all of the patient's blood needs extracorporeal oxygenation for complete O<sub>2</sub> saturation of the arterial blood.

ECMO evolved from cardiopulmonary bypass with intrathoracic VA cannulation. Technological advances led to improved cannula flows and mechanics and VV has begun to supplant the VA approach, unless concomitant cardiac failure exists. While VA cannulation can support both lung and cardiac failure, VV cannulation is often

preferred for patients who have adequate intrinsic cardiac function. VV ECMO use is increasing. A retrospective review of 255 adults supported with ECMO for severe ARDS between 1989 and 2003 revealed the majority of patients were supported with VV ECMO. One hundred sixty-eight patients underwent VV ECMO, 47 underwent VA ECMO, 27 were initially placed on VV ECMO but required transition to VA ECMO, and 15 underwent VA ECMO with transition to VV ECMO once hemodynamically stable.<sup>14</sup> Survival rates among these groups were 60%, 32%, 15%, and 73%, respectively. A lower severity of illness among patients supported with VV (vs. VA) ECMO may contribute to the higher VV ECMO survival rates, although VV ECMO may be applied safely in patients with modest cardiac failure. The medical community would benefit from well-conducted and wellcontrolled RCTs of ECLS.

#### CLINICAL TRIAL EVIDENCE SUPPORTING THE USE OF ECLS IN ROUTINE CARE FOR ARDS

Because randomized controlled clinical trials provide the most compelling evidence for clinical decision making, it is pertinent to note that only three RCTs of ECLS in adults have been completed to date (Table 23-1).27,53,54 Both of the first two studies used straightforward randomization of patients at all clinical sites.<sup>27,53</sup> Neither of these two RCTs produced evidence of favorable impact of ECLS on patient outcome. A third RCT in adults has been conducted (the CESAR trial) and its study protocol and results published (see below).<sup>12,54</sup> This study involved the transport of patients to a single center providing ECLS support for consideration of ECMO while "conventional care" was delivered in all of the treatment centers. There was no within-site distribution of patients to the two therapy arms. Furthermore "conventional care" was undefined and did not include a consistent ventilator management protocol.

The first ECLS RCT in adults, the randomized multicenter trial of ECMO for ARDS, selected a subset of ARDS patients with severe disease and poor outcome only 8 (9%) of 90 randomized patients survived<sup>51,55</sup> with no difference between ECMO and conventional care.<sup>53</sup> Efforts to introduce widespread clinical use of ECMO for adults with ARDS were thereafter abandoned.

Kolobow, Gattinoni, and their colleagues subsequently introduced the concept of "lung rest." The need to ventilate the injured natural lung could be reduced in proportion to CO<sub>2</sub> removed by a spiral silicone membrane. The extracorporeal CO<sub>2</sub> removal (ECCO<sub>2</sub>R) relieved the natural lung of some of its ventilatory burden.<sup>48–50</sup> Using these innovative tools, Kolobow, Gattinoni, and their colleagues were able to reduce airway pressure, tidal volume (VT), and ventilatory rate,<sup>56</sup> with the intent of avoiding inhomogeneous overdistention damage to the lung.<sup>22</sup> Their ultimate goal was an increase in patient survival due to reduction of the putative iatrogenic lung damage during mechanical ventilation. The intermediate goal of their LFPPV-ECCO<sub>2</sub>R was to reduce the motion of the diseased lung to a minimum with almost complete elimination of ventilation (using only 3-5 breaths/minute).<sup>67</sup> The management of the natural lungs of the randomized patients in the NIH collaborative ECMO trial of 1974-1977<sup>53</sup> did not adhere to these principles of "lung rest" (Table 23-2).<sup>42</sup> Therefore, a superimposed iatrogenic lung injury due to higher end-inspiratory pressures or tidal volumes to ARDS lungs of the study subjects might have introduced enough bias to affect the ECMO trial outcome.<sup>22,67,68</sup>

Gattinoni et al reported an increase in survival of ARDS patients after use of pressure-controlled inverse ratio ventilation (PCIRV) followed by LFPPV-ECCO<sub>2</sub>R, but the study was an uncontrolled clinical application.<sup>37,68–75</sup> Morris et al. subsequently observed increased survival in their randomized controlled clinical trial of PCIRV/LFPPV-ECCO<sub>2</sub>R—the second RCT of ECLS in adults.<sup>27</sup> Unexpectedly, the 42% survival of their control patients supported

Table 23-1 RCTs of ECLS for Severe Hypoxemic Respiratory Failure					
Study (year)	Number of Subjects (Intervention/ Control)	Study Design	Intervention	Control	Survival
ECMO in severe ARDS (1979) <sup>51,53</sup>	90 (42/48)	Prospective non-blinded RCT	Mechanical ventilation + partial VA ECMO	Mechanical ventilation alone	9.5% ECMO; 8.3% control; no statistically significant difference
PCIRV and ECCO <sub>2</sub> R for ARDS (1994) <sup>27</sup>	40 (21/19)	Prospective, non-blinded RCT	Low-frequency positive-pressure ventilation + ECCO <sub>2</sub> R	Conventional positive-pressure ventilation	32% ECCO <sub>2</sub> R; 42% control; no statistically significant difference
CESAR (2009) <sup>12,85</sup>	180 (90/90) (only 68 [75%] received ECMO)	Prospective non-blinded RCT	Referral to center with an ECMO-based management protocol	Conventional positive-pressure ventilation in centers not providing ECMO	63% if considered for ECMO at ECMO center; 47% if conventional; RR = 0.69 (95% CI = 0.05-0.97, $P = .03)$

Study	ECMO <sup>51,53</sup>	LFPPV-ECCO <sub>2</sub> R <sup>27,68,69,97,98</sup>	CESAR <sup>12,54,85</sup>
GOALS			
Natural lung ventilation	Minimize F102 Traditional VT	Minimize Fio <sub>2</sub> Lung rest	Minimize F10 <sub>2</sub> Lung rest
Extracorporeal circulation	Arterial oxygenation	CO <sub>2</sub> removal (to rest lung)	Arterial oxygenation and CO <sub>2</sub> removal
TREATMENT			
Natural lung ventilation	$\label{eq:VT} \begin{array}{l} VT = 0.6 \ L \\ P_{peak} = 50 \ cm \ H_2O \\ PEEP = 10 \ cm \ H_2O \\ VR = 15/min \end{array}$	$VT low P_{peak} = 35-40 cm H_2O PEEP = 17 cm H_2O VR = 2-4/min$	$ \begin{array}{l} V \mbox{$T$ undefined$} \\ P_{\rm peak} = 20\mbox{-}25\mbox{ cm}\ H_2 O \\ P \mbox{$EEP$} = 10\mbox{-}15\mbox{ cm}\ H_2 O \\ V \mbox{$R$} = 10\mbox{/min} \end{array} $
Natural lung perfusion	Low (0.1 Qt)	High (all Qt)	High (all Qt)

Table 23-2 Natural (Patient) Lung Treatment and Extracorporeal Goals: ECMO, LFPPV-ECCO<sub>2</sub>R, and CESAR

with continuous positive pressure ventilation was not statistically significantly different from the 33% survival of patients supported with PCIRV/LFPPV-ECCO<sub>2</sub>R.<sup>27</sup>

LFPPV-ECCO<sub>2</sub>R goals were different from those in the 1974–1977 ECMO trial (see Table 23-2). The higher survival of ARDS patients after support with LFPPV-ECCO<sub>2</sub>R is intriguing. Pulmonary blood flow may be an important determinant of lung response to injury.<sup>76,77</sup> Pulmonary blood flow is preserved in VV LFPPV-ECCO<sub>2</sub>R while the 1974-1977 VA ECMO technique markedly reduced pulmonary blood flow to the natural lung. The preservation of natural lung blood flow, with the low natural lung ventilation, leads to a low overall ventilation/perfusion ( $\dot{V}/\dot{Q}$ ) ratio during VV LFPPV-ECCO<sub>2</sub>R. The 1974–1977 VA ECMO technique produced an oligemic natural lung with a high overall  $(\dot{V}/\dot{Q})$  ratio.<sup>53</sup> Based on observations in animals, high overall  $(\dot{V}/\dot{Q})$  ratio might cause lung necrosis in patients with ARDS. Both preserved pulmonary blood flow and "lung rest" are two significant differences between LFPPV-ECCO<sub>2</sub>R and ECMO (see Table 23-2) that may be important contributors to the difference in patient survival between the LFPPV-ECCO<sub>2</sub>R<sup>27</sup> and the 1974–1977 ECMO clinical trials.<sup>5</sup>

These two randomized clinical trials of extracorporeal support for adults with ARDS enrolled only 90<sup>53</sup> and 40 patients.<sup>27</sup> The power to detect a real difference between control and LFPPV-ECCO<sub>2</sub>R therapy group survival depends on the number of patients studied.<sup>78–81</sup> Assuming that the observed survival rates of 42% for the control group and 33% for the LFPPV-ECCO<sub>2</sub>R group represent the true survival rates of these two treatment groups, the number of study patients required to detect this difference in survival 80% of the time (power = 0.8) is approximately 400 in each treatment group.<sup>81</sup> Only multicenter trials can provide sufficient patient enrollment to make such studies feasible. Adequately explicit protocols could enable the multiple clinical sites, in such a multicenter trial, to function as an extended laboratory with replicable methods.<sup>1</sup> Such protocols have already been used in the clinical trial of PCIRV/LFPPV-ECCO<sub>2</sub>R.<sup>2</sup>

The newest and recently concluded ECLS trial, CESAR, was an impressively executed multicenter trial.<sup>12</sup> The investigators wrote, "It is not possible to further define the safety and efficacy of ECMO as a treatment without a rigorous trial."<sup>54</sup> However, the methods of CESAR lack adequately explicit protocols.<sup>54</sup> They chose to conduct a pragmatic clinical trial, even though the efficacy of ECMO in hypoxemic lung failure of adults was not and is not proven. Central to their study is the identification of "... potentially reversible respiratory failure" patients by clinicians. However, the methods do not indicate exactly how this identification is achieved. They do not define how "conventional" treatment is optimized. Statements like the following make definitive interpretation of the results impossible:<sup>12,54,82</sup>

- 1. "best critical care practice available in their conventional treatment centre"
- 2. "conventional ventilatory support will receive the intensive care provided as standard"
- 3. "conventional ventilatory support can include any treatment modality thought appropriate by the patient's intensivist"
- 4. "a specific management protocol was not mandated, but treatment centres were advised to follow a lowvolume low-pressure ventilation strategy—i.e., tidal volume of 4-8 mL/kg bodyweight, and pressure plateau of less than 30 cm  $H_2O''$

In fact, it is widely recognized that the delivery, in clinical trials, of "usual care" (a synonym for "conventional care") is generally fraught with difficulty.<sup>83,84</sup> Usual care could be appropriate for a pragmatic clinical trial like CESAR, but such a pragmatic trial, like all effectiveness studies, should follow compelling efficacy study results. Such efficacy study results are not available.

The authors claim "The CESAR trial should define the appropriate use of extracorporeal life support for adults with severe potentially reversible respiratory failure." However, we are concerned that both the absence of adequately explicit methods and the lack of a consistent definition of "severe potentially reversible respiratory failure" will make duplication of this work difficult or impossible. Since reproducibility of scientific studies and results is a basis for confidence in the results, these methodological shortcomings reduce the credibility of the results of the CESAR trial. As concluded in an accompanying editorial, the methodological shortcomings of the CESAR trial prevent its results from advancing the debate about extracorporeal support for adults with hypoxemic lung failure.<sup>85</sup>

Several randomized clinical trials in neonates and children suffer from the same methodological limitations as the CESAR trial. They revealed benefits for the study subjects and neonatologists have embraced these results and incorporated ECLS in the treatment of neonates with pulmonary hypertension or severe respiratory failure. This acceptance of ECLS in spite of the absence of replicable methods raises the issue of long-standing tension between the science and art of medicine. The use of ECMO in the neonatal population is now common. The most recent of these trials, the UK trial of ECMO versus conventional therapy, revealed a survival benefit for neonates treated with ECMO with a number needed to treat of 4.86 Conventionally treated subjects had increased respiratory and behavioral morbidity at 7 years of age.<sup>87</sup> U.S. trials in neonates have revealed a similar benefit for ECMO. However, the neonatal trials did not employ consistent inclusion criteria. Commonly accepted neonatal selection criteria, after optimization (sic) of mechanical ventilation, include:<sup>8</sup>

- 1. less than 10-14 days of sustained mechanical ventilation (*sic*)
- 2. greater than 34 weeks' gestational age
- 3. greater than 2 kg body weight
- 4. oxygenation index (mean airway pressure ×  $F_{IO_2}$  × 100) /  $PaO_2$ ) of 40-60 mm Hg for 0.5-6 hours (*sic*), or  $P(A-a)_{O_2} > 605-620$  mm Hg (*sic*) for 4-12 hr, or a  $PaO_2$  of 30-40 mm Hg (*sic*)
- 5. no significant (*sic*) intracranial hemorrhage or bleeding diathesis (*sic*)
- 6. no lethal congenital anomalies or irreversible brain damage (*sic*)

We are not aware of more formal codification of these selection criteria and note that they are not adequately explicit (see (*sic*) above).

In older children, the only clinical trial was discontinued early due to increased survival in the control group, eliminating equipoise and making adequate subject recruitment impossible within a reasonable time.<sup>89</sup> Nonetheless, ECMO is used for children with refractory respiratory failure with an overall survival of 50-60%. In addition, further ECMO experience for children with sepsis has led ECMO to be included in recent guidelines for the care of infants and children with catecholamineresistant septic shock.<sup>90</sup>

To answer the questions posed earlier:

 Does ECLS have a role, based on scientifically credible evidence, in the routine management of patients with ARDS? Not yet in adults. In neonates with pulmonary hypertension or respiratory failure, ECLS is accepted treatment in spite of studies that lack replicable methods.

- 2. If so, what are the selection criteria for the patients who will benefit? Not yet standardized.
- 3. What are the methods for conducting ECLS (the detailed rules and protocols) that would enable interested clinicians or investigators to duplicate the work of ECLS developers and experts? Not yet articulated.

#### IMPORTANCE OF ADEQUATELY EXPLICIT CLINICAL TRIAL PROTOCOLS

The explicitness of protocols is variable. We define an adequately explicit protocol as one that generates specific instructions (patient-specific orders) without requiring judgments by the clinician. An adequately explicit protocol can elicit the same decision from different clinicians when they are faced with the same clinical information. Most clinical study protocols are not adequately explicit. Inadequately explicit protocols omit important details. They can elicit different clinical decisions from different clinicians because clinician decision makers must fill in the gaps in the inadequately explicit protocol logic. Clinicians' judgments will vary with their backgrounds and experience, as will their choices of the rules and variables they use to fill in the gaps of inadequately explicit guidelines and protocols. While adequately explicit computerized protocols can contain the greatest detail,<sup>27,91–93</sup> paper-based versions can also contain enough detail to be adequately explicit.32,94

Even systematic and scholarly collections of flow diagrams commonly lack necessary detail and do not standardize clinician decisions. Protocols and flow diagrams are commonly but inappropriately called *algorithms*. An algorithm in mathematics or engineering is a precise solution although its definition allows the more liberal use common in medicine ["a set of rules for solving a problem in a finite number of steps"<sup>95</sup>]. "Solving a problem" is the operative concept—our current techniques have not solved the problem. It is important to make this distinction between adequately explicit protocols and the more common guidelines and protocols because it may help us to develop more scientifically rigorous clinical trials for ECLS.<sup>1,20,96</sup>

#### **AUTHORS' RECOMMENDATIONS**

- Extracorporeal life support is a technically demanding set of strategies capable of supporting life in adults with severe lung failure.
- While ECLS will likely continue to be applied to neonates and some adults, we lack the ability to consistently identify those patients who should receive ECLS.
- Until detailed and replicable methods for conducting ECLS in either clinical care or in clinical trials have been described, investigators cannot duplicate ECLS studies.
- The role of ECLS for neonates remains only partially defined, despite widespread use.
- The role of ECLS in the routine care of children and adults with ARDS remains unknown and undefined.

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# 24 What Is Inflammation? What Is Sepsis? What Is MODS?

#### Eleni Patrozou, Steven M. Opal

Sepsis, septic shock, and their sequelae are unquestionably a major contributor to morbidity and mortality in hospitalized patients worldwide. However, the clinical definitions of sepsis and related syndromes are imprecise. This has been the source of confusion and debate among physicians, investigators, and researchers alike for many years.<sup>1</sup> Part of the problem is intrinsic to the syndrome of sepsis itself. The term sepsis encompasses a broad array of illnesses and infections involving a markedly heterogeneous patient population. Sepsis is not a distinct nosologic entity caused by a single, defined etiologic agent. There is no single diagnostic laboratory or clinical sign that confirms the diagnosis of sepsis. The terminology of sepsis is further complicated by the vague and often incorrect terms used by physicians to describe clinical events in their patients. Terms such as "septicemia," "sepsis syndrome," "endotoxic shock," and "bloodstream infection" are unevenly applied by clinicians and investigators.<sup>2</sup>

International committees and expert consensus opinion panels have made concerted efforts to standardize the definitions of sepsis. Although such approaches have proved to be of value, the lack of uniformity in the interpretation of these definitions continues to be problematic.<sup>1</sup>

#### WHAT IS INFLAMMATION?

Inflammation represents the body's response to tissue injury or microbial invasion. The pathophysiology of inflammation is a complex and highly regulated process that involves numerous interacting host response networks initiated by pathogen or danger recognition. Acute inflammatory responses culminate with either tissue repair and resolution or overwhelming systemic inflammation. Pathogens, through their microbial-associated molecular patterns (MAMPs), trigger sequential intracellular events in immune cells, epithelium, endothelium, and the neuroendocrine system. Similarly, damaged tissue induces danger signals from the extracellular leakage of endogenous intracellular proteins and lipids (dangerassociated molecular patterns, or DAMPs) following cellular necrosis or excessive apoptosis. These inflammatory signals promote the release of proinflammatory mediators that contribute to eradication of invading microorganisms and anti-inflammatory mediators that control this response and begin wound healing. This highly advantageous host response can become deleterious to the host if excessive or prolonged. The inflammatory response can lead to damage to host tissue and the prolonged anti-inflammatory responses can lead to leukocyte reprogramming and dysfunctional changes in immune status.<sup>3</sup>

The innate immune response is the first line of defense against microbial invaders. Innate immune responses trigger immediate defenses against the invading pathogens and prime the initiation of adaptive immune responses. Innate cell types such as macrophages and neutrophils have pattern recognition receptors that recognize highly conserved microbial-derived and host-derived molecules, known as MAMPs and DAMPs.<sup>4,5</sup> As a result, the innate immune system generates an immediate and nonclonal host defense response. This transcellular receptor signaling apparatus activates transcriptional factors leading to cytokine generation and an acute host response. A characteristic example of pattern recognition receptors is binding to toll-like receptors (TLRs).<sup>6,7</sup> Ten TLRs have been identified in the human genome, and they can be located at either the cell surface or the cell interior.<sup>4,8</sup> The best described is TLR4, which recognizes lipopolysaccharide (LPS, endotoxin), the major component of the cell wall of gram-negative bacteria, in association with two other extracellular pattern recognition molecules known as MD2 and CD14. Recognition of the LPS-MD2 complex by the ectodomain of TLR4 generates a transmembrane signal that is transduced by key adapter proteins leading to recruitment of protein kinases, including interleukin-1 (IL-1) receptor-associated kinase (IRAK-4) and tumor necrosis factor [TNF] receptor-associated factor (TRAF-6). In turn, this leads to a sequence of phosphorylation steps culminating in phosphorylation, ubiquitination, and degradation of IkB. Removal of IkB allows the transmigration of the transcription factor NFkB into the nucleus. This, along with other transcriptional factors, targets more than 150 genes.<sup>9</sup> TLR4 signaling and other TLRs such as TLR2 play a role in noninfectious inflammatory response from DAMPs as well. The endogenous pathway includes heparan sulfate, high-mobility group box-1 (HMGB-1), heat shock proteins, and a number of other danger signals that can stimulate the TLRs.<sup>10</sup>

In contrast to the innate immune response, the adaptive immune system is more specific in defending the host against an array of microbes. Both CD4<sup>+</sup> and CD8<sup>+</sup> helper T cells, along with NK (natural killer) cells, can secrete cytokines with two distinct and antagonistic profiles.<sup>11,12</sup> They secrete either cytokines with inflammatory (type 1, helper T cell [T<sub>H</sub>1]) properties or cytokines with antiinflammatory (type 2, helper T cell [T<sub>H</sub>2]) properties. The factors that determine whether CD4<sup>+</sup> T cells have T<sub>H</sub>1 or T<sub>H</sub>2 responses are unknown but may be influenced by the type of pathogen, the size of the bacterial inoculum, and the site of the infection.<sup>11</sup>

Although less well studied because they make up less than 5% of the lymphocytes,  $\gamma\delta$ -T lymphocytes ( $\gamma\delta$ -T cells) and NK T cells may also play an important role in the pathophysiology of inflammation and sepsis.<sup>13</sup> These cell types recognize less traditional epitopes that include nonpeptide structures such as phosphoantigens and glycolipid structures. Recent data indicate that  $\gamma\delta$ -T-cell knockout mice have markedly increased mortality following a normally nonlethal burn injury.<sup>14</sup> They also have increased mortality following gram-negative bacterial pneumonia.<sup>15</sup> NK T cells express the T-cell receptor but also express NK-cell antigens. They are not restricted by either class I or class II major histocompatibility complex (MHC) antigens and behave in a nonclonal fashion distinct from CD4 and CD8 T cells. The role of NK T cells in severe sepsis is speculative at present.16

Another important T-cell population, now known as T-regulatory (Treg) cells, plays a pivotal role in systemic inflammation. These unusual CD4<sup>+</sup> T cells are characterized by coexpression of CD25 on their cell surface. They can occur naturally (about 4% of circulating blood CD4<sup>+</sup> cells) or can be induced from conventional CD4<sup>+</sup> cells (referred to as  $T_R1$  or  $T_H3$  cells), upon conditioning with specific sets of dendritic cells. Treg cells function as suppressor cells that can directly downregulate CD8<sup>+</sup> T and NK cells and antigen-specific responses of  $CD4^+$  cells. They also secrete variable amounts of anti-inflammatory cytokines, including IL-10 and transforming growth factor-β. Treg cells likely contribute to the immunodepression observed during prolonged systemic inflammatory states and contribute to the attendant risk for secondary infections.<sup>17</sup>

The two arms of the immune system, innate and adaptive, interact closely with each other. Multiple cytokines released from cells of the innate immune system act on dendritic cells. This alters both dendritic cell phenotype and action. Monocytes of the innate immune system are one of the major sources of dendritic cells along with plasma cells. Activated dendritic cells, in turn, function as antigen-presenting cells for CD4<sup>+</sup> lymphocytes and participate in the generation of a vigorous cellular and humoral adaptive immune response.<sup>4</sup> The major cellular elements that constitute to the acute inflammatory response are listed in Table 24-1.

Additionally, the endocrine system is an intimate contributor to an intact inflammatory response to stress and is crucial for the host defense against infection.<sup>18</sup> Hypothalamic hormones, including corticotropin-releasing hormone, vasopressin, and inflammatory cytokines, such as IL-1, IL-6, and TNF- $\alpha$ , have been identified as important modulators of hypothalamic-pituitary-adrenal axis function.<sup>18</sup> During inflammation, these cytokines help maintain high levels of glucocorticoid secretion. This is vital in preventing an uncontrolled inflammatory response to cytokines that would have detrimental effects on the cardiovascular system.<sup>19</sup> The adrenal hormone epinephrine, the catecholamines of the sympathetic nervous system, and most recently the cholinergic anti-inflammatory response have all been identified<sup>20</sup> as important regulators of innate immunity.

The ultimate goal of the inflammatory response is the restoration of homeostasis. At a local site of injury or infection and during the initial appearance of the inflammatory mediators in the circulation, beneficial effects outweigh harmful effects. Only when the balance between these two paradigms is lost do these mediators become harmful. The sequelae of an unbalanced systemic inflammatory reaction include increasingly destructive immunologic dissonance, resulting in shock, multiple-organ dysfunction, and death.

#### WHAT IS SEPSIS?

In 1991, the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) convened a consensus conference to develop a set of definitions that could assist the medical community in communication about sepsis and provide for the early recognition of the septic patient. It was hoped that these definitions would incorporate readily available clinical criteria that would facilitate patient identification and enrollment in investigational trials of innovative therapeutic agents.<sup>21</sup>

The consensus conference recognized that some patients whose clinical presentation suggested sepsis lacked a positive culture or other evidence of documented infection. These individuals where classified as having the systemic inflammatory response syndrome (SIRS). Defined as the widespread systemic inflammatory response to a variety of insults, SIRS includes but is not limited to infection. SIRS was operationally defined by the presence of two or more of the following:

- 1. Temperature greater that  $38^\circ C~(100.4^\circ F)$  or less than  $36^\circ C~(96.8^\circ F)$
- 2. Heart rate more than 90 beats per minute
- 3. Respiratory rate greater than 20 breaths per minute or Paco<sub>2</sub> less than 32 mm Hg
- 4. White blood cell count (WBC) more than 12,000 cells/ mm,<sup>3</sup> or fewer than 4,000 cells/mm,<sup>3</sup> or greater than 10% immature band forms

Sepsis is the systemic inflammatory response to a documented infection (Table 24-2). The diagnosis of sepsis requires the presence of at least two of the above SIRS criteria as a response to an infection. Signs of infection include an inflammatory response to the presence of microorganisms and the invasion of normally sterile host tissue by those organisms. Severe sepsis is defined as sepsis accompanied by overt signs of end-organ injury (e.g., acute renal failure, disseminated intravascular coagulation, acute lung injury).

Septic shock is a subset of severe sepsis with hypotension despite adequate fluid resuscitation and evidence of tissue perfusion abnormalities. Patients receiving inotropic

Cell Type	Characteristics	Role in Spesis
Neutrophil	T <sub>1/2</sub> —12-24 hr, phagocytic, express CD14, CD11/ CD18, CD64, TLRs, L-selectin	Clears pathogens but proteases ROI and RNI can damage tissues
Monocyte/macrophage	T <sub>1/2</sub> —months-years, phagocytic and antigen presenting, express CD14, TLRs, B7-1, B7-2	Major source of cytokines, chemokines, acute phase proteins, and tissue factor
<b>Dendritic cells</b> —follicular, plasmacytoid, and monocytic	T <sub>1/2</sub> —months-years, antigen presenting, express CD14, TLRs, MHCII, B7-1,B7-2	Primary antigen presenting cells for CD4+ cells, produce cytokines, interferons
CD4+ lymphocyte	T <sub>1/2</sub> —decades, Th1/Th2 cytokines, MHC class II restricted, cell-mediated immune function	Th1-TNF, IFNγ, IL-2, Th2-IL-4, 10, 13; Toxic shock, selectively depleted in sepsis
CD8+ lymphocyte	T <sub>1/2</sub> —decades, Th1/Th2 cytokines, MHC class I restricted, cytotoxic cell-mediated immunity	Cytotoxicity, apoptosis of infected cells, source of TNF, IFN $\gamma$
NK cell	T <sub>1/2</sub> —decades, No αβTCR, Th1/Th2 cytokines, MHC I restricted, expresses CD16, cytotoxic	NK cells increase in sepsis, cytotoxic to damaged cells, express TNF, IL-10
NK-T cell	Invariant αβTCR, CD1d restricted, recognizes glycolipid antigens, produces IL-4, IFNγ	Unknown, immune responses to mycobacterial and fungal antigens
Gamma/delta (γδ) T cell	No αβTCR, MHC class I restricted, recognize phospho-antigens, cell-mediated immunity	Unknown, regulates local inflammation, defense against intracellular pathogens
B lymphocyte	T <sub>1/2</sub> —decades, humoral immunity, antigen presenting, CD40, MCH II, produces IL-10	Source of antibodies and antitoxins; selectively depleted in sepsis
T reg cell (Th3, or Tr1)	T <sub>1/2</sub> —decades, CD4+CD25+, Foxp3+, inhibits cytotoxic cell activity, produces IL-10, TGFβ	May play a role in sepsis-induce immunosuppression
Endothelial cell	T <sub>1/2</sub> —decades, P selectin, E selectin, surface adhesins, PAF, tissue factor expression	Adhesins and activators for neutrophils; source of nitric oxide, clotting surface
Platelet	T <sub>1/2</sub> —7-14 days, express P-selectin, GPI-VWF, GPIIb/IIIa-fibrin, TLR4, recognizes thrombin	Platelet-neutrophil aggregates; disseminated intravascular coagulation

#### Table 24-1 Cellular Components of the Inflammatory Response in Sepsis

T<sub>1/2</sub>, functional tissue and/or blood half life; TLRs, toll like receptors; MHC, major histocompatibility complex; ROI, reactive oxygen intermediates; RNI, reactive nitrogen intermediates; Th1/Th2, thymic lymphocyte helper type 1 or type 2; IFNγ, interferon gamma; TNF, tumor necrosis factor; IL-interleukin; TCR-T cell receptor; T reg-regulatory T cell; TGFβ-transforming growth factor; PAF-platelet activating factor; VWF-von Willebrand factor; GP, glycoprotein.

or vasopressor agents may no longer be hypotensive by the time they manifest hypoperfusion abnormalities or organ dysfunction. However, they would still be considered to have septic shock. Mortality rates increase stepwise according to disease severity. Validation of these conference definitions came from a prospective evaluation of University of Iowa patients who met criteria for SIRS, sepsis, severe sepsis, and septic shock. These patients demonstrated an increase in mortality as they moved down this continuum of disease severity.<sup>22</sup>

The 2001 International Sepsis Definitions Conference reaffirmed the basic utility of the clinical definitions proposed in 1991 by the ACCP/SCCM.<sup>23</sup> To enhance the clinician's ability to recognize severe sepsis and possibly to enhance the specificity of the clinical diagnosis of sepsis, the conference provided a listing of common signs and symptoms of sepsis. In addition, the International Sepsis Definitions Conference developed a classification scheme for sepsis modeled after the TNM system used in cancer staging called the PIRO classification system (Table 24-3). PIRO might assist in stratifying septic patients on the basis of predisposing conditions, the nature of the insult, the nature and magnitude of the host response, and the degree of concomitant organ dysfunction. The validity and practical utility of this proposed staging system remain to be demonstrated.

#### WHAT IS MODS?

The multiple-organ dysfunction syndrome (MODS) is the leading cause of morbidity and mortality in patients admitted to the intensive care unit (ICU). Estimates of prevalence vary with the population studied and the criteria used to define the syndrome. In the United States, MODS develops during 15% of all ICU admissions,<sup>24</sup> is associated with 80% of all ICU deaths,<sup>25</sup> and results in average cost per case of \$22,100, with annual total costs of \$16.7 billion nationally.<sup>26</sup>

MODS refers to the alteration in function of multiple organs such that normal homeostasis cannot be maintained without intervention.<sup>27</sup> Unfortunately, there is no consensus on how to define the dysfunction or failure of specific organ systems. However, most experts agree that the need for organ support or replacement therapy signifies the presence of specific organ failure (Table 24-4). Marshall and colleagues<sup>28</sup> critically evaluated the definitions of MODS adopted in the clinical literature and provided a rationale for the physiologic descriptors commonly used to define this syndrome. Worsening abnormalities in the organ-specific parameters that correlate with higher mortality are detailed in Table 24-5.<sup>28</sup>

Inadequate or maldistributed blood supply to vital tissues precedes MODS.<sup>29</sup> There are two prevailing theories

#### Table 24-2 Diagnostic Criteria for Sepsis

Infection (documented or suspected) and some of the following:

#### GENERAL VARIABLES

- Fever (core temperature > 38.3°C [101°F])
- Hypothermia (core temperature < 36°C [96.8°F])
- Heart rate > 90/min or > 2 SD above the normal value for age
- Tachypnea
- Altered mental status
- Significant edema or positive fluid balance (>20 mL/kg for more than 24 hr)
- Hyperglycemia (plasma glucose > 120 mg/dL or 7.7 mmol/L in absence of diabetes)

#### INFLAMMATORY VARIABLES

- Leukocytosis (WBC count > 12,000/µL)
- Leukopenia (WBC count < 4000/µL)</li>
- Normal WBC count with 10% immature forms (bands)
- Plasma C-reactive protein > 2 SD above the normal value
- Plasma procalcitonin > 2 SD above the normal value

#### **HEMODYNAMIC VARIABLES**

- Arterial hypotension (systolic BP < 90 mm Hg, MAP < 70; or systolic BP decrease > 40 mm Hg in adults or < 2 SD below normal for age)
- Svo<sub>2</sub> > 70%
- Cardiac index  $> 3.5 \text{ L/min/m}^2$
- Organ dysfunction variables
- Arterial hypoxemia ( $Pao_2/Fio_2 < 300$ )
- Acute oliguria (urine output < 0.5 mL/kg/hr or 45 mmol/L for at least 2 hr
- Creatinine increase > 0.5 mg/dL
- Coagulation abnormalities (INR > 1.5 or aPTT > 60 sec)
- Ileus (absent bowel sounds)
- Thrombocytopenia (platelet count < 100,000/µL)
- Hyperbilirubinemia (plasma total bilirubin > 4 mg/dL or 70 mmol/L)

#### **TISSUE PERFUSION VARIABLES**

- Hyperlactatemia (>1 mmol/L)
- Decreased capillary refill or mottling
- aPTT, activated partial thromboplastin time; BP, blood pressure; INR, international normalized ratio; MAP, mean arterial pressure; SD, standard deviation; WBC, white blood cell.
- From Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ ATS/SIS International Sepsis Definitions Conference. *Crit Care Med.* 2003;31:1250–1256.

about tissue dysoxia in sepsis. Specific capillary beds demonstrate marked heterogeneity in the level of perfusion of individual blood vessels in tissues resulting in creation of functional arteriovenous shunts. This deranged oxygen distribution within the microcirculation during sepsis can lead to inadequate oxidative phosphorylation essential for cell function.<sup>29</sup> Conversely, oxygen utilization at the cellular level might be inadequate in sepsis even if oxygen supplies are sufficient because of mitochondrial dysfunction. This form of sepsis-induced dysoxia is known as *cytopathic hypoxia*. Cytopathic hypoxia is induced by inhibition of mitochondrial respiratory enzymes by toxic oxygen and nitrogen intermediates

#### Table 24-3 PIRO Staging of Sepsis

#### PREDISPOSITION

Premorbid conditions that influence likelihood of infection, sepsis, morbidity, survival (i.e., age, gender, hormonal state, genetic polymorphisms for immune response, and coagulation proteins)

#### INFECTION

Organism associated with the sepsis response (i.e., type of organism, virulence potential, toxins, community or nosocomial acquisition)

#### RESPONSE

Clinical and immunologic manifestations of the septic response (either hyperinflammation or hypoinflammation) (e.g., procalcitonin, interleukin-6, human leukocyte antigen–D related, tumor necrosis factor, platelet-activating factor)

#### ORGAN DYSFUNCTION

Type and number of dysfunctional organs (reversible versus irreversible dysfunction), severity of dysfunction

From Levy MM, Fink MP, Marshall JE et al. 2001 SCCM/ESICM/ACCP/ATS/ SIS International Sepsis Definitions Conference. *Crit Care Med.* 2003; 31:1250–1256.

(e.g., peroxynitrite) and by loss of nicotinamide adenine dinucleotide (NAD<sup>+</sup>) through activation of poly(ADP-ribose) polymerase-1.<sup>30</sup> Both processes of disordered oxygen delivery and oxygen utilization may be operative in various phases of severe sepsis contributing to tissue dysfunction.

The failure of microcirculation to support tissue maintenance may be the result of hypoperfusion of capillary beds, redistribution of blood flow from microthrombi, platelet or white blood cell aggregates, or abnormal deformability of red blood cells. Nitric oxide, reactive oxygen and nitrogen intermediates (e.g., superoxide, hydroxyl radicals, peroxynitrite), inflammatory cytokines, and inducers of apoptosis directly damage endothelial surfaces. Endothelial swelling from the movement of intravascular fluid into the extravascular and intracellular spaces may mechanically obstruct the lumen of the capillary beds as well.<sup>31</sup>

Although the origin of multiorgan failure in sepsis is principally related to microvascular effects, myocardial performance and pulmonary function also diminish over the course of septic shock and may contribute significantly to the development of septic shock and MODS. Myocardial contractility decreases in response to a variety of myocardial depressant factors found in the plasma of septic patients.<sup>32</sup> TNF- $\alpha$  is a prominent cause of myocardial dysfunction. IL-1, IL-6, nitric oxide, and other hostderived inflammatory mediators may also be contributing factors.<sup>33</sup> Furthermore, acute lung injury occurs in septic shock as a result of damage to the pulmonary vascular circulation and the alveolar-capillary membranes. A supply-dependent dysoxia, in combination with cytopathic hypoxia, may contribute to tissue injury and multiorgan failure in sepsis.<sup>34</sup>

	pie-Organ Dyslunction Syndrome in Severe	e Sepsis
Organ System	Clinical-Metabolic Abnormalities	Histopathologic Findings
Central nervous system	Encephalopathy, decreased sensorium	Cerebral edema, microthrombi
Cardiac	Decreased myocardial performance	Altered calcium influx, interstitial edema
Respiratory	Acute respiratory distress syndrome	Exudation of fluid into the alveolar spaces, neutrophil plugging, hyaline membrane formation
Renal	Acute tubular necrosis	Hypoperfusion, focal ischemia, ischemic necrosis
Adrenal	Relative adrenal insufficiency, adrenal hemorrhage	Focal or diffuse hemorrhage, ischemic necrosis
Hepatobiliary	Cholestatic jaundice, decreased hepatic synthesis of albumin, presence of clotting factors	Zonal necrosis, acalculous cholecystitis
Gastrointestinal	Translocation of bacterial endotoxin and microorganisms, increased permeability	Diffuse interstitial edema, breaks in the epithelial membrane integrity, mucosal necrosis

#### Table 24-5 Multiple-Organ Dysfunction Score

Organ System	Clinical Descriptors
Central nervous system	Glasgow Coma Scale
Cardiac	Pressure adjusted heart rate
Respiratory	Po <sub>2</sub> /Fio <sub>2</sub> ratio
Renal	Serum creatinine
Hematologic	Platelet count
Hepatic	Serum bilirubin concentration

#### SUMMARY AND CONCLUSIONS

- Progress in the care of the critically ill patient with lifethreatening infection has been hampered by inconsistent, often confusing terminology. The imminent availability of mediatordirected therapy has created a sense of urgency to develop better methods for delineating discrete clinical syndromes and to modulate the host response.
- · Previous definitions have served well in identifying patients eligible for clinical trials and in epidemiologic surveys regarding the incidence of sepsis. However, the criteria have been criticized for their nonspecific nature and creation of a heterogeneous population for study.
- The lack of agreement on the definitions of sepsis criteria has influence on the ability of the physicians to diagnose and communicate about sepsis. A prospective international survey among intensive care physicians revealed that two thirds were concerned that a common definition is lacking, and 83% said it is likely that sepsis is frequently missed. Not more than 17% agreed on any one definition.<sup>3</sup>
- · The definitions of sepsis provide a useful intellectual framework for investigation purposes. However, it is still debatable whether they provide useful guidance in the diagnosis and treatment of acutely ill patients.

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## 25 Sepsis—Source Unknown: How Should One Work Up and Manage the Patient?

Pamela A. Lipsett

Every day, intensive care unit (ICU) practitioners face difficult clinical decisions about the evaluation, identification, prevention, and treatment of nosocomial infections. Sepsis is identified in more than 750,000 people in the United States alone, and the associated mortality rate is 28.6%.<sup>1</sup> Over the period of time from 1979 to 2000, Martin and associates reported an increasing frequency of sepsis from 82.7 cases per 100,000 U.S. population to 240.4 cases per 100,000 population.<sup>2</sup> Moreover, these authors reported an increase in the rate of sepsis due to fungal organisms (207%), with gram-positive organisms becoming the predominant pathogens after 1987.<sup>2</sup> Over a 2-week period, a multinational European cohort of ICU patients was identified as having proven or suspected infection, sepsis, severe sepsis, or septic shock using the American College of Chest Physicians and Society of Critical Care Medicine (ACCP/SCCM) consensus conference definition of infection plus two systemic inflammatory response syndrome criteria.<sup>3</sup> Of the 3147 enrolled patients, more than 64% received antibiotics. However, only 1177 (34%) had identified infection: 454 (38.6%) with an identified pathogen and source, 468 (39.8%) with a clinical suspicion of infection but without a pathogen identified, and 255 (21.7%) with one or more isolated pathogens, but without evident clinical infection. Each of these groups of patients was treated with antibiotics, and each group of patients had a mortality rate in excess of 25%.<sup>4</sup> Isolation of microbes in 50% to 70% of critically ill patients with suspected infection and sepsis, severe sepsis, or septic shock is typical.<sup>4</sup> In the study by Vincent and colleagues,<sup>4</sup> the lung was the most common site of infection (68%), followed by the abdomen (22%), blood (20%), and urinary tract (14%). The sites of infection were similar to those reported by Alberti and colleagues,<sup>5</sup> with lung representing the site of infection in 62% of patients and abdomen in 15%. In patients with severe sepsis, Angus and coworkers<sup>1</sup> reported that the lung represented the site of infection in 44% of patients and abdomen in 8.6%. Table 25-1 illustrates outcomes from large series of ICU patients with suspected infection.<sup>1,2,4–12</sup>

The balance among the identification of a likely source of infection, expected or isolated infecting microbes, and the empirical use of antibiotics in critically ill ICU patients is a delicate one. A careful assessment of the patient who is suspected of harboring an infection based on the presence of fever with an unknown source should consider both infectious and noninfectious causes.<sup>13</sup> However, the evaluation should be conducted in a clinically appropriate and cost-effective manner.

The empirical use of antibiotics for suspected infection also should be based on a careful assessment of the source of infection and the risk of nontreatment.<sup>13–17</sup> Policies and practices for antibiotic use must strike the delicate balance among the possibilities of a life-threatening infection, empirical antibiotic treatment, and the development of antimicrobial resistance associated with excessive exposure to antimicrobial agents and poor infection control practices.<sup>19–22</sup>

Microbes make up 90% of the 10<sup>14</sup> cells in the human body, and thus it is easy to understand why infection must be considered in the differential diagnosis of an acutely ill patient. Differentiating which of these microbes are invaders from those that are colonizers or from those microbes that play a beneficial role in health can be a difficult task. Although antimicrobials are undoubtedly therapeutic, excessive use can be problematic for both the patient and the ICU system. The extent to which empirical antibiotics should be employed is a subject on which many experts disagree.<sup>23</sup>

#### PATHOPHYSIOLOGY OF FEVER

Temperature is measured routinely in ICU patients, and an elevation in temperature is common. Although there is no universal consensus on what constitutes a fever, the normal mean oral temperature in healthy individuals is about 36.8°C, with a range of 35.6°C to 38.2°C, and with a slight diurnal variation.<sup>13,24</sup> The recent consensus statement from ACCP/SCCM and the Infectious Diseases Society of America suggested that any new-onset temperature above 38.3°C should be considered a fever and should prompt a clinical assessment, but not necessarily a laboratory or radiologic evaluation for infection.<sup>13,24</sup>

A variety of stimuli can induce white blood cells to produce endogenous pyrogens. The most potent of these are interleukin-1 (IL-1) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ).<sup>25</sup> Other endogenous pyrogens that are integral

Study	Study Location	Study Design	Outcomes
Cook et al, 1998 <sup>6</sup>	University surgical ICU	Retrospective, sepsis without bacterial infection	142 patients studied, 12 (8%) CMV cultured in blood/sputum or BAL
Circiumaru et al, 1999 <sup>7</sup>	University 9-bed ICU	Prospective cohort, 100 consecutive patients over 4 months, 1996	Fever (>38.4°C) present in 70%, 35 infectious, 35 noninfectious. Noninfectious fever typically early (1-2 days) and related to surgery
Alberti et al, 2001 <sup>5</sup>	28 ICUs in 8 countries, 1997-1998	Prospective cohort	14,364 patients, 6011 stayed < 24 hr, 8353 > 24 hours; 3034 (21.1%) infectious at the time of admission; 1581 (18.9%) > 24 hr had infections, 713 (45% at ICU admission). Respiratory, GI, UTI, BSI accounted for 80% of infections.
Angus et al, 2001 <sup>1</sup>	U.S., nonfederal hospitals in 7 states, 1995 discharge records	Administrative data from discharge records and population sources	6,621,559 population, 192,980 cases identified, estimated 751,000 cases in U.S., 51.1% needed ICU care, 130,000 needed ventilation in intermediate care. Site of infection 38.4% respiratory, 14.6% bloodstream, 8.7% GU, 9.3% GI. Device- related 4.9%, wound/soft tissue 8.9%, CNS 1.1%, endocarditis, 1.5%, other 12.6%
Martin et al, 2003 <sup>2</sup>	National inpatient sample, 1979-2000	Administrative data	<ul> <li>750 million hospitalizations over 22 years identified 10,319; 419 episodes of sepsis.</li> <li>52.1% caused by gram-positive organisms, gram-negative 37.6%, polymicrobial 4.7%, anaerobes 1.0%, and fungi 4.6%</li> </ul>
Barie et al, 2004 <sup>8</sup>	Weill Cornell surgical ICU	Inception-cohort of patients with a fever (>38.2°C)	<ul> <li>2419 screened patients, 626 patients with fever. 46% has identified cause of fever, 43% intraabdominal, 24% pneumonia, 20% skin/soft tissue, 5% other, and 3% line sepsis. Non-infectious cases included head injury, trauma, atelectasis, and ischemia</li> </ul>
Jaber et al, 2005 <sup>9</sup>	University medical- surgical ICU	Retrospective case-control patients with fever for >72 hrs and no source found	237 with continuous fever and negative workup; identified 40 patients with pp65 CMV antigenemia
Schey et al, 2005 <sup>10</sup>	University hospital patients having benign gynecologic procedures	Retrospective chart review, 1994-2000. Outcome of fever evaluation. Fever with body temperature >101.5°F or 2 recorded temperatures above 100.4°F within 24 hr	505 patients, 147 with fever; 92 patients had no infectious cause identified, and 55 were found to have positive cultures: blood cultures 9.7%, urine cultures 18.8%, and pneumonia 14%
Vincent et al, 2006 <sup>4</sup>	198 ICUs in 24 European countries	Multicenter cohort, observational study, May 1-15, 2002	<ul> <li>3147 patients, 1177 (34%) had sepsis; lung most common site (68%), abdomen (22%), blood (20%), UTI (14%). Cultures positive in 60%. <i>Staphylococcus aureus</i> (30%), <i>Pseudomonas</i> spp. 14%, <i>Escherichia coli</i> (13%)</li> </ul>
Golob et al, 2008 <sup>11</sup>	University trauma ICU	Retrospective cohort study to examine UTI associated with fever and leukocytosis	3839 patient days/510 patients. 42 patients had 60 UTIs. The fever and leukocytosis were not associated with UTIs.
Laupland et al, 2008 <sup>12</sup>	Calgary Health region ICUs	Retrospective cohort study of patients with a fever (38.3°C) and high fever (39.5°C)	24,204 ICU admissions. Fever occurred in 44% and high fever in 8%. 17% and 31% of patients with fever and high fever had positive cultures. Bacteremia present in 9% and 19% of first fever and high fever.

Table	25-1	Enidemiolo	av of Se	nsis in l	arge In	itensive (	are U	Init Serie
labic	20 1	Epidemiolo						

BAL, bronchoalveolar lavage; BSI, blood stream infection; CNS, central nervous system; CMV, cytomegalovirus; GI, gastrointestinal; GU, genitourinary; ICU, intensive care unit; UTI, urinary tract infection.

in the febrile response include IL-6 and the interferons.<sup>26</sup> These endogenous pyrogens act on the central nervous system by an uncertain mechanism to produce prostaglandin E2 and its downstream products. These in turn induce a febrile response. Because of the many potential endogenous and exogenous stimuli that can induce a fever, the presence of a fever is not uniformly associated with infection.

Characterizing the magnitude of a fever and its associated symptoms and signs such as rigors, pulse, and blood pressure can provide diagnostic clues to the etiology of the fever.<sup>13–17</sup> Very high fevers (>41.1°C) are less likely to be infectious and more often are caused by diseases such as heat stroke, malignant hyperthermia, or drug fever or endocrine problems such as thyrotoxicosis and adrenal insufficiency (Table 25-2). Patients who exhibit sustained hyperthermia and head injury may have a central nervous system etiology for their fever. Fever in association with a rash, eosinophilia, or relative bradycardia may be caused by medications, current or past. Providers should recognize that some patients who have been treated for a prolonged period of time with antibiotics may develop secondary fungal infections. Surgical patients commonly have a fever in the early postoperative course. In the first 3 days after surgery, patients typically have a noninfectious etiology of their fever.<sup>7,8</sup> This early fever is commonly attributed to atelectasis, but there is little agreement that atelectasis actually causes fevers. However, when bronchoalveolar lavage is performed on atelectatic lung segments in patients with the adult respiratory distress syndrome (ARDS), high concentrations of TNF- $\alpha$  and IL-6 can be measured.<sup>18</sup> Thus, the etiology of an early fever after

#### Table 25-2 Common Noninfectious Causes of Fever in the Intensive Care Unit

Aspiration pneumonitis

Medications, especially antibiotics, such as  $\beta$ -lactams

Tissue injury often early after surgery or trauma Hematoma Ischemia Tissue infarction
Atelectasis
Substance withdrawal
Blood product administration
Central nervous system disease Subarachnoid hemorrhage
Deep venous thrombosis
Pulmonary and fat emboli
Transplant rejection
Endocrine problems Thyrotoxicosis Adrenal insufficiency

surgery is most commonly related to cytokine elevation. The greatest likelihood of infection is associated fever arising 5 to 7 days after a surgical procedure. The fever may be related to an organ space infection, an anastomotic breakdown, or another postsurgical infectious complication.

## HOW TO PROCEED WITH A DIAGNOSTIC EVALUATION

The first step in assessing the patient with suspected sepsis and an unknown source is to determine the actual risk for infection and the likely source. This involves obtaining a careful history with respect to the patient's admission diagnosis and all the comorbid conditions and recent interventions. The assessment should include an understanding of the overall health of the patient, the severity of illness, and any known information regarding colonizing or infecting pathogens. The nature of any localizing symptoms and signs should be noted, as should the intensity and evolution of symptoms or signs over time. In particular, the clinician should consider the immune status of the patient and interventions or diseases that alter both the classic and nonclassic pathways of fighting infection. Important considerations in the high-risk patient include recent chemotherapy or a congenital disease that alters neutrophil number or function. Patients who are elderly, are asplenic, or have multiple chronic diseases, recent trauma or thermal injury, or end-organ injury also are at special risk. Not only do patients with altered immune function have a greater risk for acquiring infection, but also the presentation and clinical appearance may be altered because occult infection is more common in patients with altered immune function. Patients with normal immune function typically have cardinal localizing signs such as erythema, pain, swelling, loss of function, and heat in the affected area. Additional signs are systemic and include fever, tachypnea or tachycardia, confusion, and ileus. Patients with altered immune function may present with more occult signs. These include gastrointestinal bleeding, ileus, confusion, shock, water retention, and delayed wound healing. Any break in the skin or mucosal surface can be a source of exogenous or endogenous infection. The presence of a foreign body or invasive device imparts risk and often is the source of infection. Therefore, all invasive devices and foreign bodies should be considered suspect in the search for a possible septic source.

In addition to a review of the patient's general history, the clinician should review all interventions, medications, recent blood products, and laboratory and radiologic tests.

Although the physical examination may be unrewarding because of lack of localizing signs, specific items should be carefully examined. If the patient has recently (within 3 to 14 days) undergone surgery, there should be a specific examination of the surgical wound site and associated drains, with particular attention to the character and drainage pattern over the past several days. All lines and devices should be assessed, as should proximal and associated tissues. A rectal examination may reveal signs of pelvic or prostatic infection. The skin may be a potential site for decubitus ulcers, and the legs should be checked for areas of swelling or tenderness, the neck for potential stiffness, and of course the lungs for localizing signs.

After assessment of probability of infection based on historical risk and physical examination, patients with suspected sepsis should undergo laboratory, microbiologic, and often radiologic evaluation. As noted previously, although this evaluation may be initiated based solely on the presence of fever or leukocytosis, fever is not universally associated with infection, and infection may be present with hypothermia or leukopenia.

The white blood cell count is widely used as a general indicator of the presence (or absence) of infection.<sup>13</sup> However, the white cell count actually tells the clinician little specific information even when band forms are considered. Additional laboratory values that should be considered in assessing infection include thrombocytosis, thrombocytopenia, hyperglycemia, metabolic acidosis, and changes in the inflammatory status such as elevation of the erythrocyte sedimentation rate, level of C-reactive protein, procalcitonin, IL-6, and TNF. Although all are associated with the presence of infection, these markers also are associated with inflammation and organ dysfunction and do not assist in distinguishing between infectious and noninfectious causes. Although TNF, IL-1, IL-6, IL-8, and IL-10 are all important in sepsis, they do not have diagnostic or prognostic value today for sepsis. Several meta-analyses have been performed on the use of serum values of C-reactive protein or procalcitonin in differentiating patients with bacterial infections from those without infectious causes for significant or critical illness in both adults and children (Table 25-3).<sup>27–31</sup>

#### **Microbiologic Approach to Diagnosis**

After the previously discussed measures have been completed, initial blood cultures should be obtained in all patients in whom an infectious cause is suspected. As indicated in the recent SCCM/IDSA guidelines on the evaluation of a new fever in a critically ill patient, two sets of blood cultures from two separate sites should be drawn when the clinical evaluation does not strongly suggest a noninfectious cause of fever.<sup>13</sup> Some authors suggest that if the patient is neither neutropenic nor unstable, the patient should be observed without empirical antibiotics while considering further diagnostic evaluation.<sup>23</sup> If localizing signs are present at catheter sites, wound or drain cultures of those sites should be obtained. When pneumonia is suspected, the diagnosis may be established by considering clinical signs, sputum assessment by either invasive or noninvasive means, and qualitative or quantitative cultures. Organ- or site-specific infections are discussed elsewhere. Based on large studies of sepsis, Table 25-1 illustrates the likely infectious causes and Table 25-2 common noninfectious causes of fever and suspected infection in critically ill patients.

Radiographs can be useful in identifying and localizing infectious sources. Plain radiographs in general are unhelpful and do not provide incremental information above clinical examinations. Ultrasonography can be performed at the beside and, when the patient body habitus allows, can assist in localizing a fluid collection. In addition, an ultrasound may allow for percutaneous aspiration and drainage of an infection. An ultrasound may also identify the presence of gallstones or an inflamed gallbladder or pancreas. Computed tomography (CT) is more

### Table 25-3 Meta-Analysis of the Diagnostic Value of Procalcitonin and C-Reactive Protein in Determining the Presence of Bacterial Infection

Study	No. of Trials	No. of Subjects (Intervention/No Intervention)	Sensitivity	Specificity	Outcomes
Simon et al, 2004 <sup>27</sup>	12	Procalcitonin: 898 C-reactive protein: 873	88 (80-93) 75 (62-84)	81 (67-90) 67 (56-77)	+ LR 3.58 (2.99-4.28); -LR 0.18 (0.15-0.23) + LR 2.43 (2.3-2.92); -LR 0.42 (0.36-049)
Uzzan et al, 2006 <sup>28</sup>	33/15 Studies used both tests	Procalcitonin: 3943 patients; 1825 sepsis, severe sepsis, septic shock; 1545 SIRS			OR 14.69 (7.12-03.27); Q value 0.78 (0.71-0.84) OR 5.43 (3.19-9.23); 0.71 (0.64-0.76) For SIRS: OR 15.7 (9.1-27.1) OR 5.4 (3.2-9.2)
Tang et al, 2007 <sup>29</sup>	18	2097	0.71 (0.61-0.76)	0.71 (0.67-0.76)	Q value 0.72 Phase II trials (495 patients) OR 7.79 (5.86-10.35)
Jones et al, 2007 <sup>30</sup>	17	2008	0.76 (0.66-0.84)	0.70 (0.60-0.70)	Q = 0.77 OR 9.86 (5.72-17.02)
Sanders et al, 2008 <sup>31</sup>	6	C-reactive protein: 1071	0.77 (0.68-0.83)	0.79 (0.74-0.83)	+LR 3.64 (2.99-4.43); -LR 0.29 (0.22-0.40)

LR, likelihood ratios; OR, odds ratio; SIRS, systemic inflammatory response syndrome.

often performed to assist in the evaluation of a patient with suspected infection in almost any location in the body. A CT scan with oral and intravenous contrast can reliably identify an intra-abdominal source of infection. CT scans can also diagnosis alternatives such as bowel obstruction and infarction with an overall sensitivity of 82% to 100%. The CT scan is the procedure of choice for the identification of intra-abdominal conditions such as abscess, inflammatory bowel disease, pseudomembranous colitis, fistula formation, perforation, mesenteric pathology, and sinus tracts.<sup>32,33</sup>

In patients with fever of unknown origin (FUO), infection is ultimately identified in 24.5% of patients, inflammatory conditions in 23.5%, malignancy in 14.5%, other diagnoses in 7.5%, and no diagnosis in 30%. In 19% of cases of FUO,<sup>34–41</sup> a CT scan of the abdomen will identify either an intra-abdominal abscess or lymphoproliferative disease. Technetium-based studies have the highest reported specificity (93% to 94% in 10 studies) but are insensitive (40% to 75%) when FUO is present.<sup>36</sup> White blood cell scans labeled with indium-111 and indium-111 immunoglobulin G have poor sensitivity (45% to 82%) and a specificity that ranges from 69% to 86%. Technetium scans were most likely to have diagnostic value (positive likelihood ratio, 5.7 to 12.5) in the evaluation of an FUO because of their high specificity. In a meta-analysis of 1199 patients with nuclear medicine studies done for localizing occult infection in patients with a FUO, fluorodeoxyglucose positron-emission tomography (FDG-PET) scan had a 95% sensitivity, 88% specificity, a positivepredictive value of 91%, a negative-predictive value of 95%, and 92% accuracy. Although these data may hold true for FUO patients, it is not clear when or if these studies are helpful in more acutely ill patients.<sup>35,36,40,41</sup>

#### INTERPRETATION OF THE DATA AND CONCLUSION

Every patient with suspected infection should undergo a careful assessment of risk. This is best accomplished by review of the medical history, events, and medications and a careful physical examination with laboratory evaluation to include routine items and, possibly, serum procalcitonin (Table 25-4).<sup>13,37–39</sup> Although the white cell count, electrolytes, and liver function tests are not likely to specify the presence or absence of an infection, they may indicate abnormalities that require further investigation, such as an ultrasound of the gallbladder. A very low procalcitonin level (<0.1) is unlikely to be due to infection, and antibiotics may be withheld pending further study. Similarly, with elevated levels of procalcitonin (>0.5), antibiotics should be considered. Levels between 0.1 and 0.5 should be individually considered depending on the individual's immunocompetence. This strategy has been successfully applied in 1200 patients with lower respiratory tract infection.42

Table 25-4 Diagnostic Approach and General Therapy					
Site	Diagnostic Approach	Treatment			
Surgical site infection Superficial Deep, organ space	Clinical examination Computed tomography (CT) scan	Local care, open wound, dressing changes, packing Drainage of collections			
Ventilator-associated pneumonia	Chest radiograph or CT scan; noninvasive or invasive cultures	Culture specific			
Bloodstream infection, central line associated Endocarditis, septic thrombophlebitis	Catheter and simultaneous blood cultures from periphery plus catheter removal; catheter blood culture and peripheral blood cultures for quantitative cultures (>5:1) or for time to positivity Blood cultures, echocardiogram	Remove short-term catheters and all nonessential long-term catheters; directed antibiotics Antibiotics, prolonged duration			
Urinary tract infection	Quantitative cultures	Catheter removal or change; directed treatment in upper tract disease			
Antibiotic-associated diarrhea	Assessment for Clostridium difficile	Discontinue antibiotics, vancomycin, or metronidazole			
Sinusitis	CT scan, direct aspiration of sinus for culture	Remove nasal tubes, drainage of sinuses, antibiotics			
Intra-abdominal source not associated with operation Cholecystitis, acalculous	CT scan	Percutaneous drainage			
Central nervous system infection	Neck stiffness, cerebrospinal fluid analysis	Directed antibiotics			
Osteomyelitis, prosthetic joint infection	Clinical examination, plain film, magnetic resonance imaging, nuclear medicine, fluorodeoxyglucose positron-emission tomography	Débridement and antibiotics			

The presence of recent surgery, lines, tubes, and invasive devices should prompt close inspection of these sites. Clinicians should recognize that pneumonia, surgical site infection, urinary tract infection, and central line-associated infection account for most infections in critically ill patients but about only 50% of all causes of fever. Therefore, the initial focus should be on these possibilities. Additional infectious causes such as Clostridium difficile, sinusitis, and cholecystitis should be considered in at-risk individuals. Radiography should be considered, and CT scans are particularly useful for patients with any abdominal history, symptoms, or signs. With fever for extended periods of time, all medications that are unessential should be withdrawn; if fever persists, an abdominal CT scan, followed by technetium scan if a focus has not been identified and tissue obtained, may be indicated. If blood cultures or clinical history suggest endocarditis, the Duke criteria should be applied to rule in or out infectious endocarditis. Doppler examination of the legs should be performed.

#### AUTHOR'S RECOMMENDATIONS

- Defining and locating the presence of infection in a critically ill patient, often with organ failure, is a difficult task that requires careful assessment and reassessment of all aspects of the patient, from recent history and procedures, medications, and invasive lines, to a detailed and careful physical examination.
- Full consideration of noninfectious causes should also be considered and ruled out as appropriate.
- Basic clinical signs suggestive of infection such as fever and leukocytosis are nonspecific, as are the other signs of inflammation, such as C-reactive protein, IL-1, and IL-6.
- Procalcitonin has been studied most recently for its use in distinguishing infected and noninfected states. However, the overall sensitivity and specificity for this serum marker are generally in the mid-70s range, limiting its overall usefulness as a definitive marker of the presence or absence of infection.
- Microbiologic samples should be liberally obtained from sites that are likely by history, recent intervention, or physical examination to be infected.
- Radiologic studies, especially CT scans, will help identify an abscess when present. Additional radiologic studies can be used when a careful search has not identified a cause for suspected infection.

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# Which Organs Become Dysfunctional in Sepsis? How Does This Occur? How Is It Diagnosed and Managed?

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#### HOW IS ORGAN DYSFUNCTION DEFINED?

Organ dysfunction is defined by the need to intervene to maintain organ system homeostasis and function in the context of acute illness.<sup>1</sup> Organ dysfunction is common in critically ill patients, particularly in those with the sepsis syndromes.<sup>2</sup>

A large European, multicenter observational study (Sepsis Occurrence in Acutely III Patients, or SOAP, Fig. 26-1) suggested that more than 35% of intensive care unit (ICU) patients suffered from sepsis at some point during their stay. Of these, about 27% died. Further, 41% of patients with sepsis displayed evidence of organ dysfunction. Failure of two or more organs was significantly higher in patients with sepsis than in those without (75% versus 43%, respectively). Those patients with four or more organ failures had a mortality rate of 65%.<sup>3</sup>

In patients with sepsis, organ failure is rarely isolated (see Fig. 26-1). However, failure rates for individual systems or in combination in the SOAP study were cardiovascular (62.6%), renal (51.2%), respiratory (49.8%), central nervous system (41.3%), coagulation (20.1%), and hepatic (12.2%).<sup>3</sup> Other publications have included data concerning hematologic (failure rates of 7% to 16%, 73% in septic shock),<sup>4</sup> metabolic, and endocrine failure in the context of sepsis.

#### WHAT INITIATES THE PROCESSES THAT LIKELY LEAD TO ORGAN FAILURE IN SEPSIS?

Although our understanding of the mechanisms that induce the sepsis syndromes has increased, the precise pathophysiology remains unknown. It appears that following a noninfective (systemic inflammatory response syndrome, or SIRS) or infective (sepsis) insult, a complex and intricate cascade of inflammatory mediators is activated.<sup>5</sup> Briefly, pathogens have a range of exogenous molecules on their surfaces that are recognized by toll-like receptors (TLRs) embedded in the cell membrane and by cytoplasmic pattern recognition receptors present on monocytes, tissue macrophages, and endothelial cells. Activation of these triggers the host immune response,<sup>6</sup> resulting in cleavage of proinflammatory cytokines (e.g., interleukin-1 [IL-1], IL-6, IL-8, and tumor necrosis factor [TNF]). These upregulate NF $\kappa$ B, a transcription factor that binds to target DNA in the nucleus and induces further production of cytokines, chemokines, and adhesion molecules.<sup>7,8</sup> This leads to endothelial activation, changing vasomotor tone, cell and nutrient trafficking, blood viscosity, and coagulation and capillary permeability.

#### WHAT IS THE ROLE OF THE ENDOTHELIUM IN THE PATHOPHYSIOLOGY OF ORGAN DYSFUNCTION?

During sepsis, activated endothelial cells undergo structural and functional changes.<sup>9</sup> In the intact vasculature, endothelial cells form a continuous semipermeable barrier that varies in integrity and control in different vascular beds. In sepsis, the barrier function is impaired or lost. This results in increased permeability, chemical shift, and tissue edema. TNF and thrombin act synergistically to induce barrier dysfunction.<sup>9</sup> Fluid that redistributes from the intravascular space to the interstitium contributes to hypovolemia, hemoconcentration, and impaired capillary perfusion.

Second, the vasomotor function of endothelial cells changes during inflammation. Nitric oxide (NO) is released from activated endothelium following upregulation of inducible nitric oxide synthase (iNOS) in vascular smooth muscle by cytokines, pathogen antigens, and NFkB. NO causes vasodilation and hypotension.<sup>10</sup> NO also is involved in cell signaling and reacts rapidly with superoxide species to produce peroxynitrite anions (OONO–). These form toxic hydroxyl radicals. Although these reactive nitrogen species are beneficial when used by leukocytes to kill microbes, overproduction can cause local tissue damage or alter cell signaling.<sup>10</sup>

Third, pathogens stimulate the arachidonic acid cascade within endothelial cells, generating further



**Figure 26-1.** Incidence and mortality by number of failed organ systems. (*From Vincent JL, Sakr Y, Sprung CL, et al. Sepsis in European intensive care units: Results of the SOAP study.* Crit Care Med. 2006;34:433-453.)

proinflammatory prostaglandins, thromboxanes, and leukotrienes.<sup>6,8</sup> This leads to increased vascular permeability (through histamine and serotonin), neutrophil attraction (to form pus), platelet-activating factor (PAF) release, and platelet aggregation. Normal endothelium has anticoagulant and profibrinolytic properties. In sepsis, tissue factor (TF) expression on the surfaces of circulating monocytes and tissue macrophages is upregulated. This activates the clotting cascade and promotes thrombin and fibrin formation.<sup>9</sup> The activity of natural coagulation inhibitors such as antithrombin III and protein C is depressed, and fibrinolysis is inhibited. This causes coagulation and the consumption of clotting factors.9 Fibrin deposition occurs, trapping platelets, resulting in the formation of microthrombi. Thrombin signaling in endothelial cells results in changes in cell shape, cell permeability, and leukocyte adhesion and trafficking. In addition, thrombin signaling induces the secretion of von Willebrand factor and stimulates the release of soluble mediators such as PAF, IL-8, chemoattractant proteins, growth factors, and matrix metalloproteinases.<sup>9</sup> Poor blood flow states in sepsis reduce clearance of activated clotting factors, promoting further clotting

Fourth, although inflammatory activation also upregulates the transcription of anti-inflammatory mediators (the anti-inflammatory response syndrome<sup>9</sup>), these compensatory mechanisms are impaired in sepsis. Apoptosis (or programmed cell death) in lymphocytes is accelerated, presumably due to severe cytotoxic stress. This results in anergy (a state of nonresponsiveness to antigen), immune suppression, an inability to clear infection, and a predisposition for nosocomial infection.<sup>5,11</sup> Neutrophil apoptosis is also delayed, resulting in sustained inflammation and increased tissue and organ damage through cytotoxic enzymes and oxygen free radicals. This is particularly marked in the lung.

Finally, the clinical phenotype is determined by the interplay between proinflammatory and anti-inflammatory and coagulation systems; excessive or sustained inflammation manifests as the sepsis syndromes with or without

#### Table 26-1 Endothelial Abnormalities in Sepsis

Endothelial abnormalities in sepsis include:

- Changes in vasomotor tone, via nitric oxide (NO)
- Increased expression of adhesion molecules, leukocyte adherence, and migration
- Increased platelet aggregation, via NO and platelet-activating factor
- · Loss of barrier function leading to tissue edema
- Release of further inflammatory mediators
- Promotion of clotting, via clotting factors and thrombin
- Apoptosis secondary to activated monocytes promoting programmed cell death, which in turn accelerates the proinflammatory response

associated organ dysfunction. This imbalance appears to be influenced by genetic factors, in that polymorphisms of various types appear to predispose to susceptibility to septic shock and clinical outcome<sup>5,12</sup> (Table 26-1).

#### WHY DO ORGANS BECOME DYSFUNCTIONAL AFTER THE ONSET OF INFLAMMATION?

Autopsy studies have shown that there is a discordance between histologic findings and the degree of organ dysfunction seen in patients who have died from sepsis. Immunocytochemistry shows that although there was a profound loss of cells of the adaptive immune system, cell death in the heart, kidney, liver, and lung was relatively minor and not reflective of the clinical severity of organ dysfunction.<sup>11</sup> Moreover, despite changes in the microvasculature, elevated tissue oxygen levels have been demonstrated in experimental sepsis, suggesting inefficiency of cellular oxygen utilization may be more significant than a failure of oxygen delivery or microvascular shunting.<sup>5</sup> This results in an inability of cells to perform normal processes such as protein synthesis, DNA repair, and membrane pump activity. When this failure is severe and widespread, organ function is compromised.<sup>13</sup> Further, NO and its metabolite peroxynitrite are potent inhibitors of the electron transport chain and have been shown to inhibit mitochondrial function (and therefore oxygen utilization) in several studies.<sup>13</sup> Clinically, patients with sepsis have a low oxygen extraction ratio (defined as the oxygen uptake/oxygen delivery ratio), indicating poor tissue uptake or utilization. This is shown by an elevated mixed venous saturation measured through a pulmonary artery catheter.<sup>14</sup> Decreased oxygen utilization may be an adaptive mechanism to survive severe and prolonged physiologic stress, but the mechanisms are as yet unproved.<sup>13</sup>

## HOW DOES INFLAMMATION AFFECT INDIVIDUAL ORGAN SYSTEMS?

#### Cardiovascular System

In a recently published study, global left ventricular (LV) hypokinesia (as defined by LV ejection fraction, EF, of <45%) was present in about 60% of patients with septic

shock. Primary LV dysfunction (defined as LVEF of <45% on admission) was present in 39% of patients on admission, and a further 21% developed LV hypokinesia over the next 1 to 2 days (secondary hypokinesia). Right ventricular kinetics correlated with LV findings in this study.<sup>15</sup> Previous studies have revealed similar results.<sup>16</sup> These changes were reversible in survivors within 7 to 10 days.<sup>17,18</sup> The changes were less profound in those who died.

Survivors of septic shock have decreased systolic function, a reduced EF, and an increase in left ventricular end diastolic volume (LVEDV). Decreased cardiac filling is almost universally present in early sepsis owing to increased vascular permeability and venodilation. This reduces stroke volume and cardiac output and causes a potential oxygen supply and demand problem for various vascular beds. Baroreceptor-mediated tachycardia occurs to maintain cardiac output in the event of decreased stroke volume. Excessive tachycardia leads to a decrease in diastolic filling time and decreased LVEDV. Despite reduced EF, cardiac output tends toward normal or increased despite moderate to severe myocardial dysfunction. This is achieved through a combination of tachycardia, increased diastolic ventricular dimension, and decreased systemic vascular resistance (SVR).

The physiologic response to a reduced EF is an increase in LVEDV, which increases myocardial fiber stretch and, through Starling's law, provides an increase in stroke volume.<sup>7</sup> After fluid resuscitation, septic patients manifest decreased SVR and increased cardiac index. Therefore, frequent fluid boluses may be required to maintain adequate stroke volume and mean arterial blood pressure (MAP). A decrease in heart rate after fluid resuscitation is associated with improved outcome.<sup>7</sup>

LV diastolic dysfunction is defined by abnormalities of diastolic distensibility, filling, or relaxation, independent of the EF.<sup>7</sup> The inability of the LV to fill at low atrial pressures can result from impaired ventricular compliance (a material property of the myocardium) or from alteration in ventricular relaxation (an active process). It has been hypothesized that impaired compliance occurs as a result of neutrophil infiltration, myocardial edema, ionic derangements, impaired intracellular calcium trafficking, and reduced myofilament calcium sensitivity. Extracardiac factors such as pericardial disease and intrathoracic pressure also affect ventricular stiffness and, hence, filling.<sup>5</sup>

Early theories of myocardial dysfunction suggested that global myocardial ischemia was a potential cause of impaired function. However, in contrast to patients with shock attributable to other causes, those with sepsis have high coronary blood flow, low vascular resistance, and diminished coronary artery–coronary sinus oxygen difference—decreased oxygen extraction, analogous to that seen in peripheral circulation. Increased lactate extraction, decreased free fatty acid extraction, and decreased glucose uptake provide further evidence that global ischemia is not present in patients with septic shock.<sup>17,18</sup> In sepsis, endothelial and vascular endothelial cells can produce substances likely to alter vascular tone, cause hyporeactivity to pressor agents, and depress myocyte contractility.<sup>17</sup> Thus, NO has been implicated in the reduction of calcium

influx through cyclic guanosine monophosphate inhibition of  $\beta$ -adrenergic receptors leading to depressed myocardial function. In sepsis, the large amounts of NO produced by iNOS substantially decrease vascular tone and are thought to contribute to decreased reactivity to pressor agents, causing a reduction in systemic vascular resistance and therefore afterload, which can be beneficial in the context of LV dysfunction.<sup>17</sup> Elevated levels of NO are also associated with downregulation of  $\beta$ -adrenergic responses, resulting in decreased autonomic control of both heart and vascular systems. Heart rate variability (HRV) is strongly influenced by sympathetic and parasympathetic tone. Poor HRV is a sign of autonomic dysfunction and cardiac dysfunction in sepsis.

Serum levels of troponin are elevated in sepsis. Higher levels are associated with lower EF, higher catecholamine requirements, and a higher mortality rate, but are nonspecific. Elevated B-type natriuretic peptide, also elevated in sepsis, is associated with poorer outcome, but again, is not specific to cardiac dysfunction in sepsis.

Resuscitation strategies include the administration of fluids and catecholamines to restore vascular tone and contractility. Vasopressin has been used as an adjunct to catecholamines in patients who have septic shock.<sup>19</sup> Patients with sepsis are relatively vasopressin deficient in addition to being hyporeactive to  $\beta$ -adrenergic agonists. It is thought that exogenous vasopressin can restore vascular tone and blood pressure, reducing the need for high-dose, potentially toxic, catecholamine inotropes and pressors. Although low-dose vasopressin therapy does not reduce mortality rates compared with noradrenaline alone, in the subgroup of patients with less severe shock, the mortality benefit is significant (risk reduction, 25.8%). These findings are in keeping with previous laboratory models in which vascular responsiveness correlated with shock severity.<sup>20</sup> Further investigation is required to establish the role of high-dose vasopressin in the management of severe septic shock.

#### **Renal System**

Acute renal failure is classically defined as an abrupt and sustained decrease in renal function. Acute renal failure may occur in 19% of patients with moderate sepsis, 23% of patients with severe sepsis, and 51% with septic shock.<sup>21</sup> The combination of acute renal failure and sepsis is associated with a 70% mortality rate, compared with 45% for acute renal failure alone.<sup>21</sup>

Deficiencies in existing definitions led to a consensus of the Acute Dialysis Quality Initiative group (2003), who have proposed criteria for three grades of increasing severity based on the RIFLE classification (*r*isk of acute renal failure, *in*jury to the kidney, and *f*ailure of kidney function and two outcome classes—loss of kidney function and *e*nd-stage kidney disease).<sup>22</sup> The subsequently modified RIFLE criteria do not require prior knowledge of baseline creatinine but rather of only two values over 48 hours (Table 26-2).

Septic acute renal failure is defined as RIFLE criteria for acute kidney injury (AKI) plus consensus criteria for sepsis.<sup>1</sup> In a recent study from the United Kingdom, 35.8% of patients admitted to the ICU fulfilled criteria for AKI. Any

Stage	RIFLE Creatinine Criteria	Modified Rifle Creatinine Criteria	Urine Output		
AKI stage 1: risk	Increase in serum creatinine $\times$ 1.5 from baseline or decrease of GFR $>$ 25%	Serum Cr 0.3 mg/dL (>26.4 μmol/L) or increase to > 1.5 to 2 times initial	<0.5 mL/kg/hr for >6 hr		
AKI stage 2: injury	Increase in serum creatinine $\times$ 2 from baseline or decrease of GFR $> 50\%$	Increased serum $> 2$ to 3 times initial	<0.5 mL/kg/hr for >12 hr		
AKI stage 3: failure	Increase in serum creatinine $\times$ 3 from baseline or decrease GFR $>$ 75% or serum Cr $>$ 4 mg/dL	Increased serum $> 3$ times initial or serum Cr $> 4$ mg/dL (>354 $\mu$ mol/L) with acute rise of at least 0.5 mg/dL	<0.3 mL/kg/hr for >24 hr or anuria for 12 hr		

Table 2	26-2 <b>Co</b> r	nparison	of Modified	I RIFLE and	I RIFLE Crite	eria for Acu	te Kidnev	Injury

AKI, acute kidney injury; Cr, creatinine; GFR, glomerular filtration rate.

(From Ostermann M, Chang RW. Acute kidney injury in the intensive care unit according to RIFLE. Crit Care Med. 2007;35:1837-1843; and Joannides M. Diagnosis of acute renal failure. In: Waldmann C, Soni N, Rhodes A, ed. Oxford Desk Reference Critical Care. New York: Oxford University Press; 2008.)

degree of AKI was associated with increased all-cause ICU and hospital mortality. In all RIFLE categories, hospital mortality increased as the number of failed organ systems increased. This mortality was further enhanced by severity of renal impairment.<sup>22</sup>

Renal blood flow cannot be measured continuously in humans. Whether AKI is secondary to changes in cardiac output in sepsis is unclear. However, some studies have shown decreased cardiac output leading to decreased renal blood flow, a fall in glomerular filtration rate (GFR), metabolic deterioration, and cell death. Others have shown that renal blood flow participates in systemic vasodilation seen during sepsis, so renal blood flow does not diminish, and ARF occurs in the setting of adequate or enhanced renal perfusion.<sup>24</sup> Human sepsis is normally hyperdynamic, with normal or raised renal blood flow and decreased renal vascular resistance. Glomerular function is dependent on the glomerular filtration pressure (GFP). This is maintained by afferent and efferent arteriolar contraction. If the afferent arteriole constricts, GFP falls, resulting in decreased GFR and reduced urine output. If the afferent arteriole dilates, the converse happens. In the context of systemic hyperemia, if the afferent arteriole dilates, but the efferent arteriole dilates even more, despite increased blood flow, the GFP still falls, reducing GFR.<sup>24,25</sup> There is no firm evidence to support this hypothesis, although it is physiologically plausible. A decreased GFR would be achieved by either afferent constriction or efferent dilatation.

NO-induced arteriolar dilation results in arterial underfilling and baroreceptor activation. This increases sympathetic activity in the cardiorespiratory center of the brain, with release of vasopressin from the posterior pituitary, increased sympathetic tone, and activation of the renin-angiotensin system. As a result, renal efferent arterioles constrict, with sodium and water retention. Cytokine activation and the arachidonic acid-derived thromboxanes and leukotrienes reduce renal blood flow. Finally, the kidney is susceptible to leukocyte-mediated tissue injury with neutrophil aggregation in response to chemokines and production of proteases and reactive oxygen species. Peroxynitrite causes tubular damage, and glomerular microthrombi contribute to AKI. Kidney damage appears to be toxically, rather than hemodynamically, mediated, although intrarenal blood flow varies, global renal perfusion is related to cardiac output, and there is little evidence that this is reduced in human sepsis.<sup>21</sup>

#### **Respiratory System**

Respiratory dysfunction is common in patients with SIRS or sepsis and manifests as tachypnea, hypoxemia, and respiratory alkalosis. About 35% of patients with sepsis develop mild to moderate acute lung injury (ALI), and up to one fourth develop acute respiratory distress syndrome (ARDS). ALI and ARDS are defined clinically by gas exchange and chest radiographic abnormalities that occur shortly after a known predisposing injury in the absence of heart failure (Table 26-3).<sup>14,26,27</sup>

Table 26-3 Recommended Diagnostic Criteria for ALI and ARDS						
Criteria	ALI	ARDS				
Onset	Acute and persistent	Acute and persistent				
Oxygenation	$Pao_2/Fio_2 < 300 \text{ mm Hg or } 26.6 \text{ kPa}$	$Pao_2/Fio_2 < 200 \text{ mm Hg or } 39.9 \text{ kPa}$				
Chest radiograph	Bilateral infiltrates	Bilateral infiltrates				
Pulmonary artery wedge pressure	≤18 mm Hg; no evidence of increased left atrial pressure	≤18 mm Hg; no evidence of raised left atrial pressure				

ALI, acute lung injury; ARDS, acute respiratory distress syndrome. Data from references 14, 26, and 27.

Lung injury rarely occurs in isolation; it is usually the result of a pan-endothelial insult with inflammatory vascular dysfunction secondary to the cytokine storm seen in sepsis. The pulmonary bed is particularly prone to collecting interstitial fluid. The damage to the pulmonary vasculature increases the permeability of the endothelial membrane to fluids, resulting in capillary leakage of protein and immune cell–rich exudative fluid into the interstitium and alveoli.

Direct alveolar epithelial cell damage prevents fluid removal from the air spaces. Injury to pulmonary lymphatics also decreases fluid drainage and removal. Permeable pulmonary edema, fluid-filled airspaces, alveolar derecruitment, and intrapulmonary right-to-left shunting are hallmarks of lung injury. These factors reduce resting lung volume, decrease lung compliance, increase work of breathing, and adversely affect oxygenation.

ALI evolves through exudative, inflammatory, and fibroproliferative phases over a 2- to 3-week period. These phases are characterized by fluid accumulation, ingress of activated neutrophils, loss of surfactant and significant amounts of proteinaceous fluid, and markedly hemorrhagic interstitial and alveolar edema with eosinophilic hyaline membrane formation within the alveolus.<sup>12,28,29</sup> Neutrophils are the dominant cell type found on bronchoalveolar lavage in ARDS. They cause damage through production of free radicals, inflammatory mediators, and proteases. The proliferative phase occurs during the second or third week and is characterized by organization of the exudates and fibrosis within the intraalveolar space.<sup>28</sup> Later, the pathology is characterized by mononuclear cell infiltration, type II pneumocyte proliferation, and interstitial fibrosis-the fibrotic phase. The vasculature is grossly deranged as vessels are narrowed with mural fibrosis and intimal thickening.<sup>28</sup> Mild pulmonary hypertension occurs in ARDS as a result of vasoconstriction and occlusion of pulmonary microvasculature. Pulmonary interstitial edema may cause vascular compression and an increase in pulmonary arteriolar pressure. This, in turn, may promote hydrostatic edema formation. Hypoxic pulmonary vasoconstriction normally shunts blood from hypoxic to normoxic areas of lung. However, in ARDS, this has been shown to be unreliable because of exposure to both constricting and vasodilating mediators.<sup>28</sup> Constriction predominates despite circulating NO.

Thromboxane A<sub>2</sub> is a potent vasoconstrictor found in increased levels in ARDS. It promotes the formation of microemboli, ischemia-reperfusion injury, and vasoconstriction, causing perfusion abnormalities and impaired gas exchange.<sup>27</sup> Endothelin-1 release during sepsis also contributes to the pulmonary vasoconstriction. Microvascular thrombi are present in 95% of ARDS cases. Macroemboli have also been found and cause arteriolar occlusion, potentiating hypertension and hypoxemia.<sup>27</sup>

Inflammation leads to damage of type II pneumocytes, causing a reduction in synthesis and recirculation of surfactant. Alveolar surfactant is contaminated by proteinaceous alveolar exudates, reducing its functional capacity.<sup>28</sup> This leads to further decreases in compliance and atelectasis. Ventilatory strategies, oxygen toxicity, and large-volume fluid resuscitation amplify the degree

of lung dysfunction. Epithelial cell apoptosis and necrosis occur as a result of recruitment and de-recruitment shear stress. There is some evidence that adverse ventilatory strategies (low positive end-expiratory pressure, high tidal volume) increase capillary stretch, increase hydrostatic pressure, increase fluid leak, increase production of lung-derived cytokines, and cause endotoxin and bacterial translocation from lung to the systemic circulation.<sup>29,30</sup>

#### **Central Nervous System**

Interactions between the immune and the central nervous systems are considered to be a major factor in the pathogenesis of the host response in septic shock. The prevalence of encephalopathy in sepsis varies from 9% to 71% depending on the definition. The severity of encephalopathy is related to severity of illness as assessed by the Acute Physiology and Chronic Health Evaluation (APACHE) II or organ dysfunction scores. It also is associated with mortality.<sup>31</sup> Septic patients present with clinical features of encephalopathy that include agitation, confusion, and coma.

In postmortem studies, various cerebral lesions have been found. These include ischemia, hemorrhage (26%), microthrombi (9%), microabscesses (9%), and multifocal necrotizing leukoencephalopathy (9%).<sup>12,31</sup>

Septic encephalopathy can be defined as an impaired mental state in the context of defined extracranial infection and sepsis.<sup>32</sup> Septic patients also may have renal and hepatic dysfunction, electrolyte disturbances, acid-base alterations, hypoglycemia or hyperglycemia, hypotension, hypoxemia, and hypothermia or hyperthermia. They may be sedated, ventilated, or paralyzed, all of which affect neurologic status and confuse the diagnosis of septic encephalopathy. Electroencephalography is useful in diagnosing septic encephalopathy in these circumstances.<sup>32</sup> It is sensitive and noninvasive. The severity of encephalopathy can be graded on electroencephalographic criteria or Glasgow Coma Scale.<sup>32</sup>

Disturbances to the central nervous system result in behavioral, neuroendocrine, and autonomic dysfunction. The brain is normally well protected from the immune system by the blood-brain barrier. However, as seen in other organ systems, endothelial dysfunction and disruption alter the permeability of the barrier and allow entry of inflammatory mediators and neurotoxic molecules. Endothelial inflammation also results in cerebrovascular dysfunction, hypoperfusion, and ischemia.<sup>31</sup>

TNF- $\alpha$  enhances the production of endothelin, inhibits the formation of NO in cerebral endothelial and smooth muscle cells, reduces cerebral oxygen uptake and cerebral blood flow, and raises intracranial pressure.<sup>32</sup> Disruption of the blood-brain barrier allows the high levels of circulating catecholamines to influence cerebral vascular resistance directly. Cerebral perivascular edema limits diffusion of oxygen, nutrients, and cellular waste.<sup>32</sup> Activated leukocytes generate oxygen free radicals that react with erythrocyte cell membranes and reduce the deformability of the cells. These abnormally shaped erythrocytes are unable to squeeze through microvessels, exacerbating hypoperfusion.<sup>32</sup> Muscle catabolism causes increased circulating and cerebral levels of tyrosine, tryptophan, and phenylalanine. The severity of septic encephalopathy can be predicted from plasma concentrations of these amino acids, suggesting that they contribute to the pathophysiology, perhaps by altering levels of neurotransmitters.<sup>32</sup>

#### **Neuroendocrine System**

The brain modulates the response to stress through four efferent pathways: the hypothalamic-pituitary-adrenal axis, vasopressin (see "Renal System"), the sympathetic nervous system (see "Cardiovascular System"), and the cholinergic anti-inflammatory pathway. NO activity within the brain appears particularly active toward neuroendocrine and autonomic nuclei, causing apoptosis and disrupting the response to sepsis.<sup>31</sup> Suppression of the hypothalamic-pituitary-adrenal axis is common in sepsis. This results in loss of circadian rhythm and may cause adrenal insufficiency. Adrenal insufficiency is defined as baseline cortisol level of less than 15  $\mu$ g/dL, or a change of less than 9  $\mu$ g/dL after administration of 250  $\mu$ g of adrenocorticotropic hormone (ACTH).

Historically, a flat ACTH stimulation test was associated with a poor response to pressors and increased mortality<sup>31</sup>; however, the use of such tests and subsequent treatment with hydrocortisone have been controversial. The effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality were evaluated in patients with septic shock, separating patients into "responders" and "nonresponders" based on their response to a short ACTH stimulation test.<sup>33,34</sup> Although steroid therapy significantly reduced mortality in nonresponders from 63% to 53%, there was no difference in mortality in responders. The suggestion was that all septic patients should have a short ACTH stimulation test and that steroids should be commenced for 7 to 11 days pending test results. By contrast, a large-scale recent study showed that low-dose steroid treatment had no effect on mortality at 28 days in either responders or nonresponders. The authors recommended that low-dose hydrocortisone should only be prescribed in patients with "vasopressor-resistant" septic shock, a significant change from previous recommendations.<sup>34</sup>

#### Hepatosplanchnic System

The portal system drains directly into the liver. One third of the liver's blood supply also comes directly from the systemic circulation. The liver is well placed to detect the presence of microbes and toxins from either the gut or the systemic circulation.<sup>12</sup> As part of the reticuloendothelial system, it is an important site for clearance of bacterial endotoxin, and hepatic production of proinflammatory cytokines can result in distant effects, particularly on the lung.<sup>12</sup> When the liver is injured, cytokines are released, resulting in an SIRS response. Microcirculatory changes in liver sinusoids, neutrophil sequestration, and platelet activation contribute to hepatic dysfunction.<sup>35</sup> Decreased arterial pressure and splanchnic blood flow result in decreased hepatic sinusoidal perfusion. Decreased perfusion to hepatic Kupffer cells and endothelial cells results in release of inflammatory mediators, swelling, distention, and leakage of endothelium and tissue injury.<sup>36</sup>

The endothelium becomes procoagulant, leading to the formation of fibrin clots and microemboli. These plug sinusoids, reducing sinusoidal flow velocity, microvascular ischemia, and dysfunction. The liver appears to be well protected from septic insult. Generally, liver dysfunction occurs late in sepsis and is associated with worse outcome.<sup>12</sup> The defining clinical symptoms are coagulopathy (Prothrombin time [PT] > 30; international normalized ratio > 2.0) and encephalopathy. Hypoglycemia may occur.<sup>37</sup>

The intestinal mucosa functions as a major local defense barrier, preventing bacteria and endotoxin within the gut lumen from escaping into the systemic circulation. Injury can occur directly or may be secondary to generalized inflammation.<sup>38</sup> Damage to the gut may alter barrier function. This may be important in the maintenance and amplification of the inflammatory response.<sup>39</sup>

Nutritional support may help prevent organ failure by providing substrates to cells involved in wound healing and the immune response and preserving muscle function in the catabolic state. Enteral feeding can preserve gut integrity and function, maintain bile secretion, maintain immunoglobulin A secretion and function of gut-associated lymphoid tissue (which plays a major role as a barrier against intestinal translocation of bacteria), and enhance splanchnic blood flow and mesenteric oxygen utilization in sepsis.<sup>40</sup> Early nutritional support, provided within 24 hours of admission, may reduce mortality in the critically ill by 8% to 13%,<sup>41</sup> although a recent randomized controlled trial failed to show a reduction.<sup>42</sup>

#### Hematologic Abnormalities

Coagulation abnormalities have been discussed in the context of endothelial dysfunction and inflammation. Disseminated intravascular coagulation (DIC) may complicate sepsis. It is an acquired syndrome characterized by the formation and deposition of fibrin in the microvasculature. This leads to diffuse obstruction of the vascular bed resulting in diffuse skin necrosis, ischemia, and progressive organ dysfunction. Diffuse bleeding may result from consumption of clotting factors.<sup>43</sup> Thrombocytopenia, prolonged prothrombin time and activated partial thromboplastin time, low fibrinogen levels, and elevated D-dimers (or fibrin degradation products) are characteristic of DIC.

Because sepsis is inherently procoagulant, anticoagulant therapies have been studied as potential treatments. Drotrecogin alfa (activated) is the recombinant form of human activated protein C (APC). APC is an endogenous protein that has been shown to inhibit thrombin generation and inflammation and to promote fibrinolysis. As such, it is an important modulator of coagulation and inflammation. Therapy with APC may decrease mortality and reduce organ failure in patients with severe sepsis (APACHE II score > 25, or multiorgan failure),<sup>44,45</sup> but is not effective in those at low risk for death. Moreover, a trend toward a higher rate of serious bleeding in APC recipients suggests recent trauma or stroke, and gastrointestinal ulceration or markedly abnormal clotting profile should be considered risk factors and may preclude treatment.<sup>44,45</sup> The trial data are the subject of much discussion, and the use of APC should be dictated by local protocol.

#### **Metabolic Dysfunction**

The acute toxicity of high glucose levels may be related to cellular glucose overload, resulting in oxidative stress. This effect is most profound in areas of high glucose uptake: liver, neurones, gut, renal tubular cells, immune cells, and endothelium.<sup>12</sup> Protein metabolism is also profoundly affected in sepsis, and skeletal muscle catabolism increases, resulting in wasting and weakness.

#### HOW CAN THE CLINICIAN DETECT ORGAN DYSFUNCTION?

The sepsis syndromes are defined by clinical perturbations. Consequently, although C-reactive protein and procalcitonin levels are raised in sepsis, they represent nonspecific markers of inflammation, and a full clinical history and examination are mandatory in providing relevant background information concerning the precipitating condition. A full assessment must include bedside monitoring of those indices that define the sepsis syndromes: body temperature, respiratory rate and pattern, pulse rate, blood pressure, peripheral perfusion, and capillary refill rate. Urine output, serum creatinine levels, and Glasgow Coma Scale provide some indication of renal and central nervous system function.

Hematologic and biochemical indices (blood count, electrolytes, blood-urea nitrogen, creatinine, liver function, coagulation profile, C-reactive protein, glucose, lactate, and random blood cortical) provide more specific information concerning organ dysfunction. Further, formal assessments of global tissue perfusion are helpful. These include assessment of acid-base status, mixed venous blood oxygen saturation, and lactate levels. Each may indirectly reflect the balance between oxygen supply and demand. Interpretation of these markers is aided by hemodynamic and preferably echocardiographic monitoring of cardiac output, contractility, filling, and response to fluid challenge and vocative (pressor, isotropic) therapies.

Microbiologic assessment through culture of relevant tissue and biologic fluids and serologic assessment are mandatory. This may necessitate bronchoscopy and lung lavage, lumbar puncture, or other invasive procedures.

Specialized investigations may be required either to quantify organ dysfunction (e.g., electroencephalography if septic encephalopathy is considered) or to facilitate diagnosis (e.g., abdominal ultrasound or computed tomography to eliminate obstruction of the genitourinary tract). Evaluation of capillary blood flow through the use of fiberoptic systems, measurements of tissue oxygen consumption, and tissue biopsy to assess mitochondria function remain research tools at present.<sup>46–49</sup>

#### HOW DOES ORGAN DYSFUNCTION CONTRIBUTE TO PROGNOSIS AND CLINICAL OUTCOME?

Mortality increases with increasing numbers of dysfunctional organs and the duration of such failure and is reflected in severity of illness scoring systems. Indeed, these were devised to provide standardized definitions of organ dysfunction so that the incidence and relevance of morbidity (rather than mortality) could be compared. Thus, the Multiple Organ Dysfunction Score (MODS), which is used to measure severity of organ failure, correlates strongly with ultimate risk for ICU and in-hospital mortality and has been shown to reflect the progression of organ dysfunction when measured sequentially.<sup>46</sup> The Sequential Organ Failure Score (SOFA), devised by the European Society of Intensive Care Medicine, also is well validated, simple, and reliable. A third system, the logistic organ regression score, was developed using analysis of physiologic variables in a large cohort of ICU patients. In contrast to others, it was devised to maximize predictive value for mortality, although its prognostic value is no better than that of other scores.

Organ dysfunction scores may be inferior to severity of illness scores (e.g., APACHE III, Simplified Acute Physiology Score [SAPS]) because they do not consider premorbid status.<sup>2,46</sup> Rather, they can be used to monitor disease progression. Specific factors that influence the prognosis in sepsis include the type and source of infection, the age and response of the host, and predisposing and preexisting clinical conditions. Cardiovascular dysfunction has the most significant effect on mortality in sepsis, followed by renal, neurologic, and respiratory systems.<sup>2,46</sup>

#### AUTHORS' RECOMMENDATIONS

- The pathophysiology of multiorgan failure in sepsis is the product of a complex and intricate host response to insult comprising inflammatory mediators, extracellular and intracellular cell signaling pathways, the microvasculature, and cell metabolism.
- Multiple-organ dysfunction significantly worsens prognosis and outcome.
- Early assessment, diagnosis, and treatment are vital to improve survival.

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## Bacterial Translocation and Gut-Derived Sepsis: Do They Exist?

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Any attempt at answering questions concerning bacterial translocation and gut-derived sepsis is confounded by both these terms meaning different things to different people. Therefore, the first step in discussing this topic is to establish a common vocabulary (Table 27-1) and to clarify the important point that bacterial translocation and gut-derived sepsis may occur *independently* of each other. That is, bacterial translocation may occur in the absence of gut-derived sepsis, or the patient may have gut-derived sepsis in the absence of documented bacterial translocation. Therefore, in addressing the question of whether bacterial translocation and gut-derived sepsis exist, the two terms should not be linked together but looked at separately. In fact, as will be documented later in this review, the phenomenon and clinical relevance of bacterial translocation have been studied mainly in patients undergoing abdominal surgery. In contrast, the incidence and clinical importance of gut-derived sepsis and its consequences, such as organ failure, have been studied mainly in critically ill or injured intensive care unit (ICU) patients, in whom the diagnosis is based on measurements of gut permeability and not bacterial translocation. Thus, the patient populations in which bacterial translocation can be

#### Table 27-1 Bacterial Translocation and Gut-Derived Sepsis: A Common Vocabulary

*Bacterial translocation* is best defined as the process by which intestinal bacteria or candida cross the intestinal mucosal barrier to reach the mesenteric lymph nodes, from which they may or may not spread systemically and cause infection.

- The diagnosis of bacterial translocation requires the identification of intestinal bacteria in the intestinal lymph nodes.
- *Gut-derived sepsis* is best defined as the process whereby gut-derived proinflammatory, tissue-injurious microbial and nonmicrobial factors induce or contribute to the development of systemic inflammatory response syndrome, acute respiratory distress syndrome, or multiple-organ dysfunction syndrome. This process may or may not occur in presence or absence of gut-origin systemic infection or bacterial translocation.
  - The diagnosis of gut-derived sepsis is based on measurements of gut barrier function (permeability) in conjunction with the clinical response of the patient.

directly measured are not critically ill and have a low likelihood of developing multiple-organ dysfunction syndrome (MODS). In contrast, bacterial translocation cannot be directly measured in critically ill patients, who are at the highest risk for developing gut-derived sepsis and MODS.

During the past three decades, the notion that the gut and its contents can induce, contribute to, or perpetuate systemic inflammatory response syndrome (SIRS), acute lung injury (ALI), acute respiratory distress syndrome (ARDS), and MODS, as well as function as a reservoir for bacterial infection, has gained attention.<sup>1</sup> During this time period, literally hundreds of studies have examined the role and relevance of intestinal barrier failure, bacterial translocation, and gut-derived sepsis in multiple patient populations. Based on both clinical and experimental studies, the answer to the question, Do bacterial translocation and gut-derived sepsis exist? appears to be yes. However, the clinical relevance of bacterial translocation in the pathogenesis of sepsis and organ failure is more controversial. The controversy revolves around the failure to consistently find gut-derived bacteria or bacterial products, such as endotoxin, in the blood of critically ill or injured septic-appearing patients with MODS. We believe that the first step in resolving this controversy concerning the clinical relevance of the stressed gut in the pathogenesis of sepsis, ARDS, and MODS is to expand our focus from bacterial translocation to include gut barrier failure and gut-derived nonmicrobial, proinflammatory, tissue-injurious factors. This concept is based on the notions that loss of gut barrier function, even in the absence of systemic bacteremia or endotoxemia, can cause a septic state and contribute to distant organ dysfunction and that nonmicrobial factors released from the stressed gut are sufficient to induce both organ injury and a septic state.<sup>2</sup> Simply stated, it is now time to dissociate the process of bacterial translocation from the pathophysiology of gut-derived sepsis because, although the two may occur together, gut-origin sepsis does not require bacterial translocation. Thus, the goal of this chapter is to trace the evolution of gut-origin sepsis and MODS and put these disorders, as well as the phenomenon of bacterial translocation, into clinical perspective. To do this, we use the results of clinical and some preclinical studies to answer
the following questions concerning gut-derived sepsis and bacterial translocation: Do they exist? Are they of clinical relevance? What can we do about each of them?

# DO BACTERIAL TRANSLOCATION AND GUT-DERIVED SEPSIS EXIST, AND ARE THEY CLINICALLY RELEVANT?

The idea of translocation of normal intestinal microflora is not new. As early as the 1940s, experimental studies showed live bacteria of enteric origin in the peritoneal washings of dogs after hemorrhagic shock.<sup>3</sup> In the 1960s, Fine and coworkers documented that bacteria and endotoxin originating from the gut can gain access to the systemic circulation in shock states.<sup>4–6</sup> In the following two decades, multiple investigators established that bacteria do translocate from the gut to the mesenteric lymph nodes and, if the insult is serious enough, to the systemic circulation. This process was termed *bacterial translocation*.<sup>7–10</sup>

The concept of bacterial translocation gained clinical attention in the late 1980s because it clarified the clinical observation of how critically ill patients could develop endotoxemia or bacteremia with enteric organisms without an identifiable source of infection being found even at autopsy.<sup>11</sup> However, studies to establish whether bacterial translocation occurs in patients were more difficult to perform than the preclinical animal studies carried out to establish the concept of bacterial translocation and gutorigin sepsis. This is because a laparotomy to harvest and culture mesenteric lymph nodes is necessary to definitively establish that bacterial translocation has occurred. Although any or all of the following clinical observations might suggest that bacterial translocation is occurring, these findings are not definitive: (1) increased gut permeability, (2) the presence of enteric bacteremias or endotoxemia in the absence of an identifiable focus of infection, and (3) the finding that the gut is the reservoir for the specific bacteria causing an infection. Consequently, the initial proof-of-principle studies that established that intestinal bacteria do translocate to intestinal lymph nodes were carried out in patients undergoing abdominal surgery either for inflammatory bowel disease<sup>12</sup> or simple small bowel obstruction.<sup>13</sup>

Subsequently, similar results were observed in a study measuring bacterial translocation in organ donors.<sup>14</sup> In this study, bacterial translocation was documented in 67% of the organ donors, and the bacteria recovered from the lymph nodes and other tissues were identical to those isolated from the bowel contents. Since then, six additional clinical series totaling 2125 patients undergoing abdominal surgery have shown that the incidence of bacterial translocation ranges from 5% to 21% and that in each of these studies, bacterial translocation was associated with a significant twofold to threefold increase in the rate of septic complications.<sup>15–20</sup> Furthermore, in about half of these patients, the same organism was identified in the mesenteric lymph nodes as in the postoperative septic focus.<sup>15–20</sup> The notion that the gut was the reservoir for these translocating bacteria has been strengthened further by genomic studies showing that the bacteria in the mesenteric lymph nodes originated from the patients, gut flora.<sup>21</sup> Thus, several studies of patients undergoing laparotomy have validated the concept that bacterial translocation occurs and that bacterial translocation is associated with a significantly higher incidence of systemic infectious complications in patients undergoing abdominal surgery.

Consistent with animal studies documenting that bacteria translocate from the gut to the pancreas in experimental pancreatitis models,<sup>22</sup> bacterial translocation has been implicated as the mechanism by which the ischemic-necrotic pancreas becomes infected in patients with severe pancreatitis. This assumption was based on work showing that intestinal permeability is increased in these patients and that increased gut permeability correlates with endotoxemia, organ failure, and morbidity.<sup>23</sup> Another disease in which bacterial translocation appears to occur is cirrhosis. In addition to animal studies, a recent clinical study documented that bacterial translocation to the mesenteric lymph nodes occurred in patients with cirrhosis and that the incidence of bacterial translocation increased from 3% to 31% as the magnitude of the liver dysfunction (Child score) increased.<sup>24</sup> Further, bacterial translocation appears to be the mechanism by which primary peritonitis occurs in cirrhosis with ascites.<sup>25</sup> Thus, bacterial translocation has been documented to occur in several groups of patients, and in many of these patient groups, the translocating bacteria are involved in the pathogenesis of infection.

Bacterial translocation and gut-derived sepsis have been studied to determine their link to the development of SIRS, ARDS, and MODS as well as systemic infection in two additional major groups of patients. These two patient groups consist of mechanically or thermally injured patients as well as critically ill ICU patients. In these patient populations, the results are more confusing because the ability to sample mesenteric lymph nodes is not possible in most of these patients. For this reason, most studies have used measures of gut barrier function to examine the hypothesis of gut-derived sepsis. Most of these studies used increased intestinal permeability as a marker for patients at risk for developing gut-derived sepsis or MODS. For example, studies have shown that intestinal permeability is increased in patients with thermal injuries shortly after the injury<sup>26</sup> and that the magnitude of the increase in gut permeability correlates with the size of the burn injury<sup>27</sup> and with the risk for developing infection.<sup>28</sup> Similarly, studies of gut permeability have consistently documented that intestinal permeability is increased in severely injured trauma patients<sup>29-32</sup> and ICU patients.<sup>33,34</sup> However, only two of these six studies<sup>29,34</sup> found a clear association between the magnitude of the increase in gut permeability and infectious complications. This casts some doubt on the hypothesis that loss of gut barrier function consistently leads to infection. On the other hand, the prospective study by Doig and associates<sup>34</sup> found that increased intestinal permeability accurately predicted the development of MODS and that the patients who developed MODS had persistently elevated levels of gut permeability. Thus, based on clinical studies using gut permeability as a surrogate marker for bacterial translocation or gut-derived sepsis, there is suggestive,

but not conclusive, evidence that loss of gut barrier function contributes to the development of systemic infection and MODS. However, in interpreting these clinical results, it is important to consider that the process of developing an infection or MODS is complex and is determined by a number of factors. These include many host-related immune, metabolic, and inflammatory factors, only one of which is altered gut permeability.<sup>35</sup>

In trauma patients, some studies have been performed to directly test for bacterial translocation. In these studies, bacterial translocation to the mesenteric lymph nodes was documented in most patients, in whom nonculture methodology, such as electron microscopy<sup>36</sup> or the measurement of bacteria-specific markers,37 was used. However, in the three clinical studies in which culture techniques were employed, the incidences of bacterial translocation to the mesenteric lymph nodes were 25%,38 33%,39 and 0%.<sup>38–40</sup> Additionally, these three studies did not demonstrate a relationship between bacterial translocation and outcome. However, only 67 patients were evaluated in these three clinical studies. Conversely, two other studies documented that a significant percentage of very severely injured trauma patients presenting to the emergency room had bacteremia.41,42

In fact, it was the clinical trauma study by Moore and colleagues<sup>38</sup> that cast the greatest amount of doubt on the hypothesis that bacterial translocation contributed to the development of sepsis and MODS. In this study, portal blood samples were not found to contain bacteria or endotoxin, even in the subgroup of patients who subsequently developed MODS. This led the authors to question the clinical relevance of bacterial translocation. Yet, this notion that loss of gut barrier function failed to contribute to the development of SIRS and MODS was based on the supposition that it is bacteria and their products exiting the gut through the portal circulation that contribute to the development of trauma-induced sepsis and organ failure. Recent studies call this assumption into question.<sup>2</sup> Specifically, based on rodent, porcine, and nonhuman primate studies, it now appears that the early onset of SIRS and organ failure after trauma or shock are due to nonbacterial, tissue-injurious, proinflammatory factors liberated from the stressed gut that reach the systemic circulation through the mesenteric lymphatics rather than the portal venous system.<sup>2</sup> This has resulted in the gutlymph hypothesis of SIRS, ARDS, and MODS.<sup>2</sup> Although these preclinical studies remain to be tested clinically, they do resolve the paradox of how gut-derived sepsis and MODS can occur, and yet neither bacteria nor endotoxin was found in the portal blood of the trauma patients shortly after injury in the study by Moore and colleagues.<sup>38</sup>

What can be learned from these clinical studies concerning the question of whether bacterial translocation and gut-derived sepsis exist and, if so, what is their potential clinical relevance? To answer these questions, one must specify the exact patient populations being studied, the methods used to identify gut-derived sepsis, and the clinical outcomes of interest. Based on direct measurements, bacterial translocation undoubtedly does occur in patients undergoing elective and urgent abdominal surgery, and in these patient populations, its occurrence significantly increases the risk for systemic infection.<sup>13–21</sup> In other high-risk patients, such as those with severe pancreatitis or cirrhosis,<sup>23-25</sup> bacterial translocation also appears to occur and contribute to septic complications. However, direct data supporting bacterial translocation in trauma,<sup>36-42</sup> burn, and ICU patients are either conflicting or nonexistent. Although several studies in burn and ICU patients find an association between gut barrier dysfunction and the development of systemic infections or organ dysfunction, 28,29,34 others do not. Thus, the answer to the question, Does bacterial translocation exist? is yes, but its clinical relevance appears to depend on the patient population being studied. However, the field of gut-origin sepsis and organ failure, especially in trauma and ICU patients, has advanced from postulating that gut failure leading to organ dysfunction and SIRS is a purely microbial phenomenon and now includes a role for nonbacterial factors in the transduction of splanchnic ischemia into distant organ dysfunction and SIRS (Fig. 27-1).

### WHAT CAN WE DO ABOUT IT?

Based on the concept that bacterial translocation and gutderived sepsis exist and that increased intestinal permeability is bad, the ability of gut-directed treatment strategies to improve clinical outcome has been tested. In developing and evaluating potential gut-directed therapeutic options, it is important to understand both the rationale behind the therapy and its target. In the specific case of bacterial translocation and gut-derived sepsis, it is possible to lump the therapeutic approaches used into one of two groups: (1) those therapies directed at the gut flora or (2) those therapies directed at limiting gut barrier dysfunction. This notion is based on extensive experimental evidence showing that the two key mechanisms underlying bacterial translocation are (1) intestinal bacterial overgrowth with potential pathogenic bacteria and (2) loss of gut barrier function.<sup>43</sup> In this context, therapies such as selective gut decontamination have been used to limit intestinal bacterial overgrowth, whereas early enteral nutrition has been used to support gut barrier function and to limit intestinal bacterial overgrowth. As discussed later, in general, these gut-directed therapies have met the goal of decreasing the incidence of systemic infection, although some have also reduced the incidence of MODS, and others have increased survival.

Prospective randomized controlled trials (RCTs) have shown that the adoption of early enteral nutrition to feed the gut as well as the body reduces the incidence of infectious complications in several different patient populations. These include trauma,<sup>44</sup> burn,<sup>45</sup> and critically ill patients.<sup>46,47</sup> Similarly, early enteral nutrition started within 6 hours of injury and shock has been shown in one prospective RCT study to reduce the incidence of organ failure and largely abrogated injury-induced increases in gut permeability when compared with patients whose feedings were started 24 hours or longer after injury.<sup>48</sup> Additionally, a second prospective RCT documented that the administration of an immuneenhancing enteral diet reduced the number of bacteremic



**Figure 27-1.** Schematic overview showing the different potential pathways and mechanisms by which a systemic insult can lead to bacterial translocation and/or gut-derived sepsis. In this paradigm, shunting of blood away from the splanchnic circulation leads to a gut ischemia-reperfusion injury, which in turn results in gut injury (loss of barrier function) and inflammation. In addition to the process of bacterial translocation, the stressed and inflamed gut appears to be the source of nonmicrobial sepsis- and multiple-organ dysfunction (MOD) syndrome–inducing factors that reach the systemic circulation through the intestinal lymphatics. ARDS, acute respiratory distress syndrome; MLN, mesenteric lymph node complex; SIRS, systemic inflammatory response syndrome.

episodes and increased survival in septic ICU patients.<sup>49</sup> Finally, early enteral nutrition has been shown to decrease septic complications and exert beneficial immunoinflammatory effects in patients with acute pancreatitis.<sup>50</sup> Thus, most prospective RCTs and meta-analyses have found that early enteral nutritional therapy is clinically beneficial in patients at increased risk for developing gut-derived sepsis and organ failure. Consequently, these clinical nutrition studies support not only the use of early enteral nutrition but also the notion that gut barrier failure is of clinical importance.

A second major approach to limiting gut-origin sepsis has been the use of selective digestive tract decontamination (SDD). The strategy of selective gut bacterial decontamination is based on the concept that life-threatening infections in critically ill or injured patients originate from the gut and that the use of oral nonabsorbable antibiotics plus a brief course of systemic antibiotics prevents intestinal bacterial overgrowth with potential pathogenic bacteria and thereby limits gut-origin infections and improves clinical outcome. Although in most studies, including meta-analyses, SDD significantly reduced the incidence of bacteremia and other systemic infections, it did not significantly improve mortality.<sup>51</sup> However, a more recent meta-analysis of SDD showed that SDD improves survival in ICU patient subgroups with predicted mortality rates of about 20% to 60%,<sup>52</sup> as did a study in patients with severe acute pancreatitis.<sup>53</sup> Thus, the results of SDD studies also support the concept that both bacterial translocation and gut-derived sepsis exist.

A new approach to controlling the gut flora is the use of enterally administered prebiotics, probiotics, and symbiotic combinations.<sup>54</sup> Prebiotics are specific plant fibers, and probiotics are specific strains of lactobacillus, whereas synbiotics are a combination of the two. Although the use of these agents for a number of gastrointestinal complaints has been advocated, recent clinical trials in several groups of patients showed that enteral administration of probiotics or synbiotics reduce infectious complications. These prospective RCTs includes patients with severe pancreatitis<sup>55</sup> as well as those undergoing major surgery<sup>56</sup> or liver transplantation.<sup>57</sup> Although conclusions cannot be made with certainty because of the limited number of clinical studies carried out to date, the concept that enterally administered prebiotics, probiotics, and synbiotics can potentially reduce gut-derived systemic infections appears promising.

#### CONCLUSION

The basic aim of this brief review was to examine the question of whether bacterial translocation and gutderived sepsis exist in patients. We believe that the clinical literature on this question clearly indicates that the answer is yes. Further, the clinical conditions found to be associated with bacterial translocation, loss of gut barrier function, gut-derived sepsis, and organ dysfunction are largely consistent with that predicted from preclinical animal studies.<sup>1,43</sup> Not only do bacterial translocation and increased gut permeability occur in a wide range of patient groups, but also this occurrence is associated with a significantly increased incidence of systemic infection and organ failure. Although gut-derived microbial and, to an increasing extent, nonmicrobial factors have been documented to contribute to sepsis and organ failure, a direct correlation between gut-derived sepsis and mortality remains to be fully established. Consistent with the notion that gut-derived sepsis is clinically relevant, multiple prospective RCTs using therapies directed at preserving gut barrier function and controlling the gut flora have been effective in reducing the incidence of systemic infections. Some have shown a reduction in the incidence of MODS or an improvement in survival. Having shown that gut-derived sepsis and MODS occur, we believe that further research will focus on the mechanisms of gut barrier failure and the exact nature and function of the gut-derived nonmicrobial factors involved in transducing intestinal ischemia into a systemic inflammatory state associated with cellular and organ dysfunction. Hopefully, the results of these mechanistic studies will result in new and effective therapeutic options to limit the phenomenon of gut-derived sepsis and its clinical sequelae.

# **AUTHORS' RECOMMENDATIONS**

- Bacterial translocation is only one manifestation of gut barrier failure and gut-origin sepsis.
- Gut barrier failure and gut-origin sepsis do occur clinically and are at the very least associated with increased morbidity.
- Current evidence suggests that nonmicrobial factors released from the ischemic gut into the intestinal lymphatics may be more important in gut-origin sepsis than the phenomenon of bacterial translocation.

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# 28 Is Invasive Hemodynamic Monitoring Useful in Sepsis?

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The cardiovascular disturbances in severe sepsis are complex, poorly understood, and difficult to either predict or characterize in critically ill patients.<sup>1</sup> The most widely used monitoring device to follow the cardiovascular status of sick patients has been the pulmonary artery catheter (PAC). This was introduced more than 30 years ago by Swan and Ganz. These pioneers suggested that pulmonary artery catheterization was both safe and accurate enough to provide data in critically ill patients that could be used to improve outcomes.<sup>2</sup> Such was the success of this technique that the procedure was widely introduced into clinical practice. Since that time, there have been many dissenting opinions regarding the value of this technique in the care of our patients.<sup>3,4</sup>

# PATHOPHYSIOLOGY AND MECHANISM OF ACTION

The PAC provides a comprehensive bedside overview of the circulatory status of sick patients. It directly measures three distinct but highly valuable groups of parameters. The first group involves pressures generated within the heart and the pulmonary circulation. These include the pulmonary artery pressure, the right atrial and ventricular pressures, and the central venous pressure (CVP) as reflected in the superior vena cava. It can also measure a surrogate of left atrial pressure—the pulmonary artery occlusion pressure (PAOP). The PAC can provide a direct assessment of cardiac function by determining cardiac output using the thermodilution principle. These data can be extrapolated to derive stroke volume, right ventricular end-diastolic volume, and ejection fraction. Finally, the position of the catheter in the pulmonary artery permits measurement of the mixed venous oxygen saturation. These last are provided continuously when modern catheters are used.

Therefore, the PAC is able to provide clinicians with highly relevant and useful functional information at the bedside. This can be compared with a metabolic marker of oxygen supply and demand to determine the adequacy of the circulation. If used properly, these data should enable clinicians to manage the circulatory status of their patients in a logical and intuitive fashion. This in turn ought to confer benefit to the patients. The PAC is only a monitor. As such, its value lies in the provision of timely data to clinicians. For this to translate into benefit, the data must first be acquired accurately, then interpreted reliably, and finally acted on in a fashion that is appropriate for the patient. Fundamental to this is the ability of users of the device to identify and extract accurate information and data. This may require a high standard of training and expertise. In recent years, the ability of bedside personnel to perform this task reliably has been questioned.<sup>5–7</sup> A number of studies have assessed the abilities of nurses and clinicians who use the PAC on a regular basis to identify and interpret waveforms and data that originate from the PAC. Each study concluded that the data were incorrectly interpreted in at least 25% of the cases.

In tandem with evidence questioning the ability of bedside clinicians to use the PAC properly has been a growing body of observational literature suggesting that use of the PAC actually may be harmful. Initially, several studies investigating acute myocardial infarction hinted that use of the PAC was associated with an increased mortality even when compensating for severity of illness.8,9 However, the authors postulated that the PAC was more likely to be used in patients with more severe disease and more substantial comorbidities, factors not accounted for in severity stratification. There were attempts to address this problem with a randomized controlled trial in the early 1990s. This failed because some investigators believed they were unable to manage these patients without the use of the PAC and refused to allow patients to be randomized.<sup>10</sup>

The controversy deepened with the 1996 publication of an observational study of 5735 patients. Those who were treated with a PAC were case-matched to patients who did not receive a PAC using a propensity score. In this study, patients treated with the PAC had an increased 30-day mortality rate (odds ratio, 1.24; 95% confidence interval, 1.03 to 1.49).<sup>11</sup> In addition, these patients had longer intensive care and hospital lengths of stay, greater resource use, and a more aggressive package of care. These results have since been confirmed by others who have repeated the design and methodology of the original paper.<sup>12</sup> These papers enabled equipoise to be reached and randomized trials testing the hypothesis that the PAC may or may not worsen outcome to be started.<sup>13</sup>

# PRESENTATION OF AVAILABLE DATA BASED ON SYSTEMATIC REVIEW

The literature contains at least 13 randomized controlled trials that have assessed the value of the PAC in mixed groups of patients. These have been summarized into a number of meta-analyses that are detailed in Table 28-1. None of the studies is specifically on patients with sepsis. Some are on perioperative patients, and the others are on mixed groups of critically ill patients. It appears clear that the timing of any intervention and also the targets and therapies involved must be specific to the individual patient. Extrapolating data from the original studies is therefore fraught with danger.

A series of papers has attempted to answer the question of whether the PAC causes harm. The first, and smallest, of these randomized 201 patients in a single center to either receive a PAC or have care directed without the use of any form of flow monitoring. This study included patients who fulfilled one of four criteria (shock, oliguria, vasoactive infusion, acute respiratory failure).<sup>14</sup> The study deliberately did not protocolize what clinicians should do with the data acquired but rather left it to normal clinical practice. This study found no difference in overall mortality between the groups, although it did not have the power to demonstrably prove this. Patients who had PAC placement appeared to receive more fluid in the first 24 hours and had an increased incidence of renal failure and thrombocytopenia.

Richard and coworkers subsequently published a study similar in design to the previous trial by Rhodes and associates.<sup>15</sup> This study was a multicenter (36 centers) randomized controlled trial of the PAC in septic shock and acute respiratory distress syndrome (ARDS) in 676 patients and had no formal protocol directing how the PAC data were to be used. This study again found no difference in either mortality or complications between the two groups.

Harvey and coworkers published the United Kingdom PAC-Man study in 2005.<sup>16</sup> It was hoped that this large multicenter randomized controlled trial would answer the question of whether the PAC harmed critically ill patients. The design was complex. There were two study arms. The first arm randomized patients to being treated with the use of data acquired from a PAC or to a group whereby management decisions were not aided by cardiac output monitoring of any sort. The second arm randomized patients to either a PAC group or to a group whereby

decisions could be aided by cardiac output monitoring so long as it was not derived from a PAC (e.g., by esophageal Doppler or a pulse pressure waveform). Two hundred twelve patients were enrolled into the first of these arms and 802 into the second. Once again, this trial was unable to demonstrate any mortality reduction with the use of the PAC. However, because clinicians favored the second of the two arms, this study actually showed that the use of data from the PAC was neither beneficial nor detrimental to use of the same data derived from other monitoring technologies.

A recent important publication is the National Institutes of Health Acute Respiratory Distress Syndrome Network (ARDSNet) Fluids and Catheters Treatment Trial (FACTT) study.<sup>17</sup> This was a multicenter clinical trial (1000 patients) of PAC versus CVP monitoring in acute lung injury following initial resuscitation. This study had a complex design with a  $2 \times 2$  factorial randomization process that enabled it to compare use of either the PAC or the CVP and, within each monitoring group, conservative and liberal fluid management strategies. This study differed from previous investigations in that it used specific hemodynamic goals and treatment strategies that included a predefined protocol to manage fluids, inotropes, vasopressors, and diuretics. The investigators were unable to demonstrate a difference between the groups in terms of mortality or morbidity benefit. It is worth noting that the protocol in this study used PAP and CVP pressures, not to direct therapies but to limit them. This is perhaps a more intuitive response, given the limitations of pressure-based measurements to predict volemic status. However, given the negative results, it cannot be justified from this study to recommend routine use of these catheters in this patient group as a whole, although specific subgroups may warrant further investigation.

Very few studies have assessed the use of the PAC in purely septic patients. Several studies have assessed differing protocols using the PAC in critically ill patients (most of whom usually are septic).<sup>19–21</sup> Hayes and colleagues demonstrated that aggressive resuscitation to supranormal levels of oxygen delivery might actually be harmful.<sup>18</sup> These findings, to some extent, have been confirmed by Gattinoni and associates.<sup>19</sup> It is worth noting that all these studies started the resuscitation process relatively late. The study by Rivers and coworkers, using less invasive central venous oxygen saturation targets in early septic shock, argues that early and aggressive resuscitation is of paramount importance.<sup>21</sup>

Study	No. of Trials	No. of Subjects (Intervention/No Intervention)	Intervention	Control	Outcomes
Ivanov et al, $2000^{22}$	12	607/478	PAC	No PAC	62% incidence in morbidity with PAC; 74% in controls (relative risk, 0.78)
Shah et al, 2005 <sup>23</sup>	13	506/507	PAC	No PAC	No difference in mortality
Harvey et al, 2006 <sup>24</sup>	4	953/970	PAC	No PAC	No difference in mortality

Table 28-1 Summary of Meta-Analyses on Pulmonary Artery Catheterization in Critically III Patients

PAC, pulmonary artery catheter.

# **INTERPRETATION OF DATA**

In recent years, there has been a plethora of studies published assessing the PAC. The fact that these studies have been performed reflects the changing views on the value of this tool in clinical practice. A rigid and hard view of the data would suggest that the PAC is of no use to our patients at least in terms of reducing mortality. However, this likely is too simplistic. We can say with some certainty that multicenter trials indicate that the routine use of the PAC is not associated with a 10% reduction in mortality. These studies, however, have been powered only to look at significant (i.e., 10%) decreases in mortality. It is not clear whether a lesser reduction is present. We also have to reflect on the fact that many of these studies did not use a protocolized approach to the use of PACderived data. This may have led to some centers using the tool well and others not, negating any overall difference. We also have to remember that there are issues with data acquisition and interpretation.

We believe that the PAC has a role in the management of complex patients such as those in resistant septic shock. It is clear that this proportion of patients is not large, and the routine use of PACs is not warranted. If the PAC is to remain in our armamentarium, education and training in its use are vital. It is perhaps worth thinking about how often the PAC needs to be used to acquire and maintain these skills. It is highly unlikely that the PAC itself will have a major effect on the outcome of our patients; it is the clinician at the bedside using the device that can confer either benefit or harm with how he or she practices medicine.

#### CONCLUSION

There is no justification for the routine use of the PAC in all patients with sepsis. However, a better understanding of the pathophysiology of some patients, perhaps those not responding to baseline therapy, may be achieved with the use of this device. This will only lead to outcome improvement if the clinician at the bedside uses this information wisely.

# **AUTHORS' RECOMMENDATIONS**

- The cardiovascular disturbances in severe sepsis are complex, poorly understood, and difficult to either predict or determine. Circulation is affected globally, with dynamic changes occurring through the course of sepsis. Hemodynamic monitoring is important because it provides an assessment of the circulation that is impossible to achieve just with clinical examination.
- The PAC provides a comprehensive overview of the circulation by measuring pressures, cardiac output, and mixed venous oxygen saturation.
- The PAC is only a monitor. It provides data for clinicians. It does not provide a treatment per se. For the PAC to be useful, the information needs to be recorded accurately and interpreted properly.

- Some studies have suggested that the use of the PAC can harm patients. Several studies have been unable to demonstrate an association between PAC use and poor outcome.
- The use of the PAC, when not coupled with an appropriate therapeutic protocol, has not been shown to improve patient outcomes.
- In the hands of expert clinicians, the PAC remains a useful tool in the management of resistant shock states.

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# 29

# What Is the Role of Empirical Antibiotic Therapy in Sepsis?

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It is intuitive that patients who are seriously ill because of infection will benefit from the earliest possible administration of antibiotics effective against the causative pathogen. However, the issue is complex, and definitive data from randomized prospective trials are lacking. Complicating issues include the timely recognition and identification of infection, the choice of antimicrobial agent, whether the antibiotics are dosed and administered properly, whether surgical source control is achieved promptly and is required, and a host of patient factors (e.g., age, medical comorbidities such as diabetes mellitus). The questions of prompt clinical diagnosis and timely laboratory confirmation are germane, but detailed discussion is beyond the scope of this focused review.

Most infections require that empirical antibiotic therapy be administered before microbial identification and susceptibility testing are reported. Pharmacotherapy is defined by the interaction between patient and drug and described by the tools of pharmacokinetics and pharmacodynamics. Antibiotic treatment differs from all other pharmacotherapy in that it is influenced by a third factor: interactions among the drug, the patient, and the microbe must all be considered (Table 29-1). Crucial factors in the decision-making process of drug selection are the type of infection, the likely pathogens, whether the organisms are likely to be resistant to one or more classes of antimicrobial agents, and whether a drug may be a poor choice from a patient safety perspective (e.g., administration of an aminoglycoside to a patient with preexisting renal insufficiency). Risk factors for antibiotic-resistant infection in the case of health care-associated pneumonia include recent hospitalization (adjusted odds ratio [OR], 4.21), residence in a nursing home (OR, 2.75), long-term hemodialysis (OR, 2.11), and intensive care unit (ICU) admission (OR, 1.62).<sup>1</sup> Studies of other infectious disease states reach similar conclusions, although many examined the risk of recent prior antibiotic therapy, as opposed to prior hospitalization (where patients may become exposed to and colonized by multidrug-resistant pathogens whether or not they receive an antibiotic), as a specific risk factor.

Once the choice of antimicrobial agents has been made, decisions must be made as to how to administer them and for how long. Numerous paradigms for antibiotic administration have been described (Table 29-2). There is some evidence to justify the concept of de-escalation (also referred to as *streamlining*) (Table 29-3). This process involves beginning therapy with broad-spectrum multidrug therapy, to minimize the possibility that the pathogen will go untreated initially, using the best available agents. Such an approach runs counter to the idea of formulary restriction or other tactics to restrict availability of antibiotics. After the microbiology data become available, antibiotic therapy is narrowed (de-escalated or streamlined) to complete the course of therapy. This should minimize the risk for toxicity and for inducing bacterial resistance by decreasing antibiotic selection pressure. Evidence indicates that concern about de-escalation leading to undertreatment is unfounded.<sup>2</sup> However, inappropriate empirical antibiotic treatment among nonbacteremic patients with health care-associated pneumonia was independently associated with mortality (OR, 2.88; 95% confidence interval [CI], 1.46 to 5.67). Escalation did not attenuate the risk for death.<sup>3</sup>

All antibiotic administration tactics are designed to increase the appropriateness or adequacy of antimicrobial therapy. Although some have made a distinction between appropriateness (i.e., choice) and adequacy (e.g., appropriateness of choice and the several other factors discussed), such a distinction seems artificial and therefore is not emphasized here.

Appropriate antibiotic therapy requires selecting the most effective route, dose, and timing of administration of an appropriate antibiotic. Initiation of inappropriate therapy is inherently a cause of delay, most often until definitive microbiology data are available (up to 48 to 72 hours with the current practices of most clinical microbiology laboratories).

That appropriate initial antibiotic therapy is important for favorable outcomes of infection has been recognized for about a decade. The report that focused attention was a prospective study of 2000 medical and surgical patients by Kollef and colleagues<sup>4</sup> (Table 29-4). The question asked was whether the pathogens identified were susceptible in vitro to the antibiotics chosen for initial antibiotic therapy. There was no analysis of dosage, timing, or duration of therapy. One hundred sixty-nine (8.5%) infected patients received inadequate antimicrobial treatment, representing 25.8% of the 655 patients with infections. Multivariable analysis of the cohort of infected patients demonstrated that the prior administration of antibiotics (OR, 3.39; 95% CI, 2.88 to 4.23), presence of a bloodstream infection (OR, 1.88; 95% CI, 1.52 to 2.32),

# Table 29-1 Interactions Among Host, Microbe,and Drug in the Pharmacotherapy of Infection

#### PATIENT FACTORS

- Age
- Disease state
- Type of infection
- Medical comorbidities
- Organ dysfunction
- Allergy

#### **MICROBIAL FACTORS**

- ICU or non-ICU infection?
- Colonist or pathogen?
- Pathogen identification and specific susceptibility pattern
- Local antibiogram—generalizable information that may or may not apply specifically

### DRUG FACTORS

- Prior antibiotic therapy
- Potential for resistance
- Need for multiple agents
- Formulary restriction
- Cost

ICU, intensive care unit.

# Table 29-2 Paradigms for Antibiotic Administration

- Monotherapy
- Combination therapy
- Heterogeneity
- Protocolized therapy
- Synergistic therapy
- Computerized decision support
- Cycling
- De-escalation
- Formulary restriction
- Novel strategies
  - Single daily-dose aminoglycoside
  - Once- or twice-daily metronidazole
  - Continuous infusion of  $\beta$ -lactam antibiotics
  - Higher-than-usual doses for organisms with borderline susceptibility (based on minimal inhibitory concentration)

increasing Acute Physiology and Chronic Health Evaluation (APACHE) II scores (OR, 1.04; 95% CI, 1.03 to 1.05) and decreasing age (per year) (OR, 1.01; 95% CI, 1.01 to 1.02) were independently associated with inadequate antimicrobial treatment. The hospital mortality rate was higher among patients who received inadequate antimicrobial treatment compared with those who did not (52.1% versus 12.2%; relative risk [RR], 4.26; 95% CI, 3.52 to 5.15; P < .001). Similarly, the attributable mortality rate for infection was significantly higher among patients who received inadequate antimicrobial treatment compared with those who did not (42.0% versus 17.7%; RR, 2.37; 95% CI, 1.83 to 3.08; P < .001). By logistic regression, inadequate antimicrobial treatment was the most important determinant of hospital mortality for the entire patient

# Table 29-3 Tactics for Administration of Antimicrobial Agents

#### TRADITIONAL APPROACH

- Clinical suspicion of infection or sepsis
- Select narrow-spectrum antibiotics
- Modified antibiotic regimen based on microbiologic data
- Risk: initial inadequate therapy

#### **DE-ESCALATION THERAPY**

- Clinical suspicion of infection or sepsis
- · Select broad-spectrum antibiotics based on risk
- Modified or narrowed antibiotic regimen based on microbiologic data
- Antibiotic therapy stopped if cultures are negative
- Risks: unnecessary therapy; multidrug antimicrobial resistance

cohort (OR, 4.27; 95% CI, 3.35 to 5.44; P < .001). Inappropriate therapy was associated with substantially increased mortality, and the two leading factors associated with inappropriate therapy were prior antibiotic therapy (implying an increased risk for resistant pathogens) and catheter-related bloodstream infection (related to resistant gram-positive cocci and failure to treat empirically for fungemia). The rate of appropriateness was low (<50%), and the pathogen most associated with initial inappropriate therapy was third-generation cephalosporin-resistant *Pseudomonas aeruginosa*.

Ibrahim and associates followed with a prospective study<sup>5</sup> (Table 29-4) of protocolized therapy for ventilator-associated pneumonia (VAP) in an attempt to increase use of appropriate therapy and improve outcomes. Fifty consecutive patients with VAP were evaluated before protocol implementation and were compared with 52 consecutive VAP patients evaluated after adoption of the protocol. Severity of illness (APACHE II;  $25.8 \pm 5.7$  versus 25.4  $\pm$  8.1 points; P = .80) and the clinical pulmonary infection score (CPIS; 6.6  $\pm$  1.0 versus 6.9  $\pm$  1.2; P = .11) were similar during the two periods. Initial administration of adequate antimicrobial treatment was more likely (94.2% versus 48.0%; P < .001) and the duration of antimicrobial treatment was shorter (8.6  $\pm$  5.1 days versus 14.8  $\pm$  8.1 days; *P* < .001) when the protocol was in effect. A second episode of VAP occurred statistically less often among patients treated using the protocol (7.7% versus 24.0%; P = .03).

Numerous retrospective and prospective studies of antibiotic therapy in both VAP<sup>6-14</sup> (see Table 29-4) and severe sepsis<sup>15–23</sup> (Table 29-5) were subsequently reported. Most demonstrated that initial appropriate antibiotic therapy reduces mortality unless the studies are underpowered. Unfortunately, none of these studies is a randomized trial nor was analysis of the timing of initial appropriate therapy detailed.

# COMMUNITY-ACQUIRED PNEUMONIA

The concept that the timing of antibiotic therapy might influence outcome was studied first in communityacquired pneumonia (CAP). Three large retrospective

Table 29-4 Summary of Trials of Inappropriate Antimicrobial Therapy							
Study	No. of Subjects (Intervention/ No Intervention)	Study Design*	Intervention	Control	Outcomes		
Kollef et al, 1998 <sup>6</sup>	130 patients who underwent mini-BAL for suspected VAP, 60 of whom had a culture positive for a pathogen	Prospective inception cohort study	None	None	Among the 60 patients with positive mini-BAL cultures, 44 (73.3%) were classified as receiving inadequate antibiotic therapy. Prior antibiotic administration remained unchanged in 51 (39.2%) patients based on the culture results, whereas in another 51 (39.2%) patients, antibiotic therapy was either begun ( $n = 7$ ) or changed ( $n = 44$ ), and in the remaining 28 (21.6%) patients, antibiotic therapy was discontinued. The hospital mortality rates of these three groups were statistically different: 33.3%, 60.8%, and 14.3%, respectively ( $P < .001$ ). By multivariable analysis, immunocompromised state (OR, 2.45; 95% CI, 1.56-3.85), and a pathogen resistant to the empirically prescribed agent(s) (OR, 3.28; 95% CI, 2.12-5.06) were associated with hospital mortality.		
Kollef et al, 1999 <sup>4</sup>	2000 medical and surgical patients. 655 patients had infection, and 165 patients received inappropriate therapy	Prospective inception cohort study	None	None	Multivariable analysis of infected patients demonstrated prior administration of antibiotics (OR, 3.39; 95% CI, 2.88-4.23), bloodstream infection (OR, 1.88; 95% CI, 1.52-2.32), increasing APACHE II scores (OR, 1.04; 95% CI, 1.03-1.05), and decreasing age (per year) (OR, 1.01; 95% CI, 1.01-1.02) were associated with inadequate antimicrobial therapy. Hospital mortality was higher among patients who received inadequate antimicrobial therapy compared with those who did not (52.1% vs. 12.2%; RR, 4.26; 95% CI, 3.52-5.15). Similarly, attributable mortality for infection was higher among patients who received inadequate antimicrobial therapy compared with those who did not (42.0% vs. 17.7%; RR, 2.37; 95% CI, 1.83-3.08). Inadequate antimicrobial treatment of infection was also the leading determinant of hospital mortality for the entire patient cohort (OR, 4.27; 95% CI, 3.35-5.44).		
Ibrahim et al, 2001 <sup>5</sup>	492 medical and surgical patients with bloodstream infections	Prospective inception cohort study	None	None	147 patients (29.9%) received inadequate antimicrobial treatment for bloodstream infection. Hospital mortality of patients with a bloodstream infection was higher after inadequate antimicrobial treatment (61.9% vs. 28.4%; RR, 2.18;, 95% CI, 1.77-2.69). By logistic regression analysis, inadequate antimicrobial treatment was an independent determinant of hospital mortality (OR, 6.86; 95% CI, 5.09-9.24). Prior antibiotic therapy (same hospitalization) (OR, 2.08; 95% CI, 1.58-2.74), decreasing serum albumin concentration (1-g/dL decrement) (OR, 1.37; 95% CI, 1.21-1.56), and increasing central venous catheter duration (1-day increments) (OR, 1.03; 95% CI, 1.02-1.04) were associated with inadequate treatment.		

Dupont et al, 2001 <sup>7</sup>	111 patients with VAP	Retrospective	None	None	Severity of illness was comparable between groups. Initial antibiotic therapy was appropriate for 55 patients (49.5%). ICU length of stay was shorter with appropriate initial therapy for survivors ( $12 + 11$ days vs. $20 + 24$ days; $P = .01$ ), but rude hospital mortality was unchanged (type II error).
Ibrahim et al, 2002 <sup>38</sup>	102 patients with VAP, 50 before guideline implementation and 52 afterward	Prospective before-after implementation trial	Implementation of a management protocol for VAP	Period before implementation	APACHE II (25.8 + 5.7 vs. 25.4 + 8.1) and CPIS scores (6.6 + 1.0 vs. 6.9 + 1.2) were similar. Initial adequate antimicrobial treatment was more frequent after compared with before (94.2% vs. 48.0%; $P < .001$ ). The duration of therapy was shorter during after compared with before (8.6 + 5.1 days vs. 14.8 + 8.1 days; $P < .001$ ). A second episode of VAP was less likely among patients after compared with before (7.7% vs. 24.0%; $P = .03$ ).
Iregui et al, 2002 <sup>8</sup>	107 consecutive patients	Prospective inception cohort study	None	None	33 of 107 patients received antibiotic therapy >24 hr after meeting diagnostic criteria for VAP, most often due to delay in order writing. <sup>25/33</sup> Mortality was 41%. <sup>44/107</sup> By multivariable regression, delayed antibiotic therapy increased the risk for death more than seven-fold (adjusted OR, 7.68; 95% CI, 4.50-13.09).
Leroy et al, 2003 <sup>9</sup>	132 consecutive patients with VAP	Prospective inception cohort study	None	None	Initial appropriate antimicrobial treatment was administered in 106 episodes. 58 patients died. By multivariable analysis, the three independent factors associated with death were multilobar involvement on chest x-ray, platelet count less than $150,000/\mu$ L), and Simplified Acute Physiology Score II higher than 37 points. Appropriate antimicrobial therapy was not associated with lower mortality (type II error).
Clec'h et al, 2004 <sup>10</sup>	142 patients with VAP ventilated mechanically for ≥48 hr	Prospective inception cohort study in six French ICUs	None	None	Patients were compared according to whether appropriate antibiotics were started when VAP was first suspected (day 0). At day 0, the rate of appropriate antibiotic therapy was 44.4%, and rose to 92% at day 2. No mortality difference was found with or without appropriate early antibiotics. When patients were classified based on the initial Logistic Organ Dysfunction score (LOD), mortality was significantly higher with inadequate early antibiotic therapy in the groups with LOD $\leq$ 4 (37% vs. 7%; <i>P</i> = .006). Multivariable logistic regression confirmed that inadequate antibiotic therapy increased mortality in patients with LOD $\leq$ 4.
Luna et al, 2006 <sup>11</sup>	76 mechanically ventilated patients with VAP	Prospective inception cohort study in six hospitals in Buenos Aires	None	None	24 of 76 patients received adequate therapy; mortality was 29.2%. The remaining 52 patients received either inappropriate therapy (IT) ( $n = 16$ ) or delayed initial therapy (DIAT) ( $n = 36$ ); the mortality was 63.5% combined, and 75.0% and 58.3% for IT and DIAT, respectively ( $P < .01$ vs. appropriate therapy). No logistic regression analysis was performed.

Continued

Table 29-4	Table 29-4 Summary of Trials of Inappropriate Antimicrobial Therapy—Cont'd						
Study	No. of Subjects (Intervention/ No Intervention)	Study Design	Intervention	Control	Outcomes		
Leone et al, 2007 <sup>12</sup>	115 patients with VAP and positive cultures	Prospective inception cohort study over a 36-mo period	Patients with VAP were treated with limited-spectrum antibiotics (i.e., no antipseudomonal activity) if they had not been hospitalized within 21 days) or had not been given antibiotics within 10 days. Otherwise, broad- spectrum agents were given.	None	Limited-spectrum therapy was used in 79 patients (69%). Empirical therapy was appropriate in 100 patients (85%). The mortality rate was significantly higher in the patients in whom empirical therapy was inappropriate (47% vs. 20%; $P < .05$ ).		
Teixeira et al, 2007 <sup>13</sup>	151 patients with a clinical diagnosis of VAP	Prospective inception cohort study	None	None	69 (45.7%) of 151 patients with a clinical diagnosis of VAP received inadequate antimicrobial treatment initially. 100 (66.2%) episodes of VAP were caused by multidrug-resistant pathogens, of which 56% were treated inadequately, whereas the rate of inadequate antimicrobial therapy for VAP caused by susceptible-drug pathogens was 25.5% ( $P < .001$ ). Multivariable analysis revealed that the risk for inadequate antimicrobial treatment was higher with late-onset VAP (OR, 2.93; 95% CI, 1.30-6.64), and also higher for patients with VAP caused by multidrug-resistant pathogens (OR, 3.07; 95% CI, 1.29-7.30) or polymicrobial VAP (OR, 3.67; 95% CI, 1.21-11.12).		
Kollef et al, 2008 <sup>14</sup>	76 patients with VAP, diagnosed by BAL and attributed to potentially resistant gram- negative bacilli, were identified over a 5-year period.	Retrospective, cost analysis	None	None	19 patients (25.0%) died in the hospital. Patients receiving the first dose of appropriate antibiotic therapy within 24 hr of BAL sampling had a lower 30-day mortality rate (17.2% vs. 50.0%; $P = .005$ ). Total hospitalization costs were similar in patients treated initially with an inappropriate vs. appropriate regimen (\$68,597 ± \$55,466 vs. \$86,644 ± \$64,433; $P = 0.39$ ).		

\*DB, double-blind; P, placebo-controlled. BAL, bronchoalveolar lavage; CI, confidence interval; ICU, intensive care unit; OR, odds ratio; RR, relative risk; VAP, ventilator-assisted pneumonia.

		on intection and sepsis			
Study	No. of Subjects (Intervention/No Intervention)	Study Design*	Intervention	Control	Outcomes
Garnacho- Montero et al, 2003 <sup>17</sup>	406 patients; sepsis was present in 105 patients (25.9%), severe sepsis in 116 (28.6%), and septic shock in 185 (45.6%).	Prospective inception cohort study	None	None	By multivariable analysis, predictors of in-hospital mortality were Sepsis-related Organ Failure Assessment (SOFA) score at ICU admission (OR, 1.29; 95% CI, 1.19-1.40), respiratory failure within the first 24 hr in the ICU (OR, 3.12; 95% CI, 1.54-6.33), and inappropriate empirical antimicrobial therapy in patients with nonsurgical sepsis (OR, 8.14; 95% CI, 1.98-33.5), whereas adequate empirical antimicrobial therapy in surgical sepsis (OR, 0.37; 95% CI, 0.18-0.77) and urologic sepsis (OR, 0.14; 95% CI, 0.05-0.41) were protective factors. Fungal infection (OR, 47.32; 95% CI, 5.56-200.97) and antibiotic therapy within the previous month (OR, 2.23; 95% CI, 1.1-5.45) predicted inappropriate administration of antibiotic therapy.
Barie et al, 2005 <sup>22</sup>	356 consecutive patients	Prospective inception cohort study	None	None	Patients were studied during their initial episode of fever (temperature > $38.2^{\circ}$ C) caused by infection. The mean APACHE III score was $74 \pm 2$ points, and mortality was $31\%$ . Appropriate antibiotic therapy was administered to $94\%$ of the patients, and duration of therapy was identical for survivors and nonsurvivors. Neither the source of infection nor the specific isolate influenced mortality. By multivariable regression, delayed antibiotic therapy increased the risk for death by 2.1% for every 30-min delay (OR, 1.021; 95% CI, 1.003-1.038).
Garnacho- Montero et al, 2006 <sup>16</sup>	224 patients with severe sepsis, 114 of whom had septic shock	Prospective inception cohort study	Three genetic polymorphisms were assessed in all patients by PCR: the TNF- $\alpha$ 308 promoter polymorphism, that of the first intron of the TNF- $\beta$ gene; and the IL-10-1082 promoter polymorphism. Patients were followed up for 90 days after hospital admission.	None	There was no association among any of the three polymorphisms and mortality. By multivariable analysis, two factors were associated with mortality: APACHE II score and delayed initiation of appropriate antibiotic therapy. In septic shock patients ( $n = 114$ ), delay of antibiotic therapy was the only predictor of mortality. Risk factors for impairment in inflammatory response were APACHE II score, positive blood culture, and delayed initiation of appropriate antibiotic therapy.

Table 29-5	Summary of Trials	on Infection and Sepsis	s–Cont'd		
Study	No. of Subjects (Intervention/No Intervention)	Study Design	Intervention	Control	Outcomes
Kumar et al, 2006 <sup>23</sup>	2731 (2154 with actual septic shock)	Retrospective study of adult patients with septic shock from 14 ICUs (4 medical, 4 surgical, 6 medical- surgical) and 10 hospitals (4 academic, 6 community) in the U.S. and Canada. The primary outcome measure was survival to hospital discharge. Time to administration of antibiotics was assessed from the time of first documented hypotension.	None	None	Administration of antimicrobials within the first hour of documented hypotension was associated with increased survival. By multivariable analysis, delay in effective antimicrobial initiation (per 1 hr delay) increased the risk for death by 12% (adjusted OR, 1.119; 95% CI, 1.103-1.136), and was the single most powerful predictor of mortality by the multivariable analysis. By the second hour, mortality was significantly more likely (OR, 1.67; 95% CI, 1.12-2.48) relative to receipt of therapy within the first hour. Despite a progressive increase in mortality with increasing delays, only 50% of septic shock patients receive effective antimicrobial therapy within 6 hr (median time to 6 hr, interquartile range 2-15 hr).
Peralta et al, 2007 <sup>21</sup>	663 patients with Escherichia coli bacteremia	Retrospective	None	None	36 (5.4%) died. Patients with multidrug-resistant (MDR) <i>E. coli</i> bacteremia had a lower frequency of correct empirical antibiotic treatment than patients with non-MDR <i>E. coli</i> bacteremia (RR, 0.53; 95% CI, 0.48-0.67) and also had higher mortality (RR, 3.31; 95% CI, 1.72-6.36). After adjustment for other significant risk factors and confounders, the inadequacy of empirical antibiotic treatment was associated with increased mortality (OR, 2.98; 95% CI, 1.25-7.11). When the adequacy of treatment was excluded from the model, the presence of MDR <i>E. coli</i> in blood cultures was also associated with mortality (OR, 3.11; 95% CI, 1.3-7.44).
Garnacho- Montero et al, 2008 <sup>15</sup>	87 patients with sepsis matched with 87 control patients without sepsis	Retrospective study of a prospectively collected database	87 patients matched for origin of sepsis, inflammatory response at admission, surgical or medical status, hospital- or community- acquired sepsis, APACHE II score (±2 points) and age (±10 yr)	87 matched patients without sepsis	Fifty-nine sepsis patients died (67.8%; 95% CI, 58.0-77.6%) vs. 25 controls (28.7%; 95% CI, 19.2%-38.2%; $P < .001$ ). Estimated excess in-hospital mortality was 39.1%. The rate of nosocomial infection was higher in patients with inadequate empirical therapy (16.1% vs. 3.4%; $P < .05$ ).

Robert et al, 2008 <sup>18</sup>	117 patients with anaerobic bloodstream infection	Retrospective	None	None	In 51 cases, patients did not receive adequate empirical antianaerobic therapy. The mortality rate was 27%. Age (OR, 1.059; 95% CI, 1.021- 1.100), cancer history (OR, 3.21; 95% CI, 1.126- 9.156), and ineffective definitive antibiotic therapy (OR, 19.292; 95% CI, 5.330-69.832) were associated independently with increased mortality.
Marschall et al, 2008 <sup>19</sup>	250 non-ICU patients with gram-negative bacteremia	Prospective inception cohort study	6-month study of non-ICU patients with gram-negative bacteremia in a tertiary-care hospital	None	79 patients (31.6%) received inappropriate empirical therapy and were more likely to have a hospital-acquired infection (OR, 1.99; 95% CI, 1.11-3.56), and less likely to have <i>E.</i> <i>coli</i> monomicrobial bacteremia (OR, 0.40; 95% CI, 0.19-0.86). Mortality (11 [13.9%] vs. 24 [14.0%]; $P = 1.0$ ] did not differ.
Subramanian et al, 2008 <sup>20</sup>	95 consecutive patients with septic shock, stratified by duration of shock without vasopressor therapy	Retrospective	None	None	Patients treated liberally with vasopressor therapy (duration of hypotension < median) had similar baseline organ impairment, were younger (median age 70 vs. 77 years; $P = .049$ ), required mechanical ventilation (78% vs. 49%; P < .001), and had progression of organ failure after 24 hr (59% vs. 37%; $P = .05$ ). Adjusted for age and mechanical ventilation, early appropriate antibiotic therapy (OR, 0.27; 95% CI, 0.09-0.76), but not liberal vasopressor use (OR, 2.13; 95% CI, 0.80-5.84), prevented progression of organ failure.

\*DB, double-blind; P, placebo-controlled. CI, confidence interval; ICU, intensive care unit; IL, interleukin; OR, odds ratio; PCR, polymerase chain reaction; RR, relative risk; TNF, tumor necrosis factor.

studies of Medicare beneficiaries form the basis of this literature. In a study involving 297 U.S. acute care hospitals, Kahn and colleagues noted reduced mortality if the time to first antibiotic dose (TFAD) was administered in less than 4 hours<sup>24</sup> (Table 29-6). Meehan and coworkers undertook a multicenter retrospective study of 14,069 patients with CAP treated in 3555 U.S. acute care hospitals.<sup>25</sup> Four processes of care were assessed: TFAD (<8 hours), 75.5% (95% CI, 73.1% to 77.9%); blood culture collection before initial hospital antibiotics, 57.3% (54.5% to 60.1%); blood culture collection within 24 hours of admission, 68.7% (95% CI, 66.2% to 71.2%); and initial oxygenation assessment within 24 hours, 89.3% (87.5% to 90.9%). Lower 30-day mortality was associated with TFAD before 8 hours of hospital arrival (OR, 0.85; 95% CI, 0.75 to 0.96) and blood culture collection within 24 hours (OR, 0.90; 95% CI, 0.81 to 1.00). However, performance in individual states and territories varied widely.

Houck and colleagues<sup>26</sup> found that antibiotic administration for CAP within 4 hours of arrival was associated with decreased mortality and length of stay (LOS) among a random sample of older inpatients who had not received antibiotics as outpatients. This retrospective study used medical records from a national random sample of 18,209 Medicare patients older than 65 years of age who were hospitalized with CAP from July 1998 through March 1999. Among 13,771 (75.6%) patients who had not received outpatient antibiotics, antibiotic administration within 4 hours of hospital arrival was associated with reduced in-hospital mortality (6.8% versus 7.4%; adjusted OR, 0.85; 95% CI, 0.74 to 0.98), mortality within 30 days of admission (11.6% versus 12.7%; OR, 0.85; 95% CI, 0.76 to 0.95), and LOS exceeding the 5-day median (42.1% versus 45.1%; OR, 0.90; 95% CI, 0.83 to 0.96). Mean LOS was 0.4 days shorter when antibiotic was administered within 4 hours. Timing was not associated with readmission.

Contradictory data were provided by Waterer and associates in a prospective inception cohort study of 451 patients with CAP.27 Immunocompetent patients hospitalized for CAP were studied. Delay in antibiotic administration was more common among patients who presented with altered mental status or minimal signs of sepsis. TFAD was considered likely to be a marker of comorbidities that manifest as an atypical presentation or mortality rather than a direct contributor to outcome. Time to first antibiotic administration greater than 4 hours (delayed administration) was associated by multivariable analysis with altered mental status (OR, 2.89; 95% CI, 1.53 to 5.45), absence of hypoxia (OR, 1.82; 95% CI, 1.09 to 3.04), absence of fever (OR, 1.59; 95% CI, 1.06 to 2.40), and older age (OR, 1.01; 95% CI, 1.00 to 1.06). Predictors of mortality by multivariable analysis were altered mental status (OR, 3.33; 95% CI, 1.28 to 8.77) and absence of fever (OR, 2.55; 95% CI, 1.02 to 6.37), but not with age (OR, 1.01; 95% CI, 0.99 to 1.04), absence of hypoxia (OR, 2.08; 95% CI, 1.15 to 6.35) or TFAD greater than 4 hours (OR, 1.85; 95% CI, 0.84 to 5.00). Additionally, the predictors of antibiotic administration within 2 hours by multivariable analysis were the presence of shock (OR, 3.63; 95% CI, 1.63 to 8.09), fever with a temperature higher than 101°F (OR, 2.20; 95% CI, 1.31 to 5.43), and hypoxia (OR, 1.69; 95% CI, 1.04 to 2.75). Similar, Welker and colleagues<sup>28</sup> retrospectively studied

548 adult patients admitted with CAP who were treated when the quality measure called for antibiotic therapy within 8 hours (n = 255) and compared them with those who were treated when the quality standard called for antibiotic therapy within 4 hours (n = 293). Reduction of the time afforded for timely antibiotic administration appeared to reduce the accuracy of the initial diagnosis of pneumonia but did not alter the actual timing of the initial administration of antibiotics. Patients treated under the 4-hour quality standard were 39% less likely to meet predefined diagnostic criteria for CAP (OR, 0.61; 95% CI, 0.42) to 0.86). There also was a greater likelihood of discrepancy between the emergency department physician's diagnosis and that of the discharging physician for patients treated under the 4-hour standard (25.5% versus 33.1%; P = .05). The mean TFAD was similar in the two periods (167  $\pm$ 119 minutes [8 hours] versus  $158 \pm 96$  minutes [4 hours]).

Recent quality improvement data are available for review in the public domain at the federal website (http:// www.hospitalcompare.hhs.gov).<sup>29</sup> For illustrative purposes, performance data for antibiotic administration for CAP during 2005 to 2008 are provided for six New York City university teaching hospitals compared with the six nearest community hospitals (Table 29-7). Although the community hospitals tended to perform better on the quality metrics, no improvements in outcome are discernible.

#### FEVER DUE TO INFECTION

Barie and associates<sup>22</sup> conducted a prospective observational study of 356 consecutive patients during an initial episode of fever (temperature  $> 38.2^{\circ}$ C.) that was proved to be caused by infection. The mean APACHE III score was 74  $\pm$  2 points, and mortality was 31%. Appropriate antibiotic therapy was administered to 94% of the patients, and duration of therapy was identical for survivors and nonsurvivors. Neither the source of infection nor the specific isolate influenced mortality. By multivariable regression, delayed antibiotic therapy increased the risk for death by 2.1% for every 30 minutes of delay (OR, 1.021; 95% CI, 1.003 to 1.038). Although not reported because of uncertain clinical relevance, the significance of delay was discernible even when delay was examined in 1-minute intervals. Because inappropriate antibiotic therapy was rare, it had no effect on outcome.

# VENTILATOR-ASSOCIATED PNEUMONIA

In 2002, Iregui and colleagues<sup>8</sup> conducted a prospective observational study of 107 patients with VAP to determine the effect of delayed antibiotic administration on mortality. All patients received antibiotic therapy that covered the isolated pathogens according to in vitro susceptibility testing. Delayed antibiotic therapy was defined as a lapse of more than 24 hours between meeting the predefined diagnostic criteria for VAP and the TFAD. The most common reason for delay was delayed order writing (76%). Notably, antibiotic administration was considered "delayed" for six cases of VAP caused by bacteria resistant to the initial empirical regimen. Thirty-three of 107 patients

Table 29-6	Table 29-6 Summary of Trials: Community-Acquired Pneumonia							
Study	No. of Subjects (Intervention/ No Intervention)	Study Design*	Intervention	Control	Outcomes			
Kahn et al, 1990 <sup>24</sup>	14,012 hospitalized Medicare patients (not all had pneumonia)	Retrospective, before-after trial of the implementation of the diagnosis- related group-based prospective payment system	None	None	Explicit process criteria and scales were developed for Medicare patients hospitalized with congestive heart failure, myocardial infarction, pneumonia, cerebrovascular accident, and hip fracture. Excluding hip fracture, a better process of care resulted in lower 30-day mortality. The process of care improved after introduction of the prospective payment system; e.g., better nursing care was associated with an expected decrease in 30-day mortality rates in pneumonia patients of 0.8 percentage points, and better physician cognitive performance was associated with a decrease of 0.4 percentage points.			
Meehan et al, 1997 <sup>25</sup>	14,069	Multicenter, retrospective cohort study with medical record review involving 3555 U.S. acute care hospitals	None	None	Four process-of-care were assessed: time from admission to antibiotic administration (<8 hr, 75.5% [95% CI, 73.1%- 77.9%]); blood culture collection before initial hospital antibiotics (57.3% [54.5%-60.1%]); blood culture collection within 24 hr of admission (68.7% [95% CI, 66.2%-71.2%]); and initial oxygenation assessment within 24 hr (89.3% [87.5%-90.9%]). Lower 30-day mortality was associated with antibiotic administration within 8 hr of hospital arrival (OR, 0.85; 95% CI, 0.75-0.96) and blood culture collection within 24 hr (OR, 0.90; 95% CI, 0.81-1.00). Performance in individual states and territories varied widely.			
Houck et al, 2004 <sup>26</sup>	Random sample of 18,209 Medicare inpatients aged > 65 yr hospitalized with CAP during 1998-1999	Retrospective	None	None	Among 13,771 (75.6%) patients who had not received outpatient antibiotics, hospital antibiotic administration within 4 hr of arrival was associated with reduced in- hospital mortality (6.8% vs. 7.4%; OR, 0.85; 95% CI, 0.74-0.98), mortality within 30 days of admission (11.6% vs. 12.7%; OR, 0.85; 95% CI, 0.76-0.95), and length of stay (LOS) exceeding the 5-day median (42.1% vs. 45.1%; OR, 0.90; 95% CI, 0.83-0.96). Mean LOS was 0.4 days shorter with antibiotic administration within 4 hr. Timing was not associated with readmission. Antibiotic administration within 4 hr of arrival was documented for 60.9% of all patients and for more than 50% of patients regardless of hospital characteristics.			
Waterer et al, 2006 <sup>27</sup>	451	Prospective inception cohort study	None	None	Immunocompetent patients hospitalized for CAP were studied. Time to first antibiotic administration > 4 hr (delayed administration) was associated by multivariable analysis with altered mental status (OR, 2.89; 95% CI, 1.53- 5.45), absence of hypoxia (OR, 1.82; 95% CI, 1.09-3.04), absence of fever (OR, 1.59; 95% CI, 1.06-2.40), and older age			

Continued

Table 29-6	Summary of Trials: Community-Acquired Pneumonia—Cont'd						
Study	No. of Subjects (Intervention/ No Intervention)	Study Design	Intervention	Control	Outcomes		
					(OR, 1.01; 95% CI, 1.00-1.06). Predictors of mortality by multivariable analysis were altered mental status (OR, 3.33; 95% CI, 1.28-8.77) and absence of fever (OR, 2.55; 95% CI, 1.02-6.37), but neither age (OR, 1.01; 95% CI, 0.99-1.04), absence of hypoxia (OR, 2.08; 95% CI, 1.15-6.35), nor time to first antibiotic administration > 4 hr (OR, 1.85; 95% CI, 0.84-5.00). Additionally, the predictors of antibiotic administration within 2 hr by multivariable analysis were the presence of shock (OR, 3.63; 95% CI, 1.63-8.09), fever with a temperature > 101°F (OR, 2.20; 95% CI, 1.31-5.43), and hypoxia (OR, 1.69; 95% CI, 1.04-2.75). Delay in antibiotic administration was more common among patients who presented with altered mental status or minimal signs of sepsis. Time to first administration of antibiotics is likely to be a marker of comorbidities that manifest as an atypical presentation or mortality rather than a direct contributor to outcome.		
Kanwar et al, 2007 <sup>35</sup>	518	Inception cohort trial comparing 6 months preimplementation <sup>2003</sup> with 6 months postimplementation <sup>200</sup>	None	None	In the 2005 patient cohort, significantly more patients had an admission diagnosis of CAP without radiographic abnormalities (91 patients [29%] vs. 41 patients [21%]; $P = .04$ ). Although more patients received timely antibiotics in 2005 (210 patients [66%] vs. 107 patients [54%]; $P = .0007$ ) and blood culturing before antibiotics also increased in 2005 (220 patients [70%] vs. 93 patients [47%]; $P < .0001$ ), the final diagnosis of CAP decreased in 2005 (59% vs. 76%; $P < .001$ ) and mean antibiotic use increased from 1.39 $\pm$ 0.58 drugs in 2003 to 1.66 $\pm$ 0.54 drugs in 2005.		
Welker et al, 2008 <sup>28</sup>	548	Retrospective comparison of adult patients with CAP who were treated when the quality measure called for antibiotic therapy within 8 hr ( $n = 255$ ) and those who were treated when the quality standard called for antibiotic therapy within 4 hr ( $n = 293$ )	None	None	Patients treated under the 4 hr quality standard were 39% less likely to meet predefined diagnostic criteria for CAP (OR, 0.61; 95% CI, 0.42-0.86). There was also a greater likelihood of discrepancy between the emergency department physician's diagnosis and that of the discharging physician for patients treated under the 4 hr standard (25.5% vs. 33.1%; $P = .05$ ). The mean time to first antibiotic dose was similar in the two periods (167 ± 119 min [8 hr] vs. 158 ± 96 min [4 hr]). Reduction of the time afforded for timely antibiotic administration appeared to reduce the accuracy of the initial diagnosis of pneumonia, while not having any effect on the actual timing of the initial administration of antibiotics.		

\*DB, double-blind; P, placebo-controlled. CAP, community-acquired pneumonia; CI, confidence interval; OR, odds ratio.

Table 29-7 Selected Metrics for Antibiotic Administration to Medicare Patients Hospitalized in the Metropolitan New York City Area for Severe Community-Acquired Pneumonia after Presentation to the Hospital's Emergency Department, 7/1/05 to 6/30/08

Metric	U.S. Average	New York Average	Percent Compliance (Range, Mean)
Percent of pneumonia Patients given initial antibiotic(s) within 6 hr after arrival	93%	93%	72%-93%, 84% (UTH) 85%-94%, 92% (CTH)
Percent of pneumonia Patients given the most appropriate initial antibiotic(s)	87%	89%	62%-93%, 82% (UTH) 84%-94%, 92% (CTH)
Hospital mortality	11.5%	N/A	7.5%-13.6%, 9.9% (UTH) 7.9%-11.3%, 10.0% (CTH)
30-Day readmission	18.2%	N/A	17.7%-23.4%, 20.0% (UTH) 18.0%-22.7%, 19.8% (CTH)

Results for six medical school university teaching hospitals (UTH) in Metropolitan New York City are compared with those from the six community teaching hospitals (CTH) nearest to the UTH facilities. Data are as taken from the website and are unadjusted.

N/A, not available

Data retrieved July 13, 2009, from http://www.hospitalcompare.hhs.gov/Hospital/Search/.

were determined to have received delayed therapy. Fortyfour patients died (41%). By multivariable logistic regression analysis, mortality was associated with increasing admission APACHE II score (adjusted OR, 1.13; 95% CI, 1.09 to 1.18), malignant disease (adjusted OR, 3.20; 95% CI, 1.79 to 5.71), and delayed administration of antibiotics (dichotomized at 24 hours; adjusted OR, 7.68; 95% CI, 4.50 to 13.09).

This VAP literature has burgeoned; the results are summarized in Table 29-5. In general, this literature supports the idea that inappropriate initial antibiotic therapy is associated with increased mortality associated with VAP. Studies that are not supportive tend to be underpowered. However, none of these studies used randomized or concealed patient allocation. Therefore, the conclusions must be applied cautiously. Moreover, inadequate antibiotic therapy is only an inferential surrogate for timing of antibiotic therapy; none of the VAP studies examined the timing question directly.

# SEPTIC SHOCK

One study has attracted considerable attention despite its retrospective nature and is the basis for the recommendation regarding timing of antibiotic therapy in the Surviving Sepsis Campaign (SSC) guideline for management of severe sepsis and septic shock<sup>30</sup> (see later). Kumar and colleagues<sup>23</sup> studied 2731 adult patients with putative septic shock (in fact, 2154 had septic shock, and these formed the core group for analysis). The study was conducted from 1989 to 2004 in 14 ICUs (4 medical, 4 surgical, 6 medical-surgical) and 10 hospitals (4 academic, 6 community) in the United States and Canada. The primary outcome measure was survival to hospital discharge. Time to administration of antibiotics was assessed from the time of first documented hypotension. Despite a progressive increase in mortality with increasing delays, only 50% of septic shock patients receive effective antimicrobial therapy within 6 hours (median time to 6 hours, interquartile range 2 to 15 hours). Administration of antimicrobials within the first hour of documented hypotension was associated with increased survival. By multivariable analysis, a 1-hour delay in effective antimicrobial initiation increased the risk for death by 12% (adjusted OR, 1.119; 95% CI, 1.103 to 1.136) and was the single most powerful predictor of mortality. By the second hour, mortality was significantly more likely (OR, 1.67; 95% CI, 1.12 to 2.48) relative to receipt of therapy within the first hour.

# TIMING OF ANTIBIOTIC ADMINISTRATION AS A PERFORMANCE STANDARD

The U.S. Department of Health and Human Services (DHHS) Centers for Medicare and Medicaid Services (CMS) has made the administration of antibiotics to Medicare patients with CAP a quality standard. The initial standard was administration within 8 hours (TFAD) based on the data of Kahn and associates<sup>24</sup> and Meehan and colleagues<sup>25</sup> but was reduced to 4 hours to conform to Houck and coworkers.<sup>26</sup> Concerns regarding unintended consequences when clinicians were pressured to administer antibiotics rapidly even in the face of diagnostic uncertainty have resulted in the standard now being relaxed to 6 hours. Data relating to the metric as a performance standard are being published or posted online.<sup>29</sup> Data for the treatment of CAP at six New York City area university teaching hospitals (UTHs) are compared with data from the six nearest community teaching hospitals (CTHs) in Table 29-7. The performance of the UTHs compared with CTHs with respect to timely antibiotic administration (mean, 84% in UTHs versus 92% in CTHs) and appropriate antibiotic choice (i.e., in compliance with guideline recommendations; mean, 87% in UTHs versus 92% in CTHs) were not statistically distinguishable. Hospital mortality averaged 11.5% in the UTH cohort versus 11.3% in the CTH cohort, and the mean 30-day readmission rates were also identical (UTH, 20.0%; CTH, 19.8%).

Was it an error to relax the standard for the time window? Are the metrics chosen poorly or irrelevant? Are the data impaired by selection bias (hospitals must submit only a sample), or problems with collection or analysis? Does timely administration of antibiotics make any difference? It may be difficult to discern from an exercise of this type.

Bratzler and associates have argued that process measures for pneumonia are "probably" valuable.<sup>31</sup> Mortality rates for CAP appear to be decreasing nationally in the United States (Table 29-8), if only for patients sick enough to require ICU care, and the pace of process improvement appears to have quickened. However, it cannot be ascertained readily from publicly reported data whether it is the timing metric that is contributing to improvement. Moreover, public reporting, the goal of which is to improve transparency and empower patients to make better choices about where to seek treatment, to increase hospital accountability about quality of care, and to allow payers to track performance over time, can clearly have unintended consequences, some of which may cause direct patient harm (e.g., inappropriate care in institutional pursuit of a high score on a performance metric; see later), or indirectly (e.g., diversion of scarce hospital resources to focus on processes of care that are being measured).<sup>31</sup>

The pitfalls of using timeliness of antibiotic administration in CAP specifically as a performance metric have been outlined in detail.<sup>32</sup> Processes of care are easier to identify and measure than outcomes, but inevitably some processes will be invalidated by flawed scientific rationale, unanticipated consequences of implementation, or data that emerge later in refutation. The three reports that formed the basis for the recommendation<sup>24-26</sup> were retrospective studies of process outcome in patients with known diagnoses. However, in reality, not every patient arrives to the emergency department with a definitive diagnosis, and it can take time to resolve the uncertainty. This is especially relevant when incorporated into a 4-hour window. The 4-hour TFAD window metric has been reported by all U.S. hospitals since 2002, and in 2006, it became part of a measure set tied to several payfor-performance pilot programs. Objections were raised almost immediately, in particular from the emergency medicine community,<sup>33</sup> regarding diagnostic uncertainty and clinical circumstances when delaying or withholding antibiotics is appropriate. It was possible to identify patients who had a provisional diagnosis of CAP but neither radiographic evidence of an infiltrate nor a final discharge diagnosis of CAP. The standard was relaxed in part because of reappraisal of the underlying evidence and recognition that "the measure was skewing emergency department priorities and promoting unnecessary antibiotic use."34

Kanwar and coworkers examined the effect of the implementation of the 4-hour treatment rule in a before (January to June 2003) and after (January to June 2005) implementation study of 518 patients with CAP.<sup>35</sup> In the 2005 patient cohort, significantly more patients had an admission diagnosis of CAP without radiographic abnormalities (91 patients [29%] versus 41 patients [21%]; P = .04). Although more patients received timely antibiotics in 2005 (210 patients [66%] versus 107 patients [54%]; P = .0007) and blood culturing before antibiotics also increased in 2005 (220 patients [70%] versus 93 patients [47%]; P < .0001), the final diagnosis of CAP

# Table 29-8 Medicare National Pneumonia Project Performance on Selected Process Measures for Therapy of Community-Acquired Pneumonia

		Year	
	2000	2002	2004
PROCESS MEASURE			
First antibiotic dose within 4 hr	59.2%	63.8%	69.8%
First antibiotic dose within 8 hr	84.4%	87.6%	89.5%
Blood culture within 24 hr	62.3%	60.4%	72.6%
OUTCOME			
In-hospital mortality (all patients)	9.5%	10.2%	7.1%
In-hospital mortality (ICU patients)	23.2%	21.3%	11.9%
In-hospital mortality (non-ICU patients)	7.8%	8.9%	8.8%*
30-Day mortality (all patients)	16.3%	15.7%	12.9%
30-Day mortality (ICU patients)	30.6%	27.7%	17.8%
30-day mortality (non-ICU patients)	14.6%	14.3%	12.4%*

\*, P value not significant for trend.

ICU, intensive care unit.

Modified from Bratzler DW, Nsa W, Houck PM. Performance measures for pneumonia: Are they valuable, and are the process measures adequate? Curr Opin Infect Dis. 2007;20:182-189.

decreased in 2005 (59% versus 76%; P < .001) and mean antibiotic use increased from  $1.39 \pm 0.58$  drugs in 2003 to  $1.66 \pm 0.54$  drugs in 2005. Linking antibiotic administration within 4 hours of hospital admission (as a quality indicator) appeared to result in a higher rate of inaccurate diagnosis of CAP, inappropriate use of antibiotics, and therefore less than optimal care.

In 2007, the Infectious Diseases Society of America and the American Thoracic Society issued joint guidelines that abolished time-specific guidelines for CAP treatment. Instead, they recommended that patients receive their first dose of antibiotics as soon as possible after a definitive diagnosis of CAP is made, preferably while still in the emergency department.<sup>36</sup> The standard was relaxed to 6 hours by the Joint Commission shortly thereafter. This was endorsed by the National Quality Forum and became the new standard in April 2008. Whether this change represents progress remains to be determined because no study has shown a benefit from adherence to a 6-hour rule.<sup>33</sup>

Performance measurements must have scientific, measurement, and application validity to be reported publicly and to be associated with differential payments.<sup>32</sup> Caution is needed in relying on retrospective studies of processoutcome links in patients with known diagnoses to prospective application of quality metrics for patients with uncertain diagnoses. Moreover, quality measurement and reporting programs should create mechanisms to assess the reliability, effects, and cost of measures shortly (1 to 2 years) after implementation to ensure validity.

# THE SURVIVING SEPSIS CAMPAIGN GUIDELINES

The 2008 iteration of the SSC guidelines<sup>30</sup> provides a comprehensive review of the evidence for the management of severe sepsis and septic shock, including the use of antibiotics (Table 29-9). Specifically, the SSC guidelines recommend that intravenous antibiotic therapy be started as early as possible within the first hour of recognition of septic shock (grade 1B) and severe sepsis without septic shock (grade 1D). Appropriate cultures should be obtained before initiating antibiotic therapy, but should not prevent prompt administration of antimicrobial therapy (grade 1D). These strong recommendations using the GRADE system<sup>7,37</sup> rely heavily on expert opinion and are based on scant literature (perhaps reflecting that the relevant literature is scant but also that a more comprehensive list of references would have made ponderous an already lengthy document). Importantly, GRADE is a complex analytical system that values expert opinion as well as published evidence but has not yet been shown to improve outcomes compared with other systems for grading evidence.

The SSC document acknowledges that competing priorities exist for the clinician's attention during the crucial first few hours after the recognition of severe sepsis and septic shock but makes clear that vascular access and initiating aggressive fluid resuscitation are the first priority. However, prompt infusion of antimicrobial agents should also be priorities and may require

#### Table 29-9 Infection-Related Guidelines from the Surviving Sepsis Campaign 2008 Guidelines

#### DIAGNOSIS OF INFECTION

Obtain appropriate cultures before administration of antibiotics, provided the administration of antibiotics is not delayed (1C)

- Obtain two or more blood cultures
- At least one blood culture should be obtained peripherally
- Obtain at least one blood culture from each vascular catheter in place >48 hr
- Culture other sites as indicated clinically

Perform imaging studies promptly to confirm and sample any source of infection, if safe to do so (1C)

#### ANTIBIOTIC THERAPY

Begin intravenous antibiotics as early as possible and always within the first hour of recognizing severe sepsis (1D) or septic shock (1B).

Therapy should be broad-spectrum: one or more agents active against likely bacterial/fungal pathogens and with good penetration into presumed source (1B)

Reassess antimicrobial regimen daily to optimize efficacy, prevent resistance, avoid toxicity, and minimize costs (1B)

- Consider combination therapy in Pseudomonas species infections (2D)
- Consider empirical combination therapy in neutropenic patients (2D)
- Limit combination therapy to  $\leq$ 3 to 5 days, and de-escalate therapy when susceptibility tests become available (2D)
- Duration of therapy should be limited typically to 7 to 10 days; longer if response is slow or there are undrainable foci or immune deficiencies (2D)

Stop antimicrobial therapy if cause is found to be noninfectious (2D)

<sup>\*</sup>GRADE classification is in parentheses.

From Dellinger RP, Levy MM, Carlet JM, for the International Surviving Sepsis Campaign Guidelines Committee; American Association of Critical-Care Nurses; American College of Chest Physicians; American College of Emergency Physicians; Canadian Critical Care Society; European Society of Clinical Microbiology and Infectious Diseases; European Society of Intensive Care Medicine; European Respiratory Society; International Sepsis Forum; Japanese Association for Acute Medicine; Japanese Society of Intensive Care Medicine; Society of Critical Care Medicine; Society of Hospital Medicine; Surgical Infection Society; and World Federation of Societies of Intensive and Critical Care Medicine. Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008 [erratum in: Crit Care Med. 2008;36:1394-1396]. Crit Care Med. 2008;36:296-327.

additional vascular access ports. If antimicrobial agents cannot be provided promptly from the pharmacy, establishing a supply of premixed antibiotics for urgent use is an appropriate strategy.

# AUTHORS' RECOMMENDATIONS

- The choice of empirical antibiotics is complex.
- Factors affecting choice include patient history, the clinical syndrome, the underlying disease, and the susceptibility patterns of pathogens in the community and hospital. Previous infections or colonizations are of particular importance.
- Recently used antibiotics generally should be avoided.
- Some antimicrobial agents have the advantage of bolus administration, whereas others require a lengthy infusion.
  Bolus drugs may be advantageous if vascular access is limited and multiple agents are to be administered.
- Because patients with severe sepsis or septic shock have little margin for error in the choice of therapy, the initial selection of antimicrobial therapy should be broad enough to cover all likely pathogens.
- There is ample indirect evidence that failure to initiate appropriate therapy (i.e., therapy with activity against the pathogen that is subsequently identified as the causative agent) correlates with increased morbidity and mortality.
- Whether timing of antibiotic administration is an appropriate performance metric remains an open question. The SSC recommendations to administer antibiotics within 1 hour to patients with severe sepsis and septic shock are based, in large part, on expert opinion because underlying data are scant.

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# What Is the Best Way to Fluid-Resuscitate a Patient with Sepsis?

Patrick J. Neligan, Niall Fanning

The cardiovascular metabolic and neurohormonal response to sepsis is characterized by a biphasic temporal process. The first phase, which occurs early, is characterized by hyperfunctionality; an increase in oxygen delivery, extraction, and consumption; and elevated demands on physiologic reserve. There is an increase in cardiac output and increased tissue blood flow associated with transcapillary refill and extravascular fluid deficit (Fig. 30-1). Depending on the patient's age, baseline health status, and degree of injury, the result will be a matching of supply and demand or the emergence of oxygen debt. This is manifest initially by a fall in the mixed venous oxygen saturation (Svo<sub>2</sub>) and subsequently by an elevation in arterial and venous lactate concentration.<sup>1</sup> There is a clear correlation among the decrement in Svo<sub>2</sub>, the magnitude of lactic acidosis, and the degree of tissue injury.<sup>2–4</sup>

After the initial hyperfunctional phase, which mirrors the acute stress response of surgery and trauma, a secondary hypofunctional phase occurs, characterized by myocardial depression, vasoplegia, and neuroendocrine dysfunction (Fig. 30-2). This may result from disordered mitochondrial activity.<sup>5</sup> The timing of fluid resuscitation may have a different effect, depending on whether it occurs in the hyperfunctional or hypofunctional phase. Current data suggest that aggressive and goal-directed resuscitation during the early part of the hyperfunctional phase may prevent the development of hypofunctional sepsis and multiorgan dysfunction (Fig. 30-3).<sup>6</sup>

In this chapter, we aim to answer the question, "What is the best way to fluid-resuscitate a patient with sepsis?" There are three components to the answer: the timing of fluid administration, the volume administered, and the physical and chemical properties of the resuscitation fluid.

# TIMING OF FLUID RESUSCITATION

The capacity of a patient to generate an adequate neurohormonal and hemodynamic response to maintain homeostasis is known as *physiologic reserve*. Shoemaker and colleagues, in 1973, characterized the relationship among demand, supply, and outcomes.<sup>7</sup> Nonsurvivors of shock were less able to generate an overall increase in tissue oxygen delivery. This has been confirmed by other groups.<sup>8,9</sup> Shoemaker's group proposed a process of supporting the cardiovascular system using fluids and inotropes to generate supranormal levels of oxygen delivery adequate to cope with and recover from critical illness. In other words, if the patient cannot generate sufficient hemodynamic goals independently, the therapeutic intervention may help them do so and save lives. Patients undergoing major surgery can be used as surrogates for critical illness in that they undergo similar initial stress responses. Shoemaker and his group looked at a 422 patients in two series<sup>10</sup> who were undergoing major surgery, randomized to goal-directed resuscitation using a pulmonary artery catheter (PAC) to supranormal goals; a control group with PAC; another investigational group using central venous pressure (CVP) to normal goals; and a CVP control group. There was a dramatic reduction in the risk for death in both series: a 13% absolute risk reduction (29% control versus 16% protocol; P < .05 for both series; number needed to treat [NNT], 8).

Fleming and colleagues<sup>11</sup> prospectively tested supranormalization of cardiac index ( $\geq$ 4.52 L/min/m<sup>2</sup>), oxygen delivery ( $\geq$ 670 mL/min/m<sup>2</sup>), and oxygen consumption ( $\geq$ 166 mL/min/m<sup>2</sup>) on outcome in trauma patients who had an estimated blood loss of 2000 mL or more. They enrolled 77 patients in total over 6 months: 33 into the supranormalization protocol and 34 control patients with similar baseline values. Eight (24%) protocol patients died, and 15 (44%) control patients died. The protocol patients had fewer mean organ failures, shorter stays in the intensive care unit (ICU), and fewer mean days requiring ventilation than control patients (P < .05 for each). Similar results were reported by Bishop and colleagues.<sup>12</sup>

Gattinoni and associates<sup>13</sup> undertook a large study of 762 critically ill patients in 56 ICUs who were randomized to one of three strategies: normalization of cardiac index, increasing the cardiac index to more than 4.5 L/m<sup>2</sup> (supranormalization), and normalization of Svo<sub>2</sub> greater than 70% (or increased by 20% above baseline). The goals were achieved using fluids, blood products, inotropes, and vasopressors. Patients in the supranormalization group had significantly greater oxygen delivery and consumption compared with the other groups. However, fewer than half of the patients in that group and about two thirds of the patients in the Svo<sub>2</sub> group met their



**Figure 30-1.** The normal stress (inflammatory) response. The *y* axis represents "functionality"—it may represent cardiac output, neuro-endocrine activity, inflammation, metabolism, and so forth. The stress response is well defined and predictable and lasts 72 hours.

goals; this compared with 93.4% of the patients in the normal group. There was no difference in outcome among the three groups. Of interest in this study was the timing of the resuscitative efforts. The patients were already in the ICU and may have been there for up to 72 hours before enrollment.

Hayes and coworkers<sup>14</sup> enrolled 109 patients who were admitted to their ICU and were given low-dose dopamine and fluids. Nine of the patients achieved resuscitation goals and were not entered into the protocol. The remaining 100 patients were randomized to either a supranormalization protocol (similar to that of Shoemaker and colleagues) or a control protocol. In that group, dobutamine, the main therapeutic intervention of the study, was only administered when the cardiac index was less than 2.8  $L/m^2$ . The patients in the supranormalization group had significantly better oxygen delivery and cardiac index than the controls. Nevertheless, in 35 of the 50 patients in the treatment group, the three target values were not achieved simultaneously despite inotropic support. However, the control patients had substantially better outcomes: the in-hospital mortality was lower in the control group (34%) than in the treatment group (54%) (P = .04; 95% confidence interval [CI], 0.9% to 39.1%). Thus, the absolute risk increase (ARI) was 20% (NNT, 5). This study has been extensively criticized because of the enormous doses of dobutamine (median dose of dobutamine was 25  $\mu/kg/min$ ) administered to the supranormalization group and the inadequate volume of fluid administered to both groups. In addition, the inability to achieve goals in the intervention group suggests that these patients were at an advanced stage of critical illness when enrolled into the study. Previous work by Shoemaker's group suggested that early, rather than late, initiation of



**Figure 30-3.** Fluid resuscitation strategy during the stress response. Phase A: 0 to 6 hours = aggressive volume resuscitation. Phase B: 6 to 36 hours = decelerating fluid resuscitation; fluid boluses administered to compensate for extravascular sequestration. Phase C: 36 to 48 hours = equilibrium phase; stop administering intravenous fluids. Phase D: 48 to 72 hours = mobilization fluids; withhold fluids and allow spontaneous diuresis (or diurese if necessary).

the supranormalization protocol is essential.<sup>15</sup> It is important to note that 31 of the 33 patients in whom target values were achieved survived.

Kern and Shoemaker meta-analyzed the 21 published trials of supranormalization in 2002.<sup>16</sup> The studies were divided into groups based on the time that goals were implemented (i.e., "early," 8 to 12 hours after surgery or before organ failure, versus "late," or after onset of organ failure) and the severity of illness, determined by the control group mortality as more than 20% (12 studies-they called them "severely ill patients") or less than 15% (9 studies). In severely ill patients (control mortalities group, >20%), 6 studies had a 23% mortality difference (P < .05) between the control and protocol groups with early optimization, but 7 studies optimized after the development of organ failure did not have significantly improved mortality. There was no mortality benefit in the subgroup involving patients with lower severity of illness. They concluded that early aggressive optimization benefited the sickest patients. There was no evidence that goal-directed resuscitation harmed patients.

This picture was finally clarified by the seminal work of Rivers and coworkers.<sup>6</sup> This group studied early goaldirected therapy (EGDT) in sepsis, in 263 patients randomized to "standard" therapy versus aggressive goal-directed therapy that included the use of an oximetric CVP line. This measured Svo<sub>2</sub> in the superior vena cava distribution. The study enrolled patients in the emergency room with two or more criteria for systemic inflammatory response secondary to infection. A bedside nurse and



Figure 30-2. How the stress response becomes sepsis. The initial hyperfunctional phase burns itself out, and a chronic hypofunctional phase emerges. This results from inadequate resuscitation, failure of source control, or delayed diagnosis.

doctor fluid-resuscitated the patients and, if necessary, administered inotropes and blood according to a specific protocol (an example of a similar protocol is in Fig. 30-4). The patients in the control group were managed conservatively until they were admitted to the ICU and then were resuscitated. The patients in the study group received significantly more fluid than the control group in the first 6 hours, more red cell transfusions overall, and an equivalent volume of intravenous fluid over the first 72 hours. There was a 16% decrease in 28-day mortality (NNT, 6) in the EGDT group. The implication of these study results is that early aggressive volume resuscitation ensures tissue blood flow. After goals are met, further resuscitation is not helpful and may be harmful.

Significant controversy persists regarding the utility of hemodynamic monitoring devices in the management of the patient with septic shock. Early enthusiasm for PACs has been tempered by two widely cited studies. In the first, Connors and colleagues, using data from the SUPPORT study with case-matched pairs, claimed that monitoring using PAC actually worsened outcomes.<sup>17</sup> A follow-up trial by a Canadian group was stopped early for futility.<sup>18</sup> The major weakness of this study was the absence of a direct protocol for fluid administration and vasopressor titration. In effect, the study demonstrated that the presence of a PAC did not worsen patient outcomes, but did not confer benefit; this is unsurprising because it is a monitoring tool, not a therapeutic intervention.

Modern approaches to volume and flow monitoring measure stroke volume using a variety of tools. Enthusiasm for these tools emerged following the publication of Connors' study.<sup>17</sup> The purpose of stroke volume monitoring is to construct Starling curves, using one of a variety of surrogates of end-diastolic volume as an index of cardiac preload. These include CVP, pulmonary artery occlusion pressure, and pulmonary artery diastolic pressure. Changes in stroke volume are more sensitive to changes in circulating volume than changes in cardiac output or cardiac index.<sup>19</sup> Several devices that measure surrogates of stroke volume or cardiac output are available. These include the esophageal Doppler monitor (EDM), peripherally inserted continuous cardiac output monitor (PiCCO), lithium dilution cardiac output, Fick principle CO<sub>2</sub> rebreathing cardiac output (noninvasive cardiac output [NICO]), bioimpedance cardiac output, and echocardiography. An example of a protocol that uses these monitors is represented by Figure 30-5. An alternative approach is to directly measure tissue perfusion or to measure surrogates of blood flow. This approach includes the use of gastric tonometry and tissue oxygen monitoring probes.





**Figure 30-4.** An example of a protocol for goal-directed volume resuscitation. CVP, central venous pressure; Hgb, hemoglobin; MAP, mean arterial pressure; RBC, red blood cell; Svo<sub>2</sub>, mixed venous oxygen saturation. (*Based on Rivers E, Nguyen B, Havstad S. Early goal-directed therapy in the treatment of severe sepsis and septic shock.* N Engl J Med. 2001;345:1368-1377.)

**Figure 30-5.** An example of a protocol that uses central venous pressure (CVP), mixed venous oxygen saturation (Svo<sub>2</sub>), and stroke volume (SV) monitoring. EDM, esophageal Doppler monitor; Hgb, hemoglobin; MAP, mean arterial pressure; PAC, pulmonary artery catheter. (*Data from references 6 and 21-25*).

A number of studies have used EDM stroke volume to guide perioperative fluid administration. As discussed earlier, the perioperative stress response may represent a reasonable model for early sepsis. Data derived for fluid resuscitation in this paradigm may be extrapolated to the septic patient. Most of these studies randomized patients to intraoperative stroke volume–guided colloid resuscitation versus conventional fluid resuscitation, with the result that patients received more fluid, principally in the form of colloid, in the operating room and less fluid after surgery. This resulted in better outcomes: higher splanchnic perfusion,<sup>20</sup> reduced ileus,<sup>21,24,25</sup> fewer major complications,<sup>20,25</sup> earlier achievement of discharge criteria,<sup>22,23</sup> and shorter ICU and hospital stays.<sup>20,21,24,25</sup>

In summary, the weight of current evidence supports the use of flow monitors in early sepsis or stress, examples of which are oximetric catheters (Svo<sub>2</sub> or equivalent) or stroke volume monitors (EDM, PiCCO, or equivalent), to guide early aggressive fluid resuscitation (an example of a suggested protocol that includes stroke volume, CVP, and Svo<sub>2</sub> is included in Fig. 30-3). Following actualization of resuscitation goals, resuscitation efforts should decelerate because it is clear that the timing rather than the volume of fluid is important.

#### TYPE OF FLUID ADMINISTERED

During sepsis, there is a dramatic increase in capillary permeability. This facilitates the extravasation of intravascular fluid into the interstitial space. Fluid sequestered in this way does not remobilize until the inflammatory response resolves. In these circumstances, up to 80% of crystalloid solutions used as volume replacement collect in extravascular tissues. This leads to weight gain and tissue edema, particularly in lax tissues and in the abdomen. Oxygen delivery is reduced.<sup>26</sup> In addition to increased capillary permeability, there is a reduction in plasma oncotic pressure caused by reduced circulating albumin concentrations due to dilution, extravasation, and reduced hepatic production (negative acute phase response). The rate of edema formation varies linearly with the volume of crystalloid administered.

High-molecular-weight solutions (colloids) are used widely as plasma substitutes. Colloids are homogeneous noncrystalline substances, consisting of large molecules or ultramicroscopic particles of one substance dispersed through a second substance.<sup>27</sup> Colloid solutions remain in the intravascular space because of their large molecular size, which leads to relative membrane impermeability. They may also plug leaky capillaries and increase colloid oncotic pressure (COP), thus expanding intravascular volume.<sup>28,29</sup> As compared with crystalloid solutions, lower volumes are required to achieve hemodynamic goals, there is volume expansion equal to or greater than the volume administered, and reduction in tissue edema occurs.<sup>26</sup>

Although colloids have an important role in maintaining intravascular volume, the oncotic effect is significantly less important in terms of extracellular volume than the osmotic effect of electrolytes, such as sodium or chloride. This is due to the significantly lower total number of osmotically active particles involved.

Despite these logical arguments, there is a strong counterargument that colloid solutions are expensive, probably leak into the extracellular space, and affect blood coagulation. Three influential meta-analyses were published in the late 1990s that suggested that colloid solutions may actually worsen patient outcomes.<sup>30-32</sup> There is reason to be skeptical about the results of these reviews. A myriad of compounds labeled "colloid" were included, many of which are no longer administered. The studies accrued data over a 30-year period during which fundamental changes occurred in the practices of anesthesia, trauma, and critical care. Moreover, the end points listed in the reviews (principally mortality) were not necessarily end points measured in the studies. Most of these studies were not carried out in controlled environments, did not use specific goals for resuscitation, and tended to compare isolated crystalloid resuscitation with isolated colloid resuscitation, not in combination. Most studies of colloids have compared one agent against another, rather than against crystalloid solutions.

#### ALBUMIN

Albumin is commercially available in concentrations of 5% (250- and 500-mL vials) and 25% (50- and 100-mL vials). The 5% solution contains 50 mg of albumin per milliliter of physiologic salt solution, whereas the 25% solution has an albumin concentration of 250 mg/mL. All commercial albumin products contain 130 to 160 mEq of sodium per liter of solution. The 5% solution is iso-oncotic with respect to human plasma; the 25% solution is 4 to 5 times more oncotically active than is an equivalent volume of normal plasma. Albumin has a very low incidence of allergic reactions (0.5% to 1%), and these are usually mild (rash, fever, chills, nausea). Albumin solutions do not appear to directly alter blood coagulation.

Albumin administration is associated with a rapid but unpredictable expansion of the plasma volume. Albumin has been widely used to minimize weight gain, prevent pulmonary edema, diminish ascites, and reduce tissue edema. There is some evidence that this agent may have some effect on improving organ function and facilitating enteral nutrition.<sup>33</sup> Beyond this, there is no evidence that albumin reduces mortality. Previous concerns that albumin may increase mortality.<sup>34</sup> appear to be unfounded. The Saline versus Albumin Fluid Evaluation (SAFE) study, an Australian randomized controlled trial that recruited more than 7000 patients, showed no differences in outcome between patients treated with 4% albumin as their resuscitation fluid and those receiving saline.<sup>35</sup> This study was neither powered nor designed to demonstrate a mortality benefit with albumin.

In summary, albumin is safe to use. Cost-effectiveness has not been established. There is no evidence that albumin administration improves outcomes in sepsis.

#### HYDROXYETHYL STARCHES

Hydroxyethyl starches (HES; hetastarch) are modified natural polysaccharides, derived from amylopectin, that structurally resemble glycogen. Solutions of starch are unstable because they are rapidly hydrolyzed by  $\alpha$ amylase. The solution is stabilized by hydroxyl ethylation. This results in hydroxyethyl substitutions predominantly at carbon 2 (c2), but also at c3 and c6, in the glucose ring. The pharmacokinetics of these starches is determined by the degree and type of hydroxylation. A higher c2/6 substitution ratio results in slower enzymatic degradation. The molecular weight of the compound affects its side effects. The main route of elimination is urinary. A fraction is taken up by the reticuloendothelial system, from which it is slowly eliminated. Hetastarch contains molecules of variable molecular weights, and the average weight is usually that listed. After infusion of HES, the dispersion of molecular weights changes: first the small molecules are rapidly eliminated, and then the large molecules are partially hydrolyzed to middle-sized molecules.

HES products can be divided into three classes by their weight-averaged molecular weight: high molecular weight (450 to 480 kD), medium molecular weight (about 200 kD), and low molecular weight (70 to 130 kD). Examples of commercially available starches are 6% high-molecular-weight hetastarch in saline (Hespan), 6% high-molecular-weight hetastarch in balanced electrolytes (Hextend), medium-molecular-weight pentastarch in saline (Pentaspan, EloHAES, HAES-steril), and lowmolecular-weight tetrastarch in saline (Voluven).

The most commonly used hydroxyethyl starch in the United States, Hespan, is a high-molecular-weight HES (480/0.7) with an average molecular weight of 450,000 D and a number-average molecular weight of 70,000 D; 80% of the polymers fall in the range of 30,000 to 2,400,000 D. This HES is usually formulated in 0.9% sodium chloride. The COP of this solution is about 30 mm Hg, and each gram of hetastarch has a waterbinding capacity of 20 mL. On average, 46% and 64% of the dose is excreted in the urine within 2 and 8 days, respectively. The average terminal half-life is 17 days. Plasma volume expansion persists for at least 48 hours,<sup>36</sup> with 40% of the peak effect persisting after 24 hours. Hetastarch produces a significantly greater increase in plasma COP compared with an equal volume of 5% albumin.

Serum amylase may increase significantly after infusion of HES owing to the formation of a stable hetastarchamylase complex that retards amylase excretion. Allergic reactions to HES are uncommon.

HES solutions have varying effects on coagulation that are dependent on the molecular weight of the polypeptide molecule. This appears to occur principally with highmolecular-weight HES formulations that dilute coagulation factors and induce abnormalities on thromboelastography but not standard coagulation tests. HES appears to induce an abnormality of platelet function by impairing von Willebrand factor and factor VIIIc. The effect on hemostasis appears to be dose related. Large volumes of hetastarch in vitro and in vivo produce progressive abnormalities in thromboelastography (TEG) studies. However, it is unclear whether this translates into increased risk for bleeding. Many clinicians assert that the dose of hetastarch should be limited to 20 mL/kg per day. Low-molecular-weight HES and pentastarch solutions appear to be associated with reduced risk for coagulopathy,<sup>37</sup> as does formulation in balanced salt solution rather than saline.<sup>38</sup>

The VISEP study<sup>39</sup> was a multicenter  $2 \times 2$  study that randomized patients with severe sepsis to tight glycemic control or conventional therapy and fluid resuscitation with either 10% pentastarch, middle-molecular-weight HES (200/0.5), or lactated Ringer solution. The authors looked at 28-day mortality and organ failure as primary end points, and the study was stopped early after 537 patients (at the first planned interim analysis) for safety reasons. Glycemic control made no difference to outcomes at 28 days, although there were some adverse events in the tight glycemic control group. Patients in the HES group had a lower median platelet count (179,600/mm<sup>3</sup>; interquartile range, 122,000 to 260,000) than did those in the lactated Ringer solution group (224,000/mm<sup>3</sup>; interquartile range, 149,800 to 314,800; P < .001) and received more units of packed red cells than did patients in the lactated Ringer solution group. In addition, HES was associated with increased 90-day mortality (57.6% versus 30.9%; ARI, 26.7%; NNT, 4) in patients with high-dose HES alone, with increased renal failure (ARI, 12%; P < .05), and with a 9.1% increase in length of dialysis.

This was potentially devastating news for the HES industry. However, some criticism of the study should be highlighted. Older starches than are currently promoted were used. The patients were administered higher than recommended doses (>20 mL/kg) for a long period (21 days). One of the colloids was hyperoncotic (10%; COP, 68) with respect to plasma. Finally, there are known adverse outcomes associated with primary colloid resuscitation. There was no difference between mortality levels at 28 days or indeed at 90 days. Hence, the published 90-day mortality difference may represent pharmacologic poisoning due to HES accumulation, rather than failure of therapy. Unique to this study are data suggesting that HES harms rather than benefits patients. This contrasts with systematic reviews that have assessed a large body of evidence over many years.<sup>40</sup>

In summary, HES formulations are widely used for fluid resuscitation in sepsis, where they have a theoretical benefit. Older, high-molecular-weight compounds should be avoided because of problems with coagulation and accumulation, particularly in patients with renal failure.

### CRYSTALLOID RESUSCITATION

Crystalloids, clear electrolyte solutions that may be isotonic, hypotonic, or hypertonic, are universally used as primary resuscitation fluids in critical illness. However, exclusive use of crystalloid is and will remain controversial. Advocates of aggressive crystalloid resuscitation have tended to ignore the effect of this fluid on tissue compartments (a dramatic increase in interstitial fluid volume), water dissociation (acid-base balance), electrolyte composition, colloid balance, and coagulation.<sup>41–43</sup> As discussed previously, proponents of an alternative system for perioperative fluid balance, goal-directed resuscitation, use dynamic flow-directed physiologic end points that emphasize timing rather than total volume for fluid administration. This usually involves the combination of crystalloids and colloids or blood products.<sup>6</sup>

Resuscitation with crystalloid fluids may actually reduce oxygen delivery and tissue perfusion. Funk and colleagues<sup>44</sup> undertook a laboratory experiment of isovolemic hemodilution of awake Syrian golden hamsters. The hamsters were given either lactated Ringer solution or dextran 60 to replace blood loss. Four times the volume of blood loss was replaced with lactated Ringer solution to maintain mean arterial pressure, CVP, and heart rate. Tissue perfusion and Pao<sub>2</sub> were unchanged in the colloid group, but reduced by 62% and 58%, respectively, in the crystalloid group. Lang and coworkers investigated the effect of colloid fluid replacement versus crystalloid therapy on tissue oxygen tension in patients undergoing major abdominal surgery.45 Forty-two patients were randomized to receive 6% HES plus lactated Ringer solution or lactated Ringer solution alone for 24 hours targeted to a CVP of 8 to 12 mm Hg. The investigators measured tissue oxygen tension in the deltoid muscle: a LICOX CMP monitoring device was placed after induction of anesthesia. Patients in the crystalloid group had received significantly more fluid by the end of surgery (5940  $\pm$  1910 mL versus  $3920 \pm 1350$  mL; P < .05) and at the end of 24 hours  $(11,740 \pm 2630 \text{ mL versus } 5950 \pm 800 \text{ mL}; P < .05)$ . The patients in the combined crystalloid-colloid group had significantly greater tissue perfusion (oxygen tension increased from baseline) compared with the crystalloidonly group (oxygen tension reduced from baseline).

An ideal resuscitative fluid would maintain intravascular volume without expanding the interstitial space. Ernest and associates investigated the volume of distribution of NaCl 0.9% versus albumin 55 in cardiac surgical patients.<sup>46</sup> Plasma and extracellular fluid volumes were measured by dilution of radiolabeled albumin and sodium. Administration of isotonic saline increased plasma volume by 9%  $\pm$  23% of the volume infused. Administration of 5% albumin increased plasma volume by  $52\% \pm 84\%$  of the volume infused. Albumin increased cardiac index significantly more than saline and had an equal effect on hemoglobin dilution. In the saline treatment group, the mean net fluid balance (fluid infusion + fluid losses) was about double the mean increase in extracellular fluid volume, which on average was distributed equally between the plasma volume (PV) and interstitial fluid volume (ISFV). In contrast, in the albumin treatment group, the net fluid balance approximated the mean increase in extracellular fluid volume, which approximated the mean increase in PV.

The tendency for crystalloids to extravasate may lead to relative hypoperfusion. Wilkes and colleagues studied the effects of saline-based intravenous fluids (crystalloid and HES) versus balanced salt solution (BSS)–based fluids (crystalloid and HES) on acid-base status and gut perfusion, estimated using gastric tonometry.<sup>47</sup> The patients who received saline were significantly more acidotic and had a lower gastric mucosal pH (indicative of gut perfusion) than the patients who received BSS. This was strongly related to increases in serum chloride.

There is emerging evidence that intravenous fluids may have indigenous proinflammatory and anti-inflammatory properties. In a pig model of volume-controlled hemorrhagic shock, Rhee and colleagues demonstrated a significant increase in neutrophil activation and oxidative burst activity, associated with the administration of lactated Ringer solution.<sup>48</sup> This solution activated inflammation regardless of whether blood was shed. This did not occur when volume was replaced with whole blood or 7.5% hypertonic saline. Similar findings were reported with isotonic saline, dextran, and HES, but not with albumin (5% or 25%), blood, or anesthesia.<sup>49</sup> Lactated Ringer solution administration was associated with expression of adhesion molecules that were increased in lung and spleen whether or not hemorrhage took place. This was not seen when the animal was not resuscitated or was resuscitated with fresh blood.<sup>50</sup> However, when preceded by shock, lactated Ringer solution resuscitation was associated with histologic evidence of pulmonary edema and inflammation.<sup>50</sup>

Ketone-buffered intravenous fluids, such as ethyl pyruvate, may have opposite anti-inflammatory effects. In a rat model, the use of ethyl pyruvate versus lactated Ringer solution resulted in significantly less pulmonary cellular apoptosis.<sup>49</sup>

In summary, crystalloid solutions are universally used for initial volume resuscitation in sepsis and septic shock, principally to "pay back" interstitial fluid debt. As sepsis proceeds, particularly into the hypofunctional phase, significant tissue accumulation of resuscitation fluid occurs, and this may result in adverse effects (see Chapter 12). Isotonic saline, when administered in large volume, is associated with hyperchloremic acidosis<sup>51</sup>; this may affect splanchnic blood flow and may indeed be nephrotoxic.<sup>47,52,53</sup> Lactated Ringer solution and other isotonic crystalloid solutions may activate inflammation and result in cellular apoptosis, possibly worsening lung injury.<sup>48</sup>

#### HYPERTONIC SALINE

Normal plasma osmolality is 280 to 295 mOsm/L. Any solution whose osmolality exceeds 310 mOsm/L is a hypertonic fluid. In practical terms, this refers to hypertonic saline and sodium bicarbonate solutions. A variety of different hypertonic saline (HS) solutions are commercially available; the most commonly used are 1.8% HS, 3% HS, 7.5% HS, and 23.4% HS.

There are two well-defined uses of hypertonic fluids. The first is intravascular volume expansion in patients in hypovolemic shock, as a means of low-volume, highimpact resuscitation. The second is a corollary, intracellular volume depletion. This approach is widely used in neurosurgery and neurocritical care to reduce cerebral volume and intracranial pressure.

HS dramatically increases the osmotic pressure in the compartment into which it is injected. Water flows along the osmotic gradient into the compartment, expanding its volume for several hours. In the intravascular space, HS causes endothelial cell shrinkage, arteriolar dilation, and reduced viscosity, thus increasing flow.<sup>54</sup> It may also increase myocardial contractility, although there are conflicting data on this issue. The metabolic consequences of HS are hypernatremia, hyperosmolality, and hyper-chloremic acidosis.<sup>55</sup> The degree of hypernatremia and hyperosmolality is lower than one would expect owing to the relatively low volume administered.<sup>56</sup>

The logic behind the use of HS in shocked states is based on two observations: (1) isotonic crystalloids are very inefficient plasma volume expanders and result in significant tissue edema, and (2) hypertonic solutions expand the plasma volume by a significantly greater amount than the volume administered. Consequently, significant hemodynamic benefit accrues from relatively low volumes of fluid administered. This may be of particular use in combat situations, in which the weight and size of medical supplies are of great importance.

Numerous small studies and case reports suggest that patients have better hemodynamic profiles when given HS than when administered isotonic crystalloid.<sup>57</sup> No study of prehospital administration of HS has shown an overall statistically significant benefit. Indeed, published benefits accrue in statistically weaker subgroup analyses. For example, Mattox and colleagues studied 422 patients in a randomized, double-blind, multicenter trial of prehospital HS plus dextran (HSD) versus an equal volume of isotonic crystalloid.<sup>58</sup> Patients who had been administered HSD and required surgery had improved survival. Wade and colleagues reported improved survival in patients with penetrating trauma who were administered HS.<sup>59</sup> A meta-analysis by the same group failed to demonstrate benefit using HS in trauma patients.<sup>60</sup> A more recent large clinical trial failed to demonstrate improved clinical outcomes at 6 months.<sup>61</sup> Currently, HS is not used in this setting. The major controversy in trauma is not the utility of HS but the timing of use. There are no large prospective studies on the use of HS in sepsis. However, the use of this fluid is likely to increase as a result of concerns about timing, effect, and absolute volume administered in early sepsis. Hypothetically, HS should improve overall systemic perfusion and presumably oxygen delivery, and it may modulate the inflammatory response.<sup>62</sup>

In summary, despite widespread enthusiasm, there are no available data to support the use of HS in the resuscitation of the septic patient.

# AUTHORS' RECOMMENDATIONS

- The weight of current evidence supports the use of flow monitors in early sepsis or stress, examples of which are oximetric catheters (Svo<sub>2</sub> or equivalent) or stroke volume monitors (EDM, PiCCO, or equivalent), to guide early aggressive fluid resuscitation.
- Following actualization of resuscitation goals, resuscitation efforts should decelerate because it is clear that the timing rather than the volume of fluid is important.
- Crystalloid solutions are universally used for initial volume resuscitation in sepsis and septic shock, principally to "pay back" interstitial fluid debt.
- Colloid solutions achieve hemodynamic goals more quickly than crystalloids with significantly less volume. Albumin is safe to use, although its cost-effectiveness has not been established, nor is there evidence of efficacy in sepsis.
- HES formulations are widely used for fluid resuscitation in sepsis. Older, high-molecular-weight compounds should be avoided because of problems with coagulation and accumulation, particularly in renal failure.

- As sepsis proceeds, particularly into the hypofunctional phase, significant tissue accumulation of resuscitation fluid occurs, and this may result in adverse effects.
- Isotonic saline, when administered in large volume, is associated with hyperchloremic acidosis; this may affect splanchnic blood flow and may indeed be nephrotoxic.
- Lactated Ringer solution and other isotonic crystalloid solutions may activate inflammation and result in cellular apoptosis, possibly worsening lung injury.
- Despite widespread enthusiasm, there are no available data to support the use of HS in the resuscitation of the septic patient.

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# 31 What Vasopressor Agent Should Be Used in the Septic Patient?

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This chapter briefly summarizes the hemodynamic upset associated with sepsis and then sequentially evaluates the various vasopressor agents that have been investigated and are in current use for the treatment of septic shock.

# HEMODYNAMIC DERANGEMENT IN SEPSIS

Early sepsis is clinically analogous to hypovolemic shock characterized by hypovolemia, lactic acidosis, and increased oxygen extraction—manifest by reduced mixed venous oxygen saturation (Svo<sub>2</sub>). This is best managed by goal-directed volume resuscitation (see Chapter 30), with or without inotropes to enhance the patient's physiologic reserve. Established (late-stage) septic shock is complex disease characterized by a variety of cardiovascular and neurohormonal anomalies. These are the subject of ongoing research, and although the hemodynamic consequences are easily described, the underlying mechanisms are incompletely understood. The major features of latestage septic shock follow:

- 1. Vasoplegia arises from loss of normal sympathetic tone associated with local vasodilator metabolites, which cause activation of adenosine triphosphate-sensitive potassium channels, leading to hyperpolarization of smooth muscle cells. There is increased production of inducible nitric oxide synthetase (iNOS), resulting in excessive production of nitric oxide. Finally, there is acute depletion of vasopressin.<sup>1</sup> Vasoplegia is associated with relative hypovolemia. Vascular tone is characteristically resistant to catecholamine therapy but very sensitive to vasopressin.
- 2. Reduced stroke volume is widely thought to be due to the presence of a circulating myocardial depressant factor, although it may result from mitochondrial dysfunction. There is reversible biventricular failure, a decreased ejection fraction, myocardial edema, and ischemia. Cardiac output is maintained by a dramatic increase in heart rate.
- 3. Microcirculatory failure manifests as dysregulation and maldistribution of blood flow, arteriovenous shunting, oxygen utilization defects, and widespread capillary leak. These abnormalities are incompletely understood. In addition, there is initial activation of

the coagulation system and deposition of intravascular clot, causing ischemia.

4. In mitochondrial dysfunction, the capacity of mitochondria to extract oxygen is impaired.<sup>2,3</sup> This results in elevated Svo<sub>2</sub> and elevated serum lactate despite adequate oxygen delivery to tissues.

Although the hemodynamic consequences of sepsis tend to dominate the clinical management of these patients, they are a part of a complex paradigm of multiorgan processes that become dysfunctional during established critical illness. These include renal injury, hepatic dysfunction, delirium, and acute hypoxic respiratory failure (acute respiratory distress syndrome [ARDS]). Attempts to simplify and clarify the management of the patient in septic shock, such as the Surviving Sepsis Campaign guidelines,<sup>4</sup> often fail to distinguish between early and late sepsis and have little to offer the patient with multiorgan failure. Unfortunately, most longer-stay patients in the intensive care unit (ICU) are in vasoplegic septic shock, and goal-targeted therapy for these patients has not been associated with improved outcomes. Indeed, there are emerging counterarguments to the "fluid and pressors" approach to late-stage septic shock. Although this is an interesting and developing academic area, the following discussion summarizes the various vasopressor agents that are currently used in septic shock, the strengths and weaknesses of each, and our recommendations based on the current literature.

# VASOPRESSOR THERAPY

Hypotension, unresponsive to fluid therapy, in sepsis, is generally agreed to be an indication for vasopressor use.<sup>4,5</sup> The question of which vasopressors to use in sepsis has long been debated.

Vasopressors are used to target mean arterial pressure (MAP), and inotropes are used to increase cardiac output, cardiac index, stroke volume, and Svo<sub>2</sub>. The exact MAP target in patients with septic shock is uncertain because each patient autoregulates within individualized limits. Autoregulation in various vascular beds can be lost below a certain MAP, leading to perfusion becoming linearly dependent on pressure. Often, the patient-specific autoregulation range is unknown. The titration of norepinephrine to an MAP of 65 mm Hg has been shown to preserve

tissue perfusion.<sup>6</sup> However, the patient with preexisting hypertension may well require a higher MAP to maintain perfusion. The ideal pressor agent would restore blood pressure while maintaining cardiac output and preferentially perfuse the midline structures of the body (brain, heart, splanchnic organs, and kidneys). Currently, norepinephrine is considered the agent of choice in the fluidresuscitated patient, although this is highly controversial, and there are insufficient published data to support one agent over another. All vasopressors are associated with adverse effects, and these are listed in Table 31-1.

#### Norepinephrine

Norepinephrine has pharmacologic effects on both  $\alpha_1$ - and  $\beta_1$ -adrenergic receptors. In low dosage ranges, the  $\beta$  effect is noticeable, and there is a mild increase in cardiac output. In most dosage ranges, vasoconstriction and increased MAP are evident. Norepinephrine does not increase heart rate. The main beneficial effect of norepinephrine is to increase organ perfusion by increasing vascular tone. Studies that have compared norepinephrine to

# Table 31-1 Potential Side Effects of Vasopressor Agents

#### CARDIOVASCULAR

- Tachyarrhythmias
- Ischemia: digital, cardiac, and mesenteric
- Thrombogenic effect
- · Increased myocardial work yet decreased metabolic efficiency
- Increased oxygen expenditure
- Thermogenic effects

#### IMMUNOLOGIC

- Cellular injury
- Increased generation of reactive oxygen species
- Increased cytokine generation; this later declines
- Reduced antioxidative defenses
- · Increased superoxide radical production
- Promotion of bacterial growth
- Biofilm formation
- Monocyte dysfunction
- Increased risk for nosocomial infection

#### SPLANCHNIC HYPOPERFUSION

- Mesenteric ischemia
- Ileus
- Malabsorption
- Stress ulceration
- Deranged liver function

#### METABOLIC (PARTICULARLY EPINEPHRINE)

- Aerobic glycolysis, lactic acidosis
- Insulin resistance and hyperglycemia
- Enhanced lipolysis leading to hepatic steatosis

#### DOPAMINE SPECIFIC

- · Interference with pituitary function, particularly thyroid
- Dysregulation of prolactin metabolism and immunosuppression

dopamine head to head have favored the former in terms of overall improvements in oxygen delivery, organ perfusion, and oxygen consumption.<sup>7</sup> However, care must be taken in the interpretation of any data that purport to compare vasopressors in septic shock. Two types of outcomes studies have been published: the first group includes cohort studies that look at patients given one or the other agent. These studies are weakened substantially by the possibility of selection bias. The second group randomized patients to one or more pressors and compared outcomes with another group. Invariably, patients are randomized only after they have been fluid-resuscitated and placed on pressors, and then changed over. An alternative study strategy is to study physiologic variables and organ perfusion without looking at mortality outcomes. There is good reason to do this: in most cases, MAP goals can be achieved with the first pressor that is used, and the differences between the agents are likely to influence morbidity rather than mortality, which is likely influenced by confounders such as baseline health status, sepsis bundles, and source control. Moreover, all studies performed in this field to date are underpowered to demonstrate true mortality benefit.

Marik and Mohedin<sup>8</sup> randomized 20 patients with vasoplegic septic shock to dopamine or norepinephrine, titrated to increase the MAP to greater than 75 mm Hg, and measured oxygen delivery, oxygen consumption, and gastric mucosal pH (pHi, determined by gastric tonometry) at baseline and after 3 hours of achieving the target MAP. Dopamine increased the MAP largely by increasing the cardiac output, principally by driving up heart rate, whereas norepinephrine increased the MAP by increasing the peripheral vascular resistance while maintaining the cardiac output. Although oxygen delivery and oxygen consumption increased in both groups of patients, the pHi increased significantly in those patients treated with norepinephrine, whereas the pHi decreased significantly in those patients receiving dopamine (P < .001, for corrected 3-hour value). Similar data were reported by Ruokenen and associates.<sup>5</sup>

Norepinephrine is less metabolically active than epinephrine and reduces serum lactate.<sup>7</sup> Norepinephrine significantly improves renal perfusion and splanchnic blood flow in sepsis,<sup>10,11</sup> particularly when combined with dobutamine.<sup>10</sup>

Martin and colleagues<sup>12</sup> undertook a prospective, observational cohort study of 97 patients with septic shock to look at outcome predictors using stepwise logistic regression analysis. The 57 patients treated with norepinephrine had significantly lower hospital mortality rates (62% versus 82%; *P* < .001; relative risk, 0.68; 95% confidence interval [CI], 0.54 to 0.87) than the 40 patients treated with vasopressors other than norepinephrine (high-dose dopamine, epinephrine, or both). This study was weakened by a number of factors: observational nonblinded status, probable selection bias, and a weak end point (hospital mortality). However, at the time, the study was significant because a large number of practitioners believed that norepinephrine administration resulted in organ hypoperfusion in critical illness. These data confirmed the work by Goncalves and colleagues.<sup>13</sup>

The SACiUCI study<sup>14</sup> was a year-long investigation of 1897 patients admitted to a number of Portuguese ICUs.

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Of the 458 patients with septic shock, 73% received norepinephrine and 50.5% dopamine. The norepinephrine group had a higher hospital mortality (52% versus 38.5%, P = .002). A Kaplan-Meier survival curve showed diminished 28-day survival in the norepinephrine group (log rank, 22.6; P < .001). A Cox proportional hazard analysis revealed that the administration of norepinephrine was associated with an increased risk for death (adjusted hazard ratio, 2.501; 95% CI, 1.413 to 4.425; P = .002). In a multivariate analysis with ICU mortality as the dependent factor, Simplified Acute Physiology Score II and norepinephrine administration were independent risk factors for ICU mortality in patients with septic shock. Indeed, dopamine and dobutamine also appeared to increase mortality. What this study appears to show is that administration of pressors is associated with worse outcomes in sepsis than nonadministration. This infers that patients who develop vasoplegic septic shock do worse than patients who do not. This is unsurprising. Hence, the study probably supports the "early goal-directed" approach to avoid pressors and late-stage sepsis. We do not believe that these data add value to the norepinephrine versus other pressors argument.

### Dopamine

Dopamine has predominantly  $\beta$ -adrenergic effects in low to moderate dose ranges (up to 10 µg/kg per minute), although there is much interpatient variability. This effect may be due to its conversion to norepinephrine in the myocardium and activation of adrenergic receptors. In higher dose ranges,  $\alpha$ -adrenergic receptor activation increases and causes vasoconstriction. The agent is thus a mixed inotrope and vasoconstrictor. At all dose ranges, dopamine is a potent chronotrope. It may be a useful agent in patients with compromised systolic function but causes more tachycardia and may be more arrhythmogenic than norepinephrine.<sup>15</sup> There has been much controversy about the other metabolic functions of this agent. Dopamine is a potent diuretic (i.e., it neither saves nor damages the kidneys).<sup>16</sup> Dopamine has complex neuroendocrine effects; it may interfere with thyroid and pituitary<sup>17</sup> function and may have an immunosuppressive effect.<sup>18</sup> Whether these affect outcomes, in terms of morbidity or mortality, is unknown.

A high-quality prospective trial<sup>16</sup> and a meta-analysis have displayed ample evidence to discourage the use of "renal-dose" dopamine because it does not change mortality, risk for developing renal failure, or the need for renal replacement therapy.<sup>19</sup>

The Sepsis Occurrence in Acutely Ill Patients (SOAP) study was a prospective, multicenter, observational study that was designed to evaluate the epidemiology of sepsis in European countries and was initiated by a working group of the European Society of Intensive Care Medicine. It has been the subject of a variety of database mining exercises, one of which looked at dopamine and outcomes.<sup>20</sup> Of the 3147 patients included in the SOAP study, 1058 (33.6%) had shock at any time; 462 (14.7%) had septic shock. Norepinephrine was the most commonly used vasopressor agent (80.2%), used as a single agent in 31.8% of patients with shock, as a single agent

in 8.8% of patients, and combined most commonly with norepinephrine (11.6%). Epinephrine was used less commonly (23.3%) but rarely as a single agent (4.5%). Dobutamine was combined with other catecholamines in 33.9% of patients, mostly with norepinephrine (15.4%). All four catecholamines were administered simultaneously in 2.6% of patients. The authors divided patients into those who received dopamine alone or in combination, and those who never received dopamine. The dopamine group had higher ICU (42.9% versus 35.7%; P = .02) and hospital (49.9% versus 41.7%; P = .01) mortality rates. A Kaplan-Meier survival curve showed diminished 30-day survival in the dopamine group (log rank, 4.6; P = .032). Patients treated with epinephrine had a worse outcome, but this may represent evidence of worse outcomes in patients with more severe shock. This study was observational and nonrandomized, and the original database was not designed to prove that one intervention would be associated with better outcomes than another because of the huge number of confounders.

Finally, why use dopamine? Dopamine is a natural precursor of norepinephrine, converted through βhydroxylation. When dopamine is administered, serum norepinephrine levels rise. Because dopamine is a neurotransmitter and has metabolic activity in many organ systems, there appears to be little benefit to using dopamine over norepinephrine. Further, a syndrome of dopamineresistant septic shock (DRSS) has been described, defined as MAP less than 70 mm Hg despite administration of 20  $\mu$ g/kg per minute.<sup>21</sup> Levy and colleagues investigated DRSS in a group of 110 patients in septic shock.<sup>22</sup> The incidence of DRSS was 60%, and those patients had a mortality rate of 78%, compared with 16% in the dopaminesensitive group. Thus, in the highest risk group of patients, the use of dopamine may be associated with delay in achieving hemodynamic goals.

# **Dobutamine**

Dobutamine is a potent  $\beta_1$ -adrenergic receptor agonist, with predominant effects in the heart, where it increases myocardial contractility and thus stroke volume and cardiac output. Dobutamine is associated with much less increase in heart rate than dopamine. In sepsis, dobutamine, although a vasodilator, increases oxygen delivery and consumption. Dobutamine appears particularly effective in splanchnic resuscitation, increasing pHi (gastric mucosal pH) and improving mucosal perfusion in comparison with dopamine.<sup>23</sup> As part of an early goal-directed resuscitation protocol that combined close medical and nursing attention and aggressive fluid and blood administration, dobutamine was associated with a significant absolute reduction in the risk for mortality. This study, however, looked at early (hypovolemic) rather than late (vasoplegic) sepsis.<sup>5</sup>

By and large, dobutamine, when administered in latestage sepsis, is used as a adjunct agent to drive up splanchnic blood flow or increase stroke volume. For example, Levy and colleagues<sup>24</sup> compared the combination of norepinephrine and dobutamine to epinephrine in septic shock; this was a physiologic study. After 6 hours, the use of epinephrine was associated with an increase in lactate
levels (from  $3.1 \pm 1.5$  to  $5.9 \pm 1.0$  mmol/L; P < .01), whereas lactate levels decreased in the norepinephrine-dobutamine group (from  $3.1 \pm 1.5$  to  $2.7 \pm 1.0$  mmol/L). The lactate-topyruvate ratio increased in the epinephrine group (from  $15.5 \pm 5.4$  to  $21 \pm 5.8$ ; P < .01) and did not change in the norepinephrine-dobutamine group ( $13.8 \pm 5$  to  $14 \pm 5.0$ ). Gastric mucosal pH (pHi) decreased (from 7.29  $\pm$  0.11 to 7.16  $\pm$  0.07; *P* < .01), and the partial pressure of carbon dioxide  $(Pco_2)$  gap (tonometer  $Pco_2$  – arterial  $Pco_2$ ) increased (from  $10 \pm 2.7$  to  $14 \pm 2.7$  mm Hg; P < .01) in the epinephrine group. In the norepinephrine-dobutamine group, pHi (from  $7.30 \pm 0.11$  to  $7.35 \pm 0.07$ ) and the Pco<sub>2</sub> gap (from  $10 \pm 3$  to 4 $\pm$  2 mm Hg) were normalized within 6 hours (P < .01). Thus, compared with epinephrine, dobutamine and norepinephrine were associated, presumably, with better splanchnic blood flow and a reduction in catecholamine-driven lactate production. Whether this is of clinical significance is unclear. Moreover, the decrease in pHi and the increase in the lactate-to-pyruvate ratio in the epinephrine group returned to normal within 24 hours. The serum lactate level normalized in 7 hours.

#### Epinephrine

Epinephrine has potent  $\beta_1$ -,  $\beta_2$ -, and  $\alpha_1$ -adrenergic activity, although the increase in MAP in sepsis is mainly from an increase in cardiac output (stroke volume). There are three major drawbacks from using this drug: (1) epinephrine increases myocardial oxygen demand; (2) it increases serum glucose and lactate,<sup>25,26</sup> which is largely a calorigenic effect (increased release and anaerobic breakdown of glucose); and (3) epinephrine appears to have adverse effects on splanchnic blood flow,<sup>24,27–29</sup> redirecting blood peripherally as part of the fight-and-flight response. As we have seen, factors 2 and 3 are of undetermined significance and are transient. Whether increasing myocardial oxygen consumption in sepsis is a good or a bad thing is unknown.

Many data support the hypothesis that epinephrine reduces splanchnic blood flow, at least initially. Seguin and colleagues prospectively studied gastric mucosal blood flow (GMBF) in a small group of ICU patients, using laser Doppler.<sup>30</sup> They showed that a combination of dopexamine-norepinephrine enhanced gastric mucosal blood flow more than epinephrine did.<sup>30</sup> Conversely, the same group had previously shown that GMBF was increased more with epinephrine than with the combination of dobutamine and norepinephrine.<sup>31</sup> Both studies only looked at GMBF for 6 hours and were unable to demonstrate differences in hepatic blood flow or oxidative stress.

Myburgh and colleagues performed a prospective, multicentered, double-blind, randomized controlled trial of 280 ICU patients comparing epinephrine to norepinephrine.<sup>32</sup> They found no difference in time to achieve target MAP. There was also no difference in the number of vaso-pressor-free days between the two drugs. However, a number of patients receiving epinephrine were withdrawn from this study owing to a significant but transient tachy-cardia, increased insulin requirements and lactic acidosis.

Annane and colleagues prospectively randomized 330 patients with septic shock treated with norepinephrine with or without dobutamine against epinephrine alone.<sup>33</sup>

There was also no difference in outcomes or safety in a prospective comparison of 330 patients. At day 28, the mortality rate was 40% in the epinephrine group and 34% in the norepinephrine plus dobutamine group; this was not statistically significant (P = .31; relative risk, 0.86; 95% CI, 0.65 to 1.14). There was no significant difference between the two groups in mortality rates at discharge from intensive care (47% versus 44%, respectively; P = .69), at hospital discharge (52% versus 49%; P = .51), at day 90 (52% versus 50%; P = .73), time to hemodynamic success (log-rank P = .67), time to vaso-pressor withdrawal (log-rank P = .09), and time course of Sequential Organ Failure Assessment (SOFA) score. Rates of serious adverse events were also similar.

In summary, epinephrine, although not currently recommended by international organizations<sup>4</sup> as first-line vasopressor therapy in sepsis, is a viable alternative. There are few data to distinguish epinephrine from norepinephrine in achievement of hemodynamic goals, and epinephrine is a superior inotrope. Concern about the impact of epinephrine on splanchnic perfusion may be misguided. It has been assumed that a lower pHi and increased Pco2 gap correlates with hypoperfusion; however, the opposite may be the case. Epinephrine may increase splanchnic oxygen utilization and CO<sub>2</sub> production through a thermogenic effect, especially if gastric blood flow does not increase to the same extent, inducing a mismatch between splanchnic oxygen delivery and splanchnic oxygen consumption.<sup>34</sup> This is supported by data from Duranteau and colleagues.35 Concern about the effect of increased serum lactate and hyperglycemia has limited the use of epinephrine. However, it is unclear whether lactate is harmful in sepsis,<sup>34</sup> and concern regarding hyperglycemia appears to be fading.<sup>34</sup>

#### Phenylephrine

Phenylephrine is an almost pure  $\alpha_1$ -adrenergic agonist with moderate potency. Although widely used in anesthesia to treat iatrogenic hypotension, it is an often ineffective agent in sepsis. Phenylephrine is the adrenergic agent least likely to cause tachycardia. Phenylephrine is a less effective vasoconstrictor than norepinephrine or epinephrine. Compared with norepinephrine, phenylephrine reduces splanchnic blood flow, oxygen delivery, and lactate uptake.<sup>37</sup> Phenylephrine may be a good therapeutic option when tachyarrhythmias limit therapy with other vasopressors.<sup>31,38</sup>

#### Vasopressin

Arginine-vasopressin is an endogenous hormone that is released in response to decreased intravascular volume and increased plasma osmolality. Vasopressin constricts vascular smooth muscle directly through V1 receptors. It also increases the responsiveness of the vasculature to catecholamines.<sup>39,40</sup>

Vasopressin has emerged as an additive vasoconstrictor in septic patients who have become resistant to catecholamines.<sup>41</sup> There appears to be a quantitative deficiency of this hormone in sepsis,<sup>42–44</sup> and administration of vasopressin in addition to norepinephrine increases splanchnic blood flow and urinary output.<sup>45</sup> Vasopressin offers theoretical advantages over epinephrine in that it does not increase myocardial oxygen demand significantly, and its receptors are relatively unaffected by acidosis.<sup>46</sup>

Early studies demonstrated that the most efficacious dose was 0.04 U/minute,<sup>47</sup> and this is not titrated. This relatively low dose has little or no effect on normotensive patients. Several small studies have demonstrated the potential utility of vasopressin (or its analogs) in sepsis, although there are few compelling supportive data.<sup>45,48–50</sup>

Russell and colleagues performed a multicenter, randomized, double-blind trial of patients in septic shock who were already receiving 5 µg of norepinephrine per minute (VASST trial).<sup>51</sup> Three hundred ninety-six patients were randomized to receive vasopressin (0.01 to 0.03 U/minute), and 382 were randomized to receive norepinephrine (5 to 15  $\mu$ g/minute) in addition to open-label vasopressors. There was no significant difference between the vasopressin and norepinephrine groups in the 28-day mortality rate (35.4% and 39.3%, respectively; P = .26) or in 90-day mortality rate (43.9% and 49.6%, respectively; P = .11). This is an example of a crossover study in which patients were already on one vasopressor and then randomized to stay on it or be crossed over. This study was underpoweredan expected mortality rate of 60% was used for the sample size planning; the actual mortality rate in the control group was 39%. In addition, the dose of vasopressin used in the study (up to 0.03 U/minute) may have been inadequate to show a response in the patients with more severe septic shock because a significant benefit was seen in patients with less severe sepsis (a 25.8% relative reduction in the 28-day mortality rate).

A subsequent retrospective analysis of the VASST study database suggested a beneficial synergy between vasopressin and corticosteroids in patients who had septic shock and were also treated with corticosteroids.<sup>52</sup> Vasopressin, compared with norepinephrine, was associated with significantly decreased mortality (35.9% versus 44.7%, respectively; P = .03). Conversely, in patients who did not receive corticosteroids, vasopressin was associated with increased mortality compared with norepinephrine (33.7% versus 21.3%, respectively; P = .06). Interestingly, in patients who received vasopressin infusion, administration of corticosteroids significantly increased plasma vasopressin levels by 33% at 6 hours (P = .006) to 67% at 24 hours (P = .025) compared with patients who did not receive corticosteroids.

#### OTHER VASOPRESSORS

Although this chapter has focused on vasoactive agents that are commonly used and studied in intensive care, a variety of other agents are available and have been used. These include phosphodiesterase inhibitors, such as milrinone and enoximone, and calcium sensitizers, such as levosimendan.<sup>653</sup> Phosphodiesterase inhibitors would appear to be an attractive alternative to dobutamine for cardiomyopathy of critical illness<sup>54,55</sup> and may indeed be efficacious for restoring splanchnic blood flow. There are currently inadequate data on these agents to recommend their use in septic shock.

#### AUTHORS' RECOMMENDATIONS

- There are two phases in the development of septic shock: an early phase that behaves like hypovolemia and responds to goal-directed fluid resuscitation and a later stage characterized by vasoplegia, myocardial dysfunction, dysregulation of the microcirculation, and abnormalities of mitochondrial activity.
- Vasopressor therapy is and will remain a core component of therapy in late-stage septic shock. The goal of treatment is to maintain blood pressure in the autoregulation range of major organs.
- Controversy continues regarding the choice of vasopressor and the method of monitoring the response to therapy. This will continue until adequately powered multicentered prospective trials are performed.
- It is essential that patients are fluid-resuscitated before commencement of vasopressor therapy.
- Few data are available suggesting the primacy of one agent over another; however, catecholamines continue to be the agent group of first choice.
- Norepinephrine is a potent vasoconstrictor that maintains cardiac output and restores midline blood flow. It is not metabolically active, and this would appear beneficial.
- Dopamine is a problematic agent. It has a variety of nonhemodynamic effects that may affect neurohormonal and immune function. It is an unpredictable vasoconstrictor; a significant cohort of patients are dopamine resistant and require changeover to epinephrine and norepinephrine.
- Epinephrine is a potent vasoconstrictor and inotrope. When commenced, it causes an early lactic acidosis secondary to aerobic glycolysis and may reduce splanchnic blood flow. The clinical significance of this is unclear, and both of these effects appear to be time limited.
- Dobutamine is a potent inotrope that is a useful adjunct to fluid resuscitation in early sepsis. In late septic shock, dobutamine is widely used in combination with norepinephrine as an inotrope.
- Phenylephrine has little or no value in the management of the patient in septic shock.
- There is an absolute deficiency of vasopressin in septic shock, and combination therapy with catecholamines should be considered. Few data support the use of vasopressin as firstline therapy. Corticosteroids appear to have an additive effect with vasopressin and may improve outcomes.
- There are inadequate data available to recommend the use of calcium sensitizers or phosphodiesterase inhibitors in septic shock.

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## 32 Should Vasopressin Be Used in Septic Shock?

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Sepsis is an important clinical problem because it is common, it is increasing in frequency, and it continues to have an unacceptably high mortality rate.<sup>1</sup> Septic shock is defined as hypotension due to sepsis despite adequate fluid resuscitation<sup>2</sup> and is characterized by a significantly decreased systemic vascular resistance. Vasopressor therapy is needed to ensure adequate blood pressure to maintain tissue perfusion. Typical vasopressors include norepinephrine, epinephrine, and dopamine. However, infusion of catecholamines may actually cause, rather than improve, organ ischemia.<sup>3</sup> Therefore, recent studies have examined the value of vasopressin, in addition to catecholamines, in the management of septic shock.

Vasopressin (antidiuretic hormone) is an endogenous nonapeptide hormone secreted from the posterior pituitary. In health, vasopressin acts primarily as an antidiuretic hormone, resulting in avid free water retention by the kidney, and has little effect on arterial pressure at physiologic levels under normal conditions. However, during hypotension and hypovolemia, vasopressin concentration increases and maintains arterial blood pressure by acting as a potent vasoconstrictor. This occurs through stimulation of V1a receptors. Vasopressin has little or no antidiuretic effect during hypotension.

#### PATHOPHYSIOLOGY AND MECHANISM OF ACTION

Vasopressin exerts its effects through interaction with a family of vasopressin receptors. V1a receptors are located on vascular smooth muscle cells and are responsible for vasoconstriction. Heterogeneity of the distribution of V1a receptor could have important clinical and therapeutic implications. For example, vasopressin causes renal efferent, but not renal afferent, artery vasoconstriction. This increases renal perfusion pressure and glomerular filtration rate. In contrast, norepinephrine interacts with  $\alpha_1$ -adrenergic receptors on both renal afferent and renal efferent arterioles. Therefore, norepinephrine at high doses may decrease renal perfusion and glomerular filtration rate. Thus, in contrast to norepinephrine, there is compelling organ-specific heterogeneity in vascular responses to vasopressin.

Activation of V2 receptors in the renal distal convoluted tubules and medullary collecting ducts is responsible for water reabsorption. V3 receptors, located in the anterior pituitary, have central effects. These include increasing adrenocorticotropin hormone production and secretion in response to vasopressin binding. This interaction of the vasopressin and corticosteroid pathways also could have relevant clinical and therapeutic importance because both vasopressin and corticosteroids are given, alone or in combination, to patients who have septic shock.

Importantly, vasopressin also binds to oxytocin receptors. These, in addition to their uterine contractile effects, mediate calcium-dependent vasodilatation through stimulation of the nitric oxide pathway in endothelial cells<sup>4</sup> of pulmonary,<sup>5</sup> coronary,<sup>6</sup> and cerebral arteries.<sup>7</sup>

#### VASOPRESSIN CONCENTRATION IN SEPTIC SHOCK

Normally, plasma vasopressin concentration in humans is less than 4 pg/mL. Hypotension is the most potent stimulus to vasopressin secretion from the posterior pituitary gland, markedly increasing levels. In cardiogenic shock, vasopressin concentration increases to more than 20 pg/mL<sup>8</sup>, and in severe hypotensive hemorrhage, vasopressin concentrations of 100 to 1000 pg/mL have been reported.<sup>9</sup> In septic shock, there is a relative vasopressin deficiency. In a small case series (n = 19) of patients who had vasodilatory shock, Landry and colleagues observed a mean plasma vasopressin concentration of 3.1 pg/mL.<sup>8</sup> Very low plasma vasopressin concentrations also have been reported in other small studies of vasopressin infusion in established septic shock. Mean baseline plasma vasopressin concentration was 1.3 pg/mL in 24 patients in a phase II trial<sup>10</sup> and 7.3 pg/mL in a small (n = 16) cohort of patients who had vasodilatory shock.<sup>11</sup> There was a slight increase in plasma vasopressin concentration in the early stages of septic shock (4.1 to 21 pg/ mL) in a study of 62 patients, although this rise was smaller than the rise seen in other forms of shock.<sup>12</sup> Furthermore, vasopressin concentrations fell significantly over time such that by 36 hours (and as quickly as 6 hours in some cases), most patients developed a relative vasopressin deficiency. In the recent VASST study, vasopressin levels were measured in a convenience sample of 107 patients.<sup>13</sup> The median plasma vasopressin level at baseline was 3.2 pmol/L and remained low in those patients treated with norepinephrine.

Low-dose vasopressin infusion consistently increases plasma vasopressin concentration. In VASST, plasma vasopressin concentration increased from 3 pmol/L to about 70 to 100 pmol/L during infusion of 0.03 U/min.<sup>13</sup> Landry and colleagues reported plasma vasopressin concentrations of 27 to 34 pg/mL with infusion of 0.01 U/minute of vasopressin,<sup>8</sup> Patel and associates found vasopressin concentration of 17.1  $\pm$  3.9 pg/mL after 4 hours of vasopressin (median dose, 0.06 U/minute),<sup>10</sup> and Tsuneyoshi and coworkers reported a vasopressin concentration of 289.3  $\pm$  64.7 pg/mL after 16 hours of 0.04 U/minute vasopressin.<sup>11</sup>

#### EFFICACY OF VASOPRESSIN IN SEPTIC SHOCK

There are few randomized controlled trials of vasopressin in septic shock (Table 32-1). Most of these trials were small proof-of-principle studies that used physiologic variables as the primary outcome. In an early study, Malay and colleagues examined 10 patients who had septic shock to assess the hemodynamic effects of vasopressin infusion.<sup>14</sup> Vasopressin, compared with saline, increased systolic and mean arterial pressure and decreased doses of conventional vasopressor infusions such as norepinephrine. The small number of patients combined with a number of early deaths in the control group made evaluation of mortality impossible.

A subsequent study by Patel and associates compared vasopressin with norepinephrine infusion in 24 patients who had septic shock and were already receiving norepinephrine.<sup>10</sup> In this randomized controlled trial, patients received blinded infusions of vasopressin or norepinephrine while the open-label norepinephrine infusion was titrated by the bedside nurse to maintain a target mean arterial pressure of 65 to 75 mm Hg for a 4-hour study period. In the vasopressin group, mean arterial pressure was maintained while the open-label norepinephrine dose was significantly reduced from 25 µg/minute to 5 µg/minute. In the norepinephrine group, there was no change in total norepinephrine dose (open-label norepinephrine plus concealed norepinephrine study drug). There were no other cardiovascular changes associated with vasopressin infusion. The other important finding was that vasopressin infusion doubled urine output and

Table 32-1 Summary of Randomized Controlled Trials										
Study	No. of Subjects (Intervention/No Intervention) Inclusion Criteria	Study Design Intervention		Control	Outcomes					
Malay et al, 1999 <sup>14</sup>	10 (5/5) Septic shock post- trauma/postsurgery	DB 24-hr study period	AVP, 0.04 U/min	Saline	↑ BP ↓ Catecholamines $\leftrightarrow$ CI, HR, PAP No safety concerns					
Patel et al, 2002 <sup>10</sup>	24 (13/11) Septic shock	DB 4-hr study period	AVP, 0.01-0.08 U/min	NE, 2-16 μg/min	↓ Catecholamines ↔ CI, HR, PAOP, ST ↑ UO No safety concerns					
Dünser et al, 2003 <sup>15</sup>	48 (24/24) Vasodilatory shock ± sepsis (>0.5 μg/kg/min NE)	DB 48-hr study period	AVP, 0.066 U/min	NE, titrated to MAP ≥70 mm Hg	<ul> <li>↑ BP, CI, SVI, LVSWI</li> <li>↓ Catecholamines</li> <li>↓ HR</li> <li>↓ Tachyarrhythmias</li> <li>↓ Platelets</li> <li>↑ Bilirubin</li> </ul>					
Lauzier et al, 2006 <sup>16</sup>	23 (13/10) Septic shock	Unblinded 48-hr study period	AVP, 0.04-0.20 U/min	NE, 0.1-2.8 μg/ kg/min	↓ Catecholamines ↓ HR, ↓ CI, ↓ DO <sub>2</sub> ↓ SOFA score ↑ Creatinine clearance 1 case ACS					
Russell et al, 2008 <sup>13</sup>	778 (396 vs. 382) Septic shock (>5 μg/ min NE, for 6-30 hr)	DB 28-day study period	AVP, 0.01-0.03 U/min	NE, 5-15 μg/min	↓ Catecholamines ↓ HR, ↓ CI, ↔ SV No significant difference in mortality overall Decreased mortality in less severe shock (<15 μg/min) No safety concerns					

ACS, acute coronary syndrome; AVP, arginine vasopressin; BP, blood pressure; CI, cardiac index; DB, double-blind study; DO<sub>2</sub>, oxygen delivery; HR, heart rate; LVSWI, left ventricular stroke work index; NE, norepinephrine; PAOP, pulmonary artery occlusion pressure; PAP, pulmonary artery pressure; SOFA, Sequential Organ Failure Assessment; SV, stroke volume; SVI, stroke volume index; UO, urine output. increased creatinine clearance by the end of the 4-hour study period.

Dünser and colleagues found a similar norepinephrine sparing effect of vasopressin in a slightly larger trial (n = 48) of patients who had vasodilatory shock (about one third of whom had septic shock). All were receiving high-dose norepinephrine (>0.5  $\mu$ g/kg per minute).<sup>15</sup> Not only did vasopressin decrease the dose of norepinephrine infusion, but also the agent increased mean arterial pressure, cardiac index, stroke volume index, and left ventricular stroke work index. Further, combined vasopressin and norepinephrine infusion improved gastrointestinal perfusion as assessed by gastric tonometry. There also were fewer tachyarrhythmias associated with vasopressin. Importantly, however, Dünser and colleagues used a higher dose (0.066 IU/minute) of vasopressin than that used in other studies. There were unexpected adverse effects in the vasopressin group. These included increased bilirubin, increased transaminase levels, and thrombocytopenia.

Lauzier and colleagues compared vasopressin and norepinephrine in a small number of patients (n = 23) who had early hyperdynamic shock.<sup>16</sup> Although patients were randomized to treatment group, the study drug was not blinded. Patients received high-dose vasopressin (0.04 to 0.20 U/minute) or norepinephrine (0.1 to 2.8  $\mu$ g/kg per minute), and hemodynamic variables and organ function were assessed over 48 hours. Despite the use of relatively high doses of vasopressin, most patients in the vasopressin group required norepinephrine infusion to maintain mean arterial pressure, although at much reduced doses of norepinephrine infusion. Vasopressin decreased cardiac index because of a decrease in heart rate, but stroke volume was unchanged. Although this study was not designed to evaluate the effects of vasopressin infusion on mortality, vasopressin infusion was associated with reduced organ dysfunction at 48 hours (as exhibited by a lower modified Sequential Organ Failure Assessment [SOFA] score). The difference in SOFA score was due mainly to the beneficial effect of vasopressin on renal function, in that creatinine clearance improved in the vasopressin-treated patients.

Despite the encouraging physiologic changes reported in these trials, none of these studies was designed to evaluate mortality. To date, the VASST study is the only randomized controlled trial of vasopressin versus norepinephrine that was powered to evaluate effects of vasopressin on mortality.<sup>13</sup> Patients in VASST had septic shock defined as (1) presence of two or more criteria for systemic inflammatory response syndrome (SIRS), (2) proven or suspected infection, (3) new dysfunction of at least one organ, and (4) hypotension despite fluid resuscitation and requiring at least 5 µg/minute of norepinephrine or equivalent. This multicenter, double-blind trial of vasopressin versus norepinephrine included 778 adult patients with septic shock who were randomized and infused with study drug (vasopressin [n = 396] or norepinephrine [n = 382]). A blinded vasopressin infusion was started at 0.01 U/minute and increased over 40 minutes to a maintenance dose of 0.03 U/minute. Similarly, a blinded norepinephrine was started at 5  $\mu$ g/minute and increased over 40 minutes to a maintenance dose of 15  $\mu$ g/minute. During the study drug initiation, the critical care nurses titrated open-label vasopressor infusions to maintain a target mean arterial pressure of 65 to 75 mm Hg. Tapering of open-label vasopressors was permitted when target mean arterial pressure had been achieved on the study drug. This infusion was tapered only when patients had maintained a stable mean arterial pressure and had been off open-label vasopressors for at least 8 hours.

Low-dose vasopressin infusion rapidly decreased the infused doses of catecholamines while maintaining mean arterial pressure. However, there was no significant difference in 28-day mortality between the treatment groups (35.4% in the vasopressin group and 39.3% in the norepinephrine group; P = .26) or in 90-day mortality (43.9% and 49.6%, respectively; P = .11). In the predefined stratum of less severe shock (defined as 5 to 15 µg/minute of norepinephrine before randomization), there was a significantly lower mortality rate in the vasopressin group compared with the norepinephrine group (26.5% versus 35.7%, respectively; P = .05). There was no difference in mortality between treatment groups in the patients who had more severe shock.

The rate of norepinephrine (or equivalent) infusion was significantly lower in the vasopressin than in the norepinephrine group over the first 4 days. In keeping with many previous studies, there was a rapid decrease in heart rate when vasopressin infusion was started, and heart rate was significantly lower in the vasopressin group compared with the norepinephrine group over the first 4 days. Similar to the findings of Lauzier and colleagues,<sup>16</sup> there was a small decrease in cardiac index but no change in stroke volume.<sup>17</sup>

Additional post hoc subgroup analyses were performed in VASST to determine whether the beneficial effect of low-dose vasopressin in less severe septic shock was robust. Low-dose vasopressin was associated with significantly decreased mortality in patients who had the lowest lactate levels (<1.4 mmol/L) (vasopressin mortality, 18.9%; norepinephrine mortality, 33.8%; P = .04) and also in patients who required only one vasopressor at baseline (vasopressin mortality, 31.3%; norepinephrine mortality, 39.9%; P = .04). These findings support the notion that patients who have less severe septic shock (defined by dose of norepinephrine infusion [5 to 15  $\mu$ g/ minute], by arterial lactate [<1.4 mmol/L], or by use of one vasopressor infusion) may benefit from low-dose vasopressin infusion, but those who have more severe shock do not. Interestingly, patients in the vasopressin group who were infused with the study drug within 12 hours after meeting inclusion criteria had a lower mortality rate than patients in the norepinephrine group who were infused with the study drug within 12 hours (33.2% versus 40.5%, respectively; P = .12). There was no difference in mortality if the study drug was started after 12 hours (37.7% versus 37.5%; P = .97).

The explanation for finding that vasopressin compared with norepinephrine decreases mortality in less severe septic shock is not yet known. Leone and Boyle<sup>18</sup> studied effects of vasopressin and norepinephrine on isolated mesenteric arteries. They found that the beneficial synergistic effects of vasopressin (on norepinephrine responsiveness) occurred under conditions similar to less severe septic shock. This synergistic effect disappeared under conditions that are similar to more severe septic shock. This study provides one potential biologic explanation for the benefits of vasopressin infusion compared with norepinephrine infusion in less severe septic shock but not in more severe septic shock.

Several strengths of VASST were the multicenter design, large sample size (and so powered for mortality), blinding of study drug infusion, selection of low-dose vasopressin, blinded evaluation of serious adverse events, well-defined inclusion and exclusion criteria, and assessment of pharmacokinetics of several days of vasopressin infusion (plasma vasopressin levels according to treatment group). The potentially beneficial effects of low-dose vasopressin infusion in less severe septic shock require discussion of the attributes of a credible subgroup.<sup>19</sup> The first important attribute is prospective definition of the subgroup. The severity of septic shock was the only former stratification variable (other than center). The second valuable attribute of a credible subgroup is that it makes up a large proportion of the sample and of the population of the disease of interest. The less severe septic shock stratum was about half of the sample in VASST. The third useful attribute of a credible subgroup is that there is a large clinical and statistical significant difference. Vasopressin infusion, as compared with norepinephrine infusion, was associated with a 10% decrease in mortality (P = .05) in the patients who had less severe septic shock. The fourth attribute of a credible subgroup is that the result should be robust or reproducible, as it was in patients who had low arterial lactate and in patients who were receiving only one vasopressor infusion.

Further recent data has generated interesting information about how vasopressin might best be used in septic shock. Additional post-hoc subgroup analysis of the VASST study found that vasopressin, compared to norepinephrine, was associated with lower rates of progression to renal failure and loss (20.8% versus 39.6%, P = .03) and need for renal replacement therapy (17.0% versus 37.7%, P = .02) in patients at risk of acute kidney injury.<sup>20</sup> The improved renal outcome was also associated with a lower mortality rate in this group of patients treated with vasopressin (30.8% versus 54.7%, P = 0.01). No difference in outcomes was seen in patients who already had more established kidney injury before vasopressin treatment.

There has also been data to suggest that there might be important interactions between vasopressin and corticosteroids in the treatment of septic shock. Both the VASST study<sup>21</sup> and another smaller randomised controlled trial<sup>22</sup> found that circulating vasopressin levels were higher in patients administered both exogenous vasopressin and corticosteroids compared to patients administered vasopressin alone. Interestingly there was also a statistically significant interaction between vasopressin infusion and corticosteroid treatment on survival in VASST.<sup>21</sup> In patients treated with corticosteroids, vasopressin compared to norepinephrine was associated with decreased mortality (35.9% versus 44.7%, P = .03). In contrast, in those patients who did not receive corticosteroids vasopressin was associated with a trend to higher mortality compared to norepinephrine (33.7% versus 21.3%, P = 0.06). A similar interaction was also seen in a small retrospective study, where the administration of vasopressin and corticosteroids was associated with more patients being alive and free of vasopressors at one week compared to vasopressin use alone (80.9% versus 47.6%, P = .02).<sup>23</sup>

#### SAFETY OF VASOPRESSIN IN SEPTIC SHOCK

Although there are few randomized controlled trials of vasopressin, there are a number of case studies reporting experience with the use of vasopressin in the management of septic shock. In general, in nonrandomized studies of septic shock, it is difficult to separate adverse events due to the therapy from those due to the underlying pathologic process. These case studies invariably have shown the catecholamine sparing effect of vasopressin but also have reported a number of possible safety concerns. A number of the studies have reported a decrease in cardiac output,<sup>8,16,17,24,25</sup> although an increase in cardiac output has been recorded.<sup>15</sup> In general, the decrease in cardiac output has been related to a decrease in heart rate because stroke volume has been unchanged.<sup>16,17,25</sup>

Other cardiac concerns include myocardial ischemia. There was one case of myocardial ischemia induced by high-dose vasopressin in a patient without known ischemic cardiac disease. This resolved when vasopressin was stopped.<sup>16</sup> In the retrospective case series by Holmes and coworkers, higher doses of vasopressin (>0.04 U/min) compared with lower doses of vasopressin infusion were associated with an increased rate of cardiac arrest.<sup>26</sup>

Vasopressin is used for its splanchnic vasoconstrictor effects in patients with bleeding esophageal varices. As a result, there has been concern that vasopressin could cause mesenteric ischemia. There is clinical equipoise regarding whether vasopressin induces mesenteric ischemia because there are studies showing vasopressin worsened, did not change, or improved mesenteric perfusion as assessed by gastric tonometry. Vasopressin increased the gastric to arterial CO<sub>2</sub> partial pressure gap compatible with gastric hypoperfusion in a dose-dependent fashion in one small case series of patients who had septic shock.<sup>27</sup> In contrast, there was an improvement in gastrointestinal perfusion as assessed by gastric tonometry in the randomized controlled trial by Dünser and colleagues.<sup>15</sup> This study did, however, report an increase in bilirubin levels, and the same group reported similar findings in a prior retrospective study, along with a fall in platelet count.<sup>25</sup> In a large case series of 316 patients who had vasodilatory shock, vasopressin infusion was associated with increased bilirubin levels and liver transaminases as well as decreased platelet count.24 Vasopressin has been shown to cause platelet aggregation,<sup>2</sup> and it has been suggested that this may contribute to ischemic skin lesions in vasopressin-treated patients during septic shock.<sup>29</sup> Interestingly, in this latter report,

increasing dose of norepinephrine (but not vasopressin) was associated with ischemic skin lesions.

In the only large randomized controlled trial of vasopressin (VASST), there were no safety concerns.<sup>13</sup> The overall serious adverse event rates were the same in the vasopressin and norepinephrine groups (10.3% and 10.5%, respectively), and there was no difference in any of the specific categories of serious adverse events. In particular, there was no significant difference in the rates of myocardial, mesenteric, or digital ischemia; cardiac arrest; life-threatening arrhythmias; hyponatremia; or cerebrovascular accident. There were fewer cases of acute mesenteric ischemia in the vasopressin group than in the norepinephrine group (9 [2.3%] versus 13 [3.4%], respectively). There were more cases of digital ischemia in the vasopressin than the norepinephrine group (8 [2%] versus 2 [0.5%], respectively). However, it is important to remember that patients at increased risk for complications from either vasopressin or norepinephrine infusion (e.g., severe cardiac disease, preexisting mesenteric ischemia) and vasospastic diatheses (e.g., Raynaud syndrome) were excluded from VASST. Therefore, care must be exercised when applying these findings to the general population of patients who have septic shock.

#### GUIDELINES

Guidelines for the management of sepsis and septic shock have been updated recently by the international Surviving Sepsis Campaign.<sup>30</sup> Regarding choice of vasopressor, the guidelines recommend "norepinephrine or dopamine as the first choice vasopressor in septic shock" (grade 1C evidence). The guidelines state: "vasopressin should not be administered as the initial vasopressor in septic shock (grade 2C). Vasopressin 0.03 units/min may be added to norepinephrine subsequently with anticipation of an effect equivalent to that of norepinephrine alone."

#### CONCLUSION

- Established septic shock is associated with a relative but physiologically important vasopressin deficiency.
- Low-dose (0.01 to 0.03 U/minute) vasopressin infusion increases plasma vasopressin levels (to about 100 pmol/L), increases mean arterial pressure, and spares other catecholamine vasopressors (i.e., decreases the dose of infused catecholamines such as norepinephrine).
- Vasopressin has a number of physiologic properties, particularly binding to the V1a receptor activity and vasoconstriction, that make it a rational therapy in septic shock.
- Vasopressin has not been proved to decrease mortality of patients who have septic shock.
- Low-dose vasopressin infusion (0.01-0.03 U/minute) may decrease mortality of patients who have less severe septic shock (defined by dose of norepinephrine, by arterial lactate level, or by use of one vasopressor at baseline).
- Low-dose vasopressin infusion appears safe (compared with norepinephrine) for the treatment of septic shock.

• Further investigations are required to fully understand the effect of vasopressin on renal function and any possible interaction between vasopressin and corticosteroids.

#### **AUTHORS' RECOMMENDATIONS**

- Low-dose vasopressin infusion is a useful vasopressor in the management of septic shock in adults. Vasopressin certainly reduces the requirements for catecholamine vasopressors, which have their own important complications.
- The potential beneficial effects of low-dose vasopressin infusion in patients who have less severe shock require further study to fully understand exactly which patients benefit most. Earlier use of vasopressin would appear more effective than use of vasopressin as rescue therapy for patients who have refractory septic shock (e.g., already requiring high-dose catecholamines). However, more evidence is needed before vasopressin can be recommended as a first-line therapy.
- Doses of vasopressin infusion greater than 0.03 U/minute should be used only in clinical studies and randomized controlled trials.

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## 3 What Is the Role of Source Control in Sepsis?

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Sepsis is defined as the systemic host response to infection.<sup>1</sup> It is considered to be severe when it results in organ dysfunction or tissue hypoperfusion. When tissue perfusion is compromised, septic shock is present. The management of life-threatening sepsis is grounded in three principles:

- 1. Resuscitation and physiologic support
- 2. Microbiologic diagnosis and rapid administration of appropriate antimicrobial therapy
- 3. Source control to prevent ongoing microbial contamination

The term *source control* was first used in the early 20th century and encompasses all physical measures that are undertaken to eradicate a focus of infection. The phrase is used in preference to *surgical therapy* because this objective is increasingly accomplished by nonoperative techniques, including, for example, removal of an infected intravascular device or image-guided drainage of an abscess. Contemporary approaches to source control are guided largely by principles and tradition and only modestly validated through randomized controlled trials (RCTs).

We used the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) system to guide assessment of quality of evidence from high (A) to very low (D) and to determine the strength of recommendations. A strong recommendation is given GRADE 1, and a weak recommendation 2. The grade of strong or weak is considered of greater clinical importance than a difference in letter level of quality of evidence. This represents a strength of this approach, especially when there is a paucity of data derived from GRADE A or B studies.

This chapter reviews the biologic and therapeutic principles that guide the use of source control in the management of the septic patient. It is written with an understanding that the decision-making process is inherently complex and requires a coordinated and multidisciplinary approach (Table 33-1).

#### SOURCE CONTROL: BIOLOGIC PRINCIPLES

Invasion of host tissues by a pathogen results in activation of an innate immune response with recruitment of inflammatory cells to the site of infectious challenge. The resulting clinical manifestations largely reflect the host response to infection rather than specific effects of microbial products on cellular function. An understanding of the biology of inflammation is invaluable in guiding clinical decisions.

Local infection activates innate host defense mechanisms, resulting in local vasodilation and increased microvascular permeability. The activation of macrophages and endothelial cells leads to the release of cytokines such as interleukin-8 (IL-8), a neutrophil chemoattractant, and IL-1, which prolongs neutrophil survival. As a result, activated neutrophils accumulate. The coagulation cascade is activated following increased expression of tissue factor. Therefore, local thrombosis is increased. These biologic changes result in the cardinal signs and symptoms of acute inflammation—*rubor* (redness), *calor* (warmth), *dolor* (pain), *tumor* (swelling), and *functio laesa* (loss of function)—and set the stage for walling off the infectious process through the formation of an abscess.

An abscess is a collection of microorganisms, tissue debris, fluid, and neutrophils enclosed within a capsule of fibrin; fibrin deposition represents the final stages of the local activation of coagulation (Fig. 33-1). The formation of an abscess prevents the dissemination of the microorganism but also isolates the contents from the body's defenses and so may prevent complete elimination of the infection. Therefore, source control measures are needed.

There are four major categories of intervention to achieve source control (Table 33-2).

#### Drainage

Drainage converts an abscess cavity or a closed-spaced infection into a controlled *sinus* (an abnormal communication with an epithelial surface) or *fistula* (an abnormal communication with two epithelially lined surfaces).

Drainage can be accomplished by several methods. It may occur spontaneously, for example, by the development of an enterocutaneous fistula following an anastomotic leak. Classically, it has been accomplished by planned surgical intervention to evacuate an abscess cavity and leave a drain in situ. With the advent of improved diagnostic imaging techniques, interventional radiologists have come to play a primary role in establishing source control, especially in deeper set infections<sup>3</sup> (Fig. 33-2).

### Table 33-1**GRADE System: Determination**of the Quality of Evidence

#### UNDERLYING METHODOLOGY

- A RCT
- B Downgraded RCT or upgraded observational studies
- C Well-done observational studies
- D Case series or expert opinion

#### FACTORS THAT MAY DECREASE THE STRENGTH OF EVIDENCE

- 1 Poor quality of planning and implementation of available RCTs suggesting high likelihood of bias
- 2 Inconsistency of results (including problems with subgroup analyses)
- 3 Indirectness of evidence (differing population, intervention, control, outcomes, comparison)
- 4 Imprecision of results
- 5 High likelihood of reporting bias

#### MAIN FACTORS THAT MAY INCREASE THE STRENGTH OF EVIDENCE

- $\label{eq:large} \begin{array}{ll} 1 & \mbox{Large magnitude of effect (direct evidence, $RR \geq 2$ with no plausible confounders)} \end{array}$
- 2 Very large magnitude of effect with  $RR \ge 5$  and no threats to validity (by two levels)
- 3 Dose response gradient

RCT, randomized controlled trial; RR, relative risk.

#### Débridement

Débridement is the removal of dead, devitalized, or infected tissue. A classic example is in the case of necrotizing fasciitis, in which surgical débridement is essential for survival.<sup>4,5</sup> Similarly, after intestinal infarction, excision of the dead bowel is potentially life saving.<sup>6</sup>

#### **Device Removal**

A colonized foreign body serves as a continuing source of infection by multiple mechanisms. The presence of the foreign body has been shown to impair local host defenses and lead to local tissue injury. In addition, many of the organisms that predominate in infections in the critically ill have the capacity to form a biofilm on invasive devices and so create a continuing focus of infection. Coagulase-negative *Staphylococci* species, for example, create a biofilm and therefore are a common cause of vascular catheter-related infections.<sup>7</sup>

#### **Definitive Control**

Ultimately, definitive control of the infectious focus is necessary to prevent continued or repeated episodes of sepsis and to restore optimal anatomic and physiologic function to the affected part. For example, perforation of the gastrointestinal tract resulting in severe sepsis may be initially managed by percutaneous drainage of the resulting abscess. However, to prevent repeated or continuing infection (e.g., following perforated diverticulitis, appendicitis, or acute cholecystitis) and to return the patient to a state of health and autonomy, definitive surgical management often is required.



**Figure 33-1.** The anatomy of an abscess. An abscess contains tissue fluid, neutrophils, bacteria, and tissue debris. Bacterial products such as endotoxin and inflammatory mediators from host immune cells induce the expression of tissue factor on resident peritoneal macrophages. This activates the coagulation cascade and results in fibrin deposition at the margins of the abscess cavity. This fibrin capsule both isolates the infection from adjacent sterile tissues and prevents the entry of phagocytic cells that might promote the resolution of infection. Drainage converts the abscess cavity to a controlled sinus or fistula. IL, interleukin.

Intervention	Definition	Examples
Drainage	The removal of fluid or purulent material from a wound or body cavity	Opening an infected wound Percutaneous cholecystotomy or nephrostomy tube Chest tube for an empyema
Débridement	Removal of dead or infected tissue	Surgical excision of necrotizing fasciitis Removal of infected pancreatic necrosis
Device removal	Removal of a colonized foreign body	Line removal for catheter-related sepsis Urinary catheter for urinary tract infection
Definitive control	Eliminate source of ongoing contamination	Intestinal resection for ischemic bowel Sigmoid resection for perforated diverticulitis Patch repair for duodenal ulcer perforation Cholecystectomy for gangrenous cholecystitis

#### Table 33-2 Principles of Source Control

#### **IDENTIFYING THE SOURCE OF SEPSIS**

A variety of imaging modalities typically enable identification of a focus of infection requiring source control. Computed tomography (CT) is particularly useful, as are magnetic resonance imaging (MRI) and ultrasonography. The improved image quality and availability of such techniques has largely, although not entirely, eliminated the need for exploratory surgery to find a focus of infection.

#### WHAT IS THE OPTIMAL TIMING OF INTERVENTION?

It is intuitively apparent that rapid identification and control of a focus of infection are desirable and mortality is reduced in patients when a source can be identified early.<sup>8</sup> A specific anatomic site of infection should be considered and sought as rapidly as possible and preferably within the first 6 hours of presentation<sup>2</sup> following successful initial resuscitation<sup>5</sup> (GRADE 1C-D).

In some circumstances, optimal resuscitation cannot be accomplished before source control. For patients with intestinal infarction or necrotizing fasciitis,<sup>9,10</sup> for example, removal of the infected necrotic tissue is necessary to facilitate successful resuscitation.

## WHAT METHOD SHOULD BE USED TO ESTABLISH SOURCE CONTROL?

The optimal method of source control depends on the location and nature of the infectious process. It follows that the benefits of obtaining source control must outweigh the risks of the chosen intervention. The goal should be to accomplish source control with the least physiologic impact as possible—for example, through percutaneous, rather than surgical, drainage of an abscess<sup>11</sup> (GRADE 1D).

Source control interventions themselves can cause further complications. These include bleeding, infection, fistula, or organ injury. Surgical intervention may become necessary when other methods are unsuccessful or when a diagnosis cannot readily be established. The more complex the patient, the greater the challenge in determining the optimal approach to source control. In a study examining surgical consensus on the optimal approach to achieve source control for persistent intra-abdominal infection, there was greater variability in the approach to source control in patients who were older or more ill, as reflected in higher Acute Physiology and Chronic Health Evaluation (APACHE II) scores (>15).<sup>12</sup> In contrast, surgeons had excellent concordance when source control was considered for such problems as perforation of a



**Figure 33-2.** Percutaneous drainage of a pelvic abscess. An axial computed tomographic scan shows a pelvic abscess (*left panel, arrows*) that developed following a damage-control procedure in an elderly patient with complex diverticulitis. A pigtail catheter was directed into the collection (*right panel, arrow*), enabling virtually complete drainage of the collection.

viscus or acute diverticulitis. Interestingly, there was less agreement on the management of complicated appendicitis and intra-abdominal abscess. The optimal approach to source control must consider patient preference, local practice patterns, and the individual clinician's expertise.

#### COMMON INFECTIOUS FOCI THAT REQUIRE SOURCE CONTROL

#### **Intra-abdominal Infection**

#### Primary Peritonitis

The term primary peritonitis refers to peritonitis that develops in the absence of a breach of the gastrointestinal tract. This term is used interchangeably with spontaneous bacterial peritonitis.<sup>13</sup> Infection arises either by the translocation of enteric organisms across an intact gut mucosa in a patient with altered gut flora and impaired host defenses or by retrograde spread through the reproductive organs in young girls. The most common cause in adults is infection of ascitic fluid in patients with advanced liver disease.<sup>14</sup> Because there is no distinct locus of intraabdominal infection, and so no possibility of creating a controlled sinus or fistula or removing necrotic infected material, no source control measures are indicated. However, if a secondary cause of peritonitis is suspected, the possibility should be investigated using radiologic methods such as CT<sup>15</sup> and the focus managed appropriately.

#### Secondary Peritonitis

Secondary peritonitis is intraperitoneal infection that arises following an anatomic breach of the gastrointestinal tract or obstruction and secondary bacterial overgrowth in a hollow viscus such as the appendix or gallbladder. The ability to obtain source control is an important prognostic factor in critically ill patients suffering from secondary peritonitis.<sup>16</sup> An adverse prognosis is associated with disease severity at intensive care unit (ICU) admission and over the ICU stay, specific comorbidities (extended malignancies, liver cirrhosis), certain sites of infection (distal esophagus, stomach), and an inadequate initial antibiotic therapy.<sup>16</sup>

#### Gastrointestinal Perforations

An anatomic breach in gastrointestinal continuity, such as occurs following perforation of a peptic ulcer or a sigmoid diverticulum, can result in leakage of the gastrointestinal contents into the peritoneal cavity (Fig. 33-3). Treatment entails drainage and removal of the contamination, and then control of the perforation.

Surgical control will depend on the anatomic location, extent of the perforation, physiologic stability to the patient, and local expertise. The specific approach used to obtain source control is of lesser importance provided that it is able to remove the contamination, manage the perforation, and eliminate ongoing leakage. For example, an RCT that compared open versus laparoscopic repair for perforated peptic ulcers found that both were safe and effective.<sup>17</sup> The laparoscopic group had a shorter operative time, less analgesia, and one less median day in hospital.



**Figure 33-3.** Intraperitoneal free air. Free air is visible under the right hemidiaphragm in a patient with a perforated duodenal ulcer. The extent of the free air suggests that source control is suboptimal.

Diverticulitis can present with a wide clinical spectrum of complications. These range from a localized phlegmon or abscess to free perforation with purulent or feculent peritonitis. Optimal management depends on the extent of perforation and stability of the patient. For a walledoff perforation, percutaneous CT-guided drainage converts the abscess to a controlled colocutaneous fistula and allows resolution and healing of the perforation<sup>18</sup> (Fig. 33-4). There are a number of surgical options to



**Figure 33-4.** Percutaneous drainage of a diverticular abscess. A percutaneous drain (*arrow*) has been placed into a peridiverticular abscess, converting the abscess to a controlled colocutaneous fistula (contrast can be seen in the sigmoid and descending colons). After resolution of the acute infectious process, an elective single-stage sigmoid resection was performed.

achieve source control objectives, including a one-stage (resection with primary anastomosis), two-stage (sigmoid resection and colostomy creation, also known as the *Hartmann procedure*, and then a second procedure to restore bowel continuity), or three-stage (first drainage and washout of contamination with colostomy, then second operation for sigmoid resection, and then hird operation to restore intestinal continuity) procedure. Pooled data from a single RCT<sup>19</sup> and six case series<sup>20–25</sup> indicate that mortality is lower for patients who undergo a resection at the time of initial surgery compared with those having colostomy and drainage without resection.<sup>26</sup> A more recent RCT also found that primary resection was superior to no resection with significantly less postoperative peritonitis, fewer reoperations, and shorter hospital stay.<sup>27</sup>

In general, primary resection is preferable to simple drainage and proximal diversion for patients with perforated diverticulitis (GRADE 1B).

There is also increasing evidence that primary anastomosis in a one-stage procedure is a safe alternative to colostomy creation<sup>26</sup> (GRADE 1D).

#### Intestinal Ischemia or Infarction

Intestinal ischemia can result from arterial occlusion by either an embolus or thrombus, venous occlusion by thrombus, or hypoperfusion resulting in a low-flow state (also termed nonocclusive mesenteric ischemia). Acute mesenteric ischemia is lethal unless blood flow is restored or necrotic bowel excised. Ischemia is potentially reversible if the cause can be treated and flow restored. Therefore, intestinal infarction is a surgical emergency that requires rapid diagnosis and surgical excision of nonviable bowel. The diagnosis is suggested by the clinical setting and a high index of diagnostic suspicion. Laboratory and radiologic signs often are nonspecific and occur only in the late courses of the disease. A multivariate analysis found that the most important prognostic factor, and the only one that can be influenced by the surgeon, remains the time interval between the onset of symptoms and surgery.<sup>28</sup> Therefore, understanding the etiology, early diagnosis, and timely surgical intervention is critical to a successful outcome for patients with severe sepsis secondary to intestinal ischemia.

#### Appendicitis, Cholecystitis, and Cholangitis

Both acute cholecystitis and appendicitis develop as a result of inflammation and bacterial growth within an obstructed hollow viscus. Although both disorders are common, they rarely lead to severe sepsis. When this does occur, definitive treatment is removal of the affected organ. However, in the acute situation, patients with a well-localized appendiceal abscess may be best managed initially with percutaneous drainage followed by an interval appendectomy.<sup>29</sup>

In the high-risk or unstable patient with cholecystitis, a percutaneous cholecystostomy may be the safer initial management option<sup>30,31</sup> (GRADE 1B).

Cholangitis results from obstruction of the common bile duct with resultant bacterial proliferation; bacteremia is common. Decompression of the obstructed bile duct is urgently required. This can be accomplished by endoscopic retrograde cholangiopancreatography (ERCP), surgical common bile duct exploration, or percutaneous transhepatic cholangiography by interventional radiology. The former is the therapy of choice because it is the least invasive, is diagnostic, and is potentially therapeutic (e.g., stone removal, stent placement).<sup>32</sup> An RCT has shown that ERCP is associated with decreased mortality in comparison to surgical decompression for severe acute cholangitis<sup>33</sup> (GRADE 1B).

#### Infected Pancreatic Necrosis

Mortality for critically ill patients with acute necrotizing pancreatitis is strongly linked to the development of infection in the necrotic pancreatic and peripancreatic tissues. The patient with sterile necrosis usually recovers without surgery, whereas nonoperative management of infected pancreatic necrosis, although described, most often is unsuccessful.<sup>34</sup> Even when infection is present, it is preferable to delay surgical intervention for at least 3 to 4 weeks to permit better demarcation of necrotic and viable pancreatic tissue and so reduce the risk for uncontrollable retroperitoneal bleeding during débridement.<sup>35,36</sup> Several case series and a single RCT have shown a reduction in mortality in patients in whom necrosectomy is delayed for at least 2 to 3 weeks after initial presentation<sup>36–38</sup> (GRADE 1B).

The development of infected necrosis can be diagnosed reliably using radiology-guided fine-needle aspiration. Traditionally, infected pancreatic necrosis was treated by open surgical necrosectomy. More recently, it has been reported that percutaneous or endoscopic necrosectomy provides less invasive alternatives for débridement of infected pancreatic necrosis.<sup>39,40</sup> Surgery should be planned if there is no clinical improvement following nonsurgical treatment.<sup>41</sup> Percutaneous drainage of the liquid component of a retroperitoneal pancreatic infection can temporize to allow better demarcation of viable and nonviable tissue, making surgical débridement safer (Fig. 33-5) (GRADE 2B).



**Figure 33-5.** Percutaneous decompression of infected peripancreatic necrosis. A percutaneous drain (*arrow*) was placed into a complex peripancreatic collection to drain the liquid component and so decompress the collection. Although residual necrotic tissue remained, percutaneous drainage permitted delay of definitive débridement for several weeks. At that time, a laparoscopic approach was used to débride residual infected necrotic tissue from the lesser sac.

#### Postoperative Peritonitis

The mortality of postoperative peritonitis is substantial, with reported rates as high as 50%.<sup>42–45</sup> It has been suggested that an aggressive surgical approach in the management of postoperative peritonitis can reduce mortality.<sup>46</sup> A retrospective review of patients managed according to a standardized surgical protocol that included exteriorization of leaking intestinal segments when possible, intubation with continuous intraluminal irrigation if exteriorization was not possible, and liberal use of a defunctioning stoma was reported to reduce mortality rates to less than 12%.<sup>46</sup> Others have championed early and aggressive surgical management of the patient with postoperative peritonitis<sup>47</sup> (GRADE 2B).

Procedures to restore intestinal continuity should be attempted only when the patient is stable, nutritionally optimized, and prepared physically and psychologically for another surgical procedure.

#### Tertiary Peritonitis

Tertiary peritonitis is peritonitis persisting or recurring after apparently adequate management of primary or secondary peritonitis. Risk factors for development include malnutrition, a high APACHE II score, the presence of organisms resistant to antimicrobial therapy, and organ system failure.<sup>48</sup> Tertiary peritonitis differs from uncomplicated secondary peritonitis in its microbial flora and lack of response to appropriate surgical and antibiotic therapy. Infectious foci often are not amenable to percutaneous drainage and may be poorly localized at laparotomy. It is unclear whether outcome can be improved by aggressive source control measures<sup>49–51</sup> (GRADE 2D).

Patients with tertiary peritonitis have a significantly longer ICU stay, higher organ dysfunction scores, and a higher ICU mortality (64% versus 33%) than patients with uncomplicated secondary peritonitis.<sup>49</sup>

#### **Foreign Body Infections**

If the source of sepsis is an infected intravascular access device, the device should be removed as expeditiously as possible,<sup>2,52</sup> preferably after alternate vascular access has been established (GRADE 1C).

Although it is preferable to re-site the catheter in many patients, vascular access is at a premium. Therefore, establishing an alternate site may be difficult or impossible. A systematic review of 12 RCTs comparing catheter changes over a guidewire with replacement at a new site found that there was a trend toward a higher rate of catheter exit-site infection and catheter-related bacteremia, but fewer mechanical complications, when guidewire exchanges were used.<sup>53</sup>

The benefits of device removal must outweigh the risks, and these, in turn, depend on the type of infected device and the ease with which it can be removed (Table 33-3). With infective endocarditis, the optimal time of surgery has to be determined, and the benefits must outweigh the risks of surgery.<sup>54</sup>

#### **Urinary Infections**

Renal abscesses can occur by hematogenous dissemination from a remote site or develop as a result of a preexisting renal infection. In the former, the causative

Table 33-3 Ease of Device Removal forDevice-Related Infections										
Increasing risk associated with removal	EASE OF DEVICE REMOVAL Urinary catheter Nasogastric, feeding tube Intravascular catheter Peritoneal dialysis catheter Endotracheal tube Prosthetic joint, orthopedic hardware Vascular graft Heart valve									

organism is usually *Staphylococcus aureus*, whereas in the latter, the offending organisms most often are gramnegative bacteria, such as *Escherichia coli* and *Proteus* and *Pseudomonas* species, that commonly are responsible for urinary tract infections.<sup>55</sup> Perinephric abscesses arise in a similar manner but also may develop secondary to infection of a perirenal hematoma.

Traditional management of renal and perirenal abscesses involved surgical exploration with either incision and drainage or nephrectomy. However, with improved antimicrobial agents and the development of CT and ultrasound imaging, percutaneous drainage has become an accepted alternative.<sup>55,56</sup> The advantages of percutaneous drainage include nephron preservation, cytologic evaluation to identify malignancy, and decreased morbidity compared with open intervention.

Infected hydronephrosis denotes bacterial infection of a hydronephrotic kidney while pyonephrosis typically refers to an end-stage infection associated with parenchymal destruction. The expressions may be used interchangeably.

Rapid institution of broad-spectrum antibiotics and drainage of infected material are fundamental to the management of pyonephrosis. A ureteral catheter can be used to drain the kidney, but if obstruction prevents this, a percutaneous nephrostomy tube should be inserted. The advantages of percutaneous nephrostomy insertion include direct access to the kidney, larger-diameter drainage tubes, and the ability to perform the procedure under local anesthetic. Evacuation of pus results in decreased bacterial load, decreased collecting system pressure, and increased renal perfusion and antibiotic delivery. In addition, culture results from the percutaneous nephrostomy may reveal pathogens other than those isolated in bladder urine cultures in greater than 35% of cases.<sup>57</sup> These additional results can help ensure proper antibiotic administration.

#### Skin and Soft Tissue Infections

In the absence of tissue necrosis, skin and soft tissue infections are rarely the cause of sepsis, and most respond to antibiotic therapy. Superficial abscesses usually respond to incision and drainage with or without antibiotics. However, necrotizing soft tissue infections are life threatening, and prognosis is directly related to the rapidity of diagnosis and surgical débridement.<sup>10</sup> There are a number of classifications of necrotizing infections. These are based on the anatomic site, the depth of tissue penetration, and the infecting species. The simplest of these characterizes such infections as polymicrobial or monomicrobial. For example, mixed infection caused by aerobic and anaerobic bacteria occurs most commonly after surgical procedures and in patients with diabetes and peripheral vascular disease. In contrast, certain microbial species such as *Clostridia* or group A streptococci can produce fulminant necrotizing soft tissue infection in the otherwise immunologically intact host.<sup>58</sup>

The diagnosis of a necrotizing soft tissue infection often can be established by history and physical examination (Fig. 33-6). However, radiologic studies may assist in detecting infection at an earlier stage or in evaluating anatomic extent. A CT scan may show signs of necrotizing infections in deeper tissues. CT is sensitive for gas, but in many cases, gas is not present.<sup>59</sup> Ultrasonography<sup>60,61</sup> appears to be more sensitive and specific than MRI<sup>62</sup> for the diagnosis. Some physicians have used punch biopsy and frozensection analysis to establish a diagnosis.<sup>63</sup> Nonetheless, surgical exploration remains the definitive diagnostic tool.

A delay in diagnosis and initiation of definitive treatment is the most important factor affecting mortality for necrotizing soft tissue infections.<sup>64–66</sup> Management consists of rapid débridement, excising necrotic tissue back to healthy bleeding tissue (GRADE 1C).

It is often necessary to reassess the adequacy of the initial surgical procedure by a planned reexploration in 24 hours to determine whether further débridement is needed. Recommendations for the timing of scheduled reoperation ranges from 6 to 48 hours<sup>65,67</sup> (GRADE 1D).

#### Septic Arthritis

The mortality of septic arthritis may be as high as 11%, and the infection is an uncommon but treatable cause of sepsis. Evidence-based guidelines for the management of the septic joint were developed by the British Society of



**Figure 33-6.** Necrotizing soft tissue infection of the extremity. Bulla formation and discoloration of the overlying skin suggest underlying soft tissue necrosis in this patient with a group A streptococcal infection of the left thigh. The full extent of tissue necrosis is best evaluated by emergent surgical exploration with débridement of all nonviable tissue.

Rheumatology. These emphasize the aspiration of synovial fluid before starting antibiotics and the removal of purulent and infected fluid from the joint space. The working group was unable to find evidence that one treatment strategy was superior to another and concluded that both arthroscopy and needle aspiration have a favorable outcome. In the case of prosthetic joints, referral to an orthopedic surgeon for consideration of surgical removal is recommended<sup>68</sup> (GRADE 1D).

#### Intrathoracic Infections

#### Empyema

An empyema is a collection of pus or infected fluid within the pleural space. Most cases arise as complications of pneumonia. Treatment involves drainage of the infected fluid, antibiotics, and reassessment to ensure that no residual loculations persist and that there is adequate lung expansion.

Surgical decortication, either by video-assisted thoracoscopic surgery (VATS) or open thoracotomy, is indicated for multiloculated empyema and when the fibrotic abscess cavity prevents reexpansion of the underlying lung.<sup>69,70</sup> A single RCT compared surgical to nonsurgical management of empyemas and showed superior treatment success and shorter hospital stay after VATS as opposed to chest tube drainage with fibrinolysis<sup>71</sup> (GRADE 2B).

Fibrinolytics administered through the thoracostomy tube for retained loculations have been used instead of surgery. A systematic review of seven studies recruiting a total of 761 patients found that fibrinolysis resulted in significant benefit in reducing the requirement for surgical intervention.<sup>72</sup> However, a higher-quality randomized double-blind trial of intrapleural administration of streptokinase showed no improvement in mortality, the rate of surgery, or the length of the hospital stay among patients with pleural infection.<sup>73</sup>

#### **Mediastinitis**

Before cardiovascular surgery, most cases of mediastinitis arose from either esophageal perforation or from contiguous spread of oral or retropharyngeal infections. Treatment of mediastinitis characteristically requires reopening of the surgical site, débridement, and drainage of the mediastinum in combination with antimicrobial therapy.<sup>74</sup> Surgical approaches include open packing, closed-wound irrigation, and resection of the sternum with primary or secondary closure using flap reconstruction or vacuum-assisted drainage systems.<sup>74-76</sup>

#### EVALUATION OF THE ADEQUACY OF SOURCE CONTROL

After initial source control has been accomplished, it is important to reevaluate to ensure that ongoing contamination is not occurring. This can be done by clinical examination, radiologic evaluation, or repeat surgery. Two surgical strategies have been championed. These are ondemand relaparotomy (as dictated by clinical course) and planned relaparotomy.

In a study examining factors affecting mortality in generalized postoperative peritonitis, early relaparotomy was found to result in improved septic source control. In addition, planned relaparotomy was beneficial whenever source control was uncertain.47 An RCT comparing ondemand with planned relaparotomy found that patients in the on-demand group had shorter median ICU stays and shorter median hospital stays without an increase in mortality.<sup>77</sup> An on-demand approach to relaparotomy following severe secondary peritonitis is an acceptable approach unless source control is uncertain. To improve overall survival, the decision to perform an on-demand relaparotomy after initially successful eradication of the source of infection should be made within 24 to 48 hours, ideally before the onset of multiple-organ dysfunction.<sup>78</sup> The early detection of persistent intra-abdominal infection was found to be an important prognostic factor of outcome<sup>79</sup> (GRADE 1A-B).

#### AUTHORS' RECOMMENDATIONS

- Source control is an essential component in the treatment of sepsis. The key elements of source control are (1) identification of an infectious focus, (2) removal and drainage of source, (3) reevaluation to ensure that ongoing contamination is not occurring, and (4) definitive measures to correct cause of original infection and to restore optimal anatomic function.
- The four categories of source control are drainage, débridement, device removal, and definitive measures to correct anatomic derangement that led to the initial contamination.
- There are few RCTs examining the role of source control or comparing differing approaches to source control. Therefore, practice is guided more by evidence derived from case series and is interpreted through an understanding of basic pathobiology.
- In general, the best method of source control is the one that produces the least physiologic insult. This usually occurs after initial stabilization, but there are circumstances, such as in necrotizing fasciitis and intestinal infarction, in which source control is critical for a successful outcome.
- Reevaluation of the patient after initial source control is obtained is essential to ensure that ongoing infection is not occurring. After patient stabilization, definitive treatment of the underlying pathology may be necessary to prevent repeated episodes of infection.

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## Is there Immune Suppression in the Critically III?

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Sepsis is a major cause of morbidity and mortality in the intensive care unit (ICU), accounting for more than 210,000 deaths in the United States alone.<sup>1</sup> The number of septic patients is increasing every year, and despite medical advances during the past 25 years, the mortality rate from sepsis remains high.<sup>1</sup> Sepsis has been defined as "the systemic inflammatory response syndrome that occurs during infection."<sup>2</sup> It was thought that mortality from sepsis was due to an overwhelming endogenous response to infection.<sup>2</sup> This idea stems from experiments in which large amounts of bacteria, or endotoxin, the antigenic component of gram-negative bacterial cell walls, were given to animals.<sup>3,4</sup> These animals died from an unbridled cytokine-mediated host response. In these models, therapies aimed at suppressing specific cytokines, such as tumor necrosis factor (TNF) and interleukin-1 (IL-1), improved survival.<sup>3,4</sup> Clinical trials using anti-inflammatory therapies, however, did not show improvement in survival and, in some circumstances, worsened outcome.<sup>5–10</sup> In fact, only certain patient populations, such as children with meningitis, mimic the scenario in which high circulating TNF- $\alpha$  levels correlate with mortality.<sup>11</sup> Groups of septic patients are inherently heterogeneous, making it difficult to perform clinical trials aimed at a specific anti-inflammatory target. These patients have multiple comorbidities and different sources of infection, and previous animal models failed to represent the clinical picture seen in the ICU. This has led to a reassessment of how patients die from sepsis.12

Clinically relevant animal models of sepsis tell us that the initial hyperinflammatory response is quickly followed by the immune system's attempt to attenuate the initial inflammation.<sup>12</sup> This downregulation of the immune system can result in a prolonged period of immune dysfunction. This period of immune hyporesponsiveness, or *immunoparalysis*, has numerous consequences. These include limiting the ability of the host to fight off primary infections, predisposing the patient to secondary nosocomial infections, multiorgan dysfunction, and ultimately death.<sup>12</sup> Despite evidence pointing to immune dysfunction, the pathophysiology is still not completely understood. This chapter reviews the available basic and clinical evidence for immune dysfunction in sepsis as well as potential methods to monitor the

immune status of a critically ill patient. We also review potential therapies aimed at stimulating the immune system of the septic patient.

#### IMMUNOLOGIC RESPONSE TO SEPSIS: SIRS TO CARS

The host response to infection is complex and varies depending on type of infection, bacterial load, and host genetic factors.<sup>12</sup> Microbial invasion of a healthy patient leads to activation of the innate immune system.<sup>13</sup> The cells of the innate immune system, which include macrophages, dendritic cells, and natural killer cells, recognize carbohydrate, lipid, protein, and DNA structures that are associated with bacterial infection.<sup>13</sup> Cell surface receptors, such as members of the toll-like receptor family, recognize these structures and trigger release of proinflammatory cytokines such as TNF- $\alpha$ , IL-6, and IL-1.<sup>13</sup> This response is nonspecific and has been called the systemic inflammatory response syndrome (SIRS).<sup>2</sup> Acute phase proteins also are released. These can bind to bacterial surface molecules and aid in complement activation and phagocytosis.<sup>13</sup> The spontaneous activity of the host is reduced, and body temperature is elevated. This is thought to be disadvantageous to bacterial growth. This proinflammatory state also is designed to localize infections by recruiting phagocytes and immune cells to the area. This response is necessary and advantageous but can also lead to septic shock. The innate system tries to prevent systemic dissemination of microorganisms until the adaptive immune system can engage. Antigen is presented to naïve T cells in the lymphoid organs. These are then primed to differentiate into either helper T ( $T_H$ ) type 1 or 2 cells. T<sub>H</sub>1 cells are involved in cell-mediated immunity and secrete interferon- $\gamma$  (IFN- $\gamma$ ) and IL-2, whereas T<sub>H</sub>2 cells are involved in humoral-mediated immunity and secrete IL-10, IL-4, IL-5, and transforming growth factor- $\beta$  (TGF- $\beta$ ).<sup>14</sup> A shift to T<sub>H</sub>2 cells is one hallmark of downregulating the inflammatory response.<sup>13</sup> This has been called the compensatory anti-inflammatory response syndrome (CARS). It may occur in patients who survived the initial response, in whom the proinflammatory SIRS state resolves, and who enter a state of immune suppression and dysfunction.

#### **IMMUNE DYSFUNCTION IN SEPSIS**

As sepsis persists, patients begin to exhibit signs of immune dysfunction. These include a loss of delayed hypersensitivity, an inability to clear infections, and a predisposition to secondary infections.<sup>15–17</sup> The body shifts from a proinflammatory state to a state of immune suppression. This state is characterized by impairment of neutrophil functions, lymphocyte and dendritic cell apoptosis, a shift to a  $T_H2$  cytokine profile, an increase in the proportion of T-regulatory cells, a release of antiinflammatory mediators, lymphocyte anergy, and monocyte deactivation (Table 34-1).<sup>15</sup> Most deaths in sepsis occur late in the course of the syndrome, after resuscitation. Those patients who survive show evidence of immune function recovery.<sup>15</sup>

#### MECHANISMS OF IMMUNE DYSFUNCTION

In both animal and human studies, sepsis induces apoptosis in both lymphocytes and gastrointestinal epithelial cells (Fig. 34-1).<sup>18-20</sup> Examination of the spleen of patients



who have died from sepsis reveals a profound depletion of cells-B cells, CD4 T cells, and follicular dendritic cells-from both the innate and adaptive immune systems that is not observed in the spleen of patients who died following trauma.<sup>20</sup> Septic patients also have absolute lymphocyte counts well below normal. This lymphopenia is associated with poor outcome, and the degree of lymphocyte apoptosis correlates with the severity of sepsis.<sup>21</sup> Loss of these cells impairs antibody production, macrophage activation, and antigen presentation. Apoptosis also impairs innate immunity by disrupting the crosstalk between the innate and adaptive immune systems. As a result, sepsis is associated with T-cell anergy.<sup>22</sup> Macrophages and dendritic cells that take up and eliminate apoptotic cells release anti-inflammatory ( $T_H2$ ) cytokines such as IL-10 and TGF- $\beta$  while suppressing proinflammatory cytokines.<sup>23</sup> T cells that come into contact with these macrophages and dendritic cells become anergic or undergo apoptosis.<sup>22</sup> T cells of patients with peritonitis also have decreased T<sub>H</sub>1 function even in the absence of  $T_H 2$  cytokines. These T cells fail to proliferate. These T-cell findings positively correlate with mortality.<sup>24</sup> Surviving T cells in trauma and burn patients are found in low numbers and are anergic.<sup>25</sup>

Studies in a clinically relevant mouse model of sepsis confirm the significance of apoptosis.<sup>26</sup> Mice were injected with either apoptotic or necrotic cells before induction of sepsis and survival was recorded. Mice adoptively transferred apoptotic cells had greater mortality compared with mice that received necrotic cells. Significantly, mice that received apoptotic as opposed to necrotic cells also exhibited  $T_H^2$  cytokine profiles and decreased IFN- $\gamma$  production by spleen cells. In a number of animal studies, apoptosis was reversed.<sup>27–29</sup> In such investigations, mice that overexpressed BCL-2, an antiapoptotic protein, in lymphocytes had lower mortality rates in both pneumonia and cecal ligation and puncture (CLP) models of sepsis.<sup>29,30</sup>



**Figure 34-1.** Apoptosis of immune effector cells lead to a dysfunctional immune response to infection. CTL, cytotoxic T lymphocyte; DC, dendritic cell; FDC, follicular dendritic cell. (*From Hotchkiss RS, Nicholson DW. Apoptosis and caspases regulate death and inflammation in sepsis.* Nat Rev Immunol. 2006;6:813-822.)

BCL-2 in gut epithelium.<sup>28</sup> The cellular mechanisms of apoptosis in sepsis are incompletely understood, but there is evidence that both the extrinsic death receptor and the intrinsic, or mitochondrial, pathways are being activated.<sup>31</sup> Death receptors activated by circulating TNF and CD95 (FasL), activate caspase 8, which then sets off an apoptotic cascade.<sup>22</sup> The mitochondrial pathway can be stimulated by a number of different agents. These include reactive oxygen species, radiation, chemotherapeutic agents, cytochrome *c*, and cytokine withdrawal. It appears that there is significant crosstalk between the two pathways and that sepsis acts through multiple mechanisms to induce cell apoptosis.

Although controversial, some investigators have reported that T-regulatory (CD4<sup>+</sup> and CD25<sup>+</sup>) cells play an important role in the immunosuppression that occurs during sepsis. T-regulatory cells modulate the immune response to pathogens by acting on other T cells and antigen-presenting cells.<sup>32</sup> T-regulatory cells release cytokines like IL-10, TGF- $\beta$ , and IL-4 and thereby mediate responses in CD4 and CD8 T cells. One recent study revealed that the proportion of T-regulatory cells increased in the blood of septic patients immediately after diagnosis and persisted only in nonsurvivors.33 This increase in T-regulatory cells also has been shown to occur in trauma patients and in clinically relevant animal models of sepsis.<sup>34–37</sup> Adoptive transfer of T-regulatory cells attenuated the hyperreactivity of innate immune cells after burns.<sup>32</sup> The suppressive activity of T-regulatory cells also has been demonstrated in humans after trauma.<sup>34</sup> T-regulatory cells may be important in the switch from a hyperinflammatory state to immune dysfunction in sepsis. A recent study demonstrated improved survival in septic mice given an antibody to the glucocorticoid-induced TNF receptor that is highly expressed on T-regulatory cells.<sup>37</sup> This antibody restored CD4<sup>+</sup> T-cell proliferation and increased T<sub>H</sub>1 and T<sub>H</sub>2 cytokines. This approach reversed the adaptive immune dysfunction seen in sepsis. T-regulatory cells may prove to play a crucial role in the development and treatment of immune dysfunction in severe sepsis.

In addition to the increased proportion of circulating T-regulatory cells, recent studies have found expansion of immature myeloid suppressor cells (Gr-1<sup>+</sup>, CD11b<sup>+</sup> cells) in the spleen, lymph nodes, and bone marrow in prolonged sepsis. These cells facilitate immune suppression in mouse cancer models and may be involved in the sepsis-associated shift from a  $T_{H1}$  to  $T_{H2}$  immune response. Depletion of these cells in septic mice challenged with T-cell-dependent antigens blocked a  $T_{H2}$  response. This evidence suggests a role for immature myeloid suppressor cells in sepsis-induced immune suppression.<sup>38</sup>

Monocytes from septic patients also are dramatically affected. In patients with postoperative sepsis, there is an immediate suppression of both pro-inflammatory and anti-inflammatory cytokines after lipopolysaccharide stimulation.<sup>39</sup> Survival among these patients correlated with a recovery of the pro-inflammatory, but not the anti-inflammatory, response. This suggests that immunosuppression in sepsis is a primary and not a compensatory event.<sup>39</sup> Monocytes from septic patients have decreased cell surface markers, notably monocyte human leukocyte anti-gen type DR (mHLA-DR).<sup>40</sup> These monocytes produce only

small amounts of TNF- $\alpha$  and IL-1 in response to bacterial challenges.<sup>41</sup> Lymphocytes from septic patients also have decreased HLA-DR expression.<sup>41</sup> When stimulated with tetanus toxoid, these lymphocytes failed to proliferate. These findings suggest that low HLA-DR expression interferes with antigen presentation.<sup>41</sup>

Numerous characteristics of immune suppression in sepsis have been identified. Nonetheless, researchers have yet to find diagnostic tests that can inform clinicians about the state of the immune system in septic patients. There are no discrete clinical signs or symptoms of immune dysfunction, and there is no gold standard available that can identify a patient in a state of immune suppression.<sup>15</sup>

#### IDENTIFYING IMMUNE DYSFUNCTION IN THE SEPTIC PATIENT

The host immune response to sepsis is complex and involves many circulating mediators and cells. Various cytokines and their correlation with mortality have been studied. Baseline circulating IL-6 and soluble-TNF receptor have been shown to correlate with disease severity and 28-day all-cause mortality<sup>42</sup> and may help in determining when an anti-inflammatory therapy may benefit. Levels of anti-inflammatory cytokines may be more helpful in determining whether a patient is immunosuppressed (Table 34-2). One study found that initially elevated and sustained levels of IL-10 were predictive of mortality.<sup>43</sup> High IL-10/TNF- $\alpha$  ratios also were predictive of poor outcome.<sup>44</sup> Another study demonstrated that high IL-10 levels were sustained in nonsurvivors for 15 days after the onset of shock.45 IL-10 correlated with the decreased expression of mHLA-DR in septic patients and, in fact, may mediate this finding.<sup>46</sup> IL-10 is an immunosuppressive cytokine, and its continued presence in the septic patient may contribute to immune dysfunction. Other immunosuppressive cytokines, such as TGF- $\beta$ , have not been found to correlate with mortality.<sup>46</sup> IL-10 has been shown to mediate endotoxin tolerance in monocytes, and antibodies to IL-10 have reversed this phenomenon, whereas antibodies to TGF- $\beta$  have not.<sup>47</sup> IL-10 may prove to be a useful marker of immune dysfunction but needs to be evaluated in larger clinical trials.

Another possibility for evaluating the robustness of the immune response is quantitation of the mHLA-DR cell surface expression in the septic patient. mHLA-DR expression was reduced in patients who develop nosocomial infections after trauma, surgery, and pancreatitis.<sup>48</sup> Patients who recovered from these complications also recovered mHLA-DR expression.<sup>48</sup> This finding became apparent only 48 hours after the onset of sepsis.<sup>49</sup> Therefore,

## Table 34-2 Possible Diagnostic Markersof Immune Dysfunction

Increased initial and sustained IL-10 levels High IL-10/TNF- $\alpha$  ratios Decreased mHLA-DR expression

IL-10, interleukin-10; mHLA-DR, monocyte human leukocyte antigen type DR; TNF-α; tumor necrosis factor-α.

measuring mHLA-DR expression in septic patients sequentially over time may be of value. However, monitoring mHLA-DR is difficult because there is no reliable, standardized testing system at this time.

Procalcitonin has been widely investigated as a serum marker to differentiate SIRS from sepsis. Several small trials indicate that procalcitonin predicts mortality in critically ill patients.<sup>50–52</sup> A recent meta-analysis reviewed the available clinical data. The authors limited the analysis to studies of critically ill patients in medical-surgical departments, ICUs, emergency departments, and general wards. The authors excluded studies that looked only at specific patient populations (e.g., cardiac surgery, pancreatitis, meningitis, burns). They concluded that procalcitonin cannot be used to distinguish sepsis from SIRS and that more studies are needed.<sup>50</sup>

Some investigators have advocated a genomic approach to monitoring immune function. Preliminary studies involving small cohorts of patients indicate that 95% of patients with the same outcome show similar change in the messenger RNA expression of 10 specific genes.<sup>53</sup> Gene chip analysis allows for the comparison of thousands of genes and may eventually reveal sepsis-associated differences in gene expression related to immune dysfunction. This direction may be limited by genetic variability and heterogeneity. This technology is still in its infancy but may prove to be useful in the future.

#### POTENTIAL THERAPIES AIMED AT IMMUNE DYSFUNCTION IN SEPSIS

Anti-inflammatory therapies, including TNF- $\alpha$  antagonists, IL-1 receptor antagonists, antiendotoxin antibodies, and corticosteroids, have not been shown to decrease overall mortality in patients with sepsis. It is possible that new approaches aimed at stimulating the immune system may succeed where interventions based on inhibiting the immune response have failed. However, clinical trials of granulocyte colony-stimulating factor did not change overall mortality in patients with either hospital- or community-acquired pneumonia.<sup>54,55</sup> IFN- $\gamma$  improved mHLA-DR expression and mortality in a small group of septic patients but has not been studied in a large clinical trial.<sup>56</sup> Intravenous immunoglobulin (IVIG) is thought to provide specific antibodies to certain pathologic microbial factors, such as endotoxin, and may restore levels of immunoglobulins that have been depressed in sepsis.<sup>57</sup> A recent meta-analysis of clinical studies of sepsis in both adults and neonates demonstrated that IgGAM preparations of IVIG reduced mortality in severe sepsis by 34% and 50%, respectively. The authors concluded that the evidence supports the use of IVIG as an adjunctive therapy for severe sepsis or septic shock.<sup>58</sup> In animal models of sepsis, preventing apoptosis improved survival. Activated protein C may reduce mortality in severe sepsis and has also been found to have antiapoptotic properties.<sup>59</sup> Technologies such as caspase inhibitors, antiapoptotic peptides, and protease inhibitors all improved survival in mouse models of sepsis.<sup>22</sup> Small interfering RNA (siRNA) is a new, exciting therapeutic possibility and may be used to target proapoptotic genes.<sup>6</sup>

#### CONCLUSION

Previous theories regarding the pathophysiology of sepsis failed to identify the sepsis-associated immune dysfunction. Most deaths in sepsis occur after the initial hyperdynamic, proinflammatory phase when patients are unable to clear either primary infection or develop secondary, nosocomial infections. This period of immune dysfunction is an important cause of mortality, and patients who recover immune function tend to resolve their infections and ultimately survive. Lymphocyte apoptosis, T-cell anergy, increased proportion of T-regulatory cells, monocyte deactivation, decreased HLA-DR expression, a  $T_{H2}$ cytokine profile, and neutrophil impairment are all hallmarks of immune dysfunction in sepsis. Diagnostic modalities that will enable the physician to track a patient's immune status and tailor treatment accordingly need to be developed. The goal is to be able to administer immune-stimulating therapies during periods of immune suppression and anti-inflammatory therapies during overexuberant immune responses.

#### **AUTHORS' RECOMMENDATIONS**

- Septic patients develop a hypoimmune state characterized by loss of delayed hypersensitivity, inability to clear primary infections, and susceptibility to secondary infections.
- Most deaths in sepsis occur late in the course of the syndrome, and survivors show evidence of immune recovery.
- Mechanisms of immune dysfunction include lymphocyte, dendritic cell, and gut apoptosis, a switch from a T<sub>H</sub>1 to a T<sub>H</sub>2 cytokine profile, release of anti-inflammatory mediators, lymphocyte anergy, and monocyte deactivation.
- Diagnostic modalities aimed at monitoring the immune response in sepsis may help tailor future therapies intended to modulate the immune system.

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# 35 Are the Concepts of SIRS and MODS Useful in Sepsis?

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Many disease processes are characterized by relatively clear signs and symptoms, and some, such as acute myocardial infarction or diabetes, have an obvious and fairly reliable diagnostic test or marker. This makes definition and diagnosis comparatively easy. Severe sepsis, however, is often associated with multiple nonspecific, often vague signs and symptoms. As a result, there is, as yet, no simple marker or imaging technique that can act as a reliable diagnostic test. Even microbiologic cultures are unreliable because they are negative in as many as 40% of patients.<sup>1</sup> In addition, severe sepsis is not a one-off event, as, for example, a myocardial infarction, with a clear onset. Rather, severe sepsis often develops over a period of time. Hence, creating a clear, precise definition for sepsis has proved difficult. Yet, definitions are importantwithout a precise definition, it is difficult to make a diagnosis, choose an appropriate therapy, or select homogeneous groups of patients for clinical trials. Problems of definition may indeed account, in part, for the apparent failure of many clinical trials in septic patients to produce positive results.<sup>2</sup> Faced with a plethora of terms and definitions of sepsis, including bacteremia, septicemia, and sepsis syndrome, each meaning different things to different people, the American College of Chest Physicians and the Society of Critical Care Medicine (ACCP/SCCM) convened a consensus conference in 1991 in an attempt to resolve some of the difficulties in defining sepsis and its sequelae.<sup>3</sup>

#### SYSTEMIC INFLAMMATORY RESPONSE SYNDROME

In recognition of the fact that some patients can present with a clinical picture of sepsis but have no infection, the participants at the ACCP/SCCM 1991 consensus conference developed the term *systemic inflammatory response syndrome* (SIRS).<sup>3</sup> According to this definition, a patient has SIRS when at least two of four parameters are present: temperature higher than 38°C or lower than 36°C; heart rate more than 90 beats/minute; respiratory rate more than 20 breaths/minute or Paco<sub>2</sub> less than 32 mm Hg; white blood cell count more than  $12 \times 10^9$ /L, less than  $4 \times 10^9$ /L, or more than 10% immature forms. SIRS can be caused by multiple infectious and noninfectious processes. *Sepsis* was thus defined as the presence of SIRS in association with a confirmed infectious process, *severe sepsis* as the presence of sepsis with either hypotension or systemic indications of hypoperfusion, and *septic shock* as sepsis with hypotension despite fluid resuscitation, plus hypoperfusion abnormalities including hyperlactatemia, oliguria, and altered mental status.

## MULTIPLE-ORGAN DYSFUNCTION SYNDROME

Severe sepsis is often followed by organ dysfunction and failure, which are most frequently the ultimate cause of death in these patients. However, defining sepsis-associated multiple-organ failure has also proved difficult, with different patients presenting various patterns and degrees of organ dysfunction. At the same 1991 ACCP/SCCM consensus conference, Bone and colleagues introduced the term *multiple-organ dysfunction syndrome* (MODS), defining it globally as "the presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention."<sup>3</sup> Four important aspects of MODS were highlighted at the conference: (1) the organ dysfunction associated with SIRS is present as a continuum rather than an on-off event; (2) improved mechanisms need to be developed to enable early recognition of organ dysfunction so that treatment can be started sooner; (3) changes in organ dysfunction over time are important in prognostication; and (4) MODS can be influenced by multiple interventional and host-related factors both before and during development. MODS also was described as *primary* (i.e., the direct result of a specific insult) or secondary (i.e., the consequence of a host-response to an insult, occurring in the context of SIRS). Many scoring systems have been developed to help characterize MODS. Most assess function of six organ systems (respiratory, cardiovascular, neurologic, renal, hepatic, and coagulation). One of the most widely used is the Sequential Organ Failure Assessment (SOFA) score.<sup>4</sup> SOFA allocates a score of 0 (normal function) to 4 (failure) to each of the organ systems, depending on the degree of dysfunction measured using easily available clinical and laboratory variables. Although not designed to predict mortality, these scores are clearly associated with outcome because increasing numbers of failing organs and increasing severity of organ dysfunction are associated with increased mortality.5

#### USE OF SIRS AND MODS IN CLINICAL TRIALS

At about the same time as the consensus conference, with increased understanding of the pathophysiology of sepsis and its systemic response, there was a sudden surge in the number of clinical trials designed to test potential new therapeutic targets. The time was ripe for a clear definition of sepsis, and despite some concern that the terminology was not in fact very helpful,<sup>6,7</sup> the SIRS concept has been widely adopted and used as inclusion criteria in many clinical trials.<sup>8</sup> Publication of the conclusions of a recent Sepsis Definitions Conference in which the SIRS criteria were replaced by a longer list of potential signs<sup>9</sup> may influence this trend in the future, although many studies that currently are recruiting patients still are using the presence of SIRS as criteria for inclusion.

To assess the use of SIRS and MODS as an entrance criterion in clinical trials in sepsis, we performed a systematic search of Medline for multicenter, randomized controlled trials of new therapeutic interventions in patients with severe sepsis published between January 1, 2000, and December 31, 2007. The search was limited to Englishlanguage publications and to studies conducted in adult patients and was conducted using the key words "sepsis" *or* "severe sepsis" *or* "septic shock." Single-center and phase 2 studies were not included. Studies of nutritional supplements were also excluded.

Perhaps not surprisingly in view of the limited number of randomized controlled studies that have been conducted in intensive care unit (ICU) patients in general,<sup>10</sup> we identified only 11 studies that met these strict inclusion criteria (Table 35-1). Of these 11 studies, all except one<sup>11</sup> used SIRS as part of the inclusion criteria, with various definitions of infection to support a diagnosis of sepsis, although some studies required more than the minimum of two criteria specified by the consensus conference. The study by Panacek and colleagues<sup>11</sup> used the earlier sepsis syndrome criteria developed by Bone and associates.<sup>12</sup> As can be seen from the table, definitions of organ dysfunction varied widely among studies, and the numbers and types of organ dysfunctions needed for study inclusion also varied.

#### BENEFITS AND LIMITATIONS OF SIRS AND MODS

The concept of SIRS has the advantage that it is simple to use and employs criteria that are easily assessed at the bedside. In addition, it reminds us that the presence of signs of sepsis does not necessarily mean that an infection is present. Regardless of the criticisms discussed below, the introduction of the term *SIRS*, along with its associated definitions of *sepsis*, *severe sepsis*, and *septic shock*, has provided some degree of standardization in the field of clinical trial development in sepsis.<sup>8</sup>

Nevertheless, there are several limitations associated with the consensus definitions, particularly with the concept of SIRS.<sup>6</sup> The first, and perhaps the most commonly cited criticism, is that the SIRS criteria are very sensitive, and most ICU patients and many general ward patients have SIRS.<sup>13–16</sup> This limits usefulness in trying to provide homogeneity. Second, simply labeling a patient as having SIRS provides no information regarding the underlying cause of the inflammatory syndrome. A "diagnosis" of SIRS simply indicates that there is some degree of inflammation. This may represent an appropriate physiologic reaction<sup>17</sup> rather than a disease process. The presence of an inflammatory response is not on its own necessarily a negative feature; the underlying cause of the response needs to be determined to enable appropriate treatment to be given if indeed any treatment is needed. Third, excessive simplicity can be harmful. Even though SIRS is very sensitive, other abnormalities, such as a high cardiac output, increased C-reactive protein (CRP) or procalcitonin concentration, unexplained disseminated intravascular coagulation (DIC), or hyperbilirubinemia could also raise suspicion of a diagnosis of sepsis. Finally, the high sensitivity of SIRS limits its usefulness as an entry criterion for clinical trials of therapeutic agents in ICU patients, although many studies (see Table 35-1) have used it for this purpose. Increasing sensitivity can limit specificity, and particularly in the field of immunomodulatory therapies in sepsis, we are increasingly realizing the importance of appropriately targeting treatments at specific patient groups. Thus, the inclusion of all patients with an inflammatory response (i.e., all SIRS patients), even when the degree of response is categorized by severity scores, will likely lead to negative trial results because any beneficial effect in a small subgroup of appropriate patients will be outbalanced by the overall negative effect in the heterogeneous group. Interestingly, of the 11 studies identified in our search, only 1 demonstrated positive effects on mortality rates.<sup>18</sup>

#### CONCLUSION

Problems with the definition of sepsis are not just a matter of wordplay and terminology but may account, in part, for the apparent failure of many trials of clinical interventions in septic patients. Huge advances in our understanding of the pathogenesis of sepsis and the complex activation of the immune response that occurs in the septic patient have not been accompanied by similar success stories in the development of novel sepsis therapies. The lack of a single clear and generally accepted means of identifying and categorizing the septic patient has meant that we have all too often used general and often nonspecific clinical signs of sepsis as entry criteria for our clinical trials. In addition, few clinical trials have used the same definitions, making comparisons of patient populations difficult and hindering application of results to the reallife clinical situation. Antimediator therapies have been almost universally ineffective in heterogeneous groups of septic patients.<sup>19-22</sup> Our basic assumption that the clinical picture reflects immune alterations and that fever, raised white cell count, and so forth are the direct result of mediator release and action is clearly inadequate. Each septic patient has multiple individual factors that make his or her "septic response" different from that of the next patient including age and sex; preexisting genetic predispositions and chronic disease processes; and the time of

## Table 35-1 SIRS and Organ Dysfunction Entry Criterion for Randomized Clinical Trials of New Therapeutic Interventions in Patients with Severe Sepsis

					ORGAN DYSFUNCTION DEFINITIONS FOR STUDY INCLUSION							
Study	Study Drug	No. of Patients	SIRS	Presence of infection								No. of Organ Dysfunctions Neces- sary for Inclusion
					Cardiovascular	Respiratory	Renal	Neurologic	Hematologic	Hepatic	Metabolic	
Bernard et al, 2001 <sup>18</sup>	Drotrecogin alfa (activated)	1690	3 or 4 criteria	Proven or suspected infection	$\begin{array}{l} SBP \leq 90 \mbox{ mm Hg} \\ or MAP \leq 70 \\ mm Hg despite \\ adequate fluid \\ resuscitation, \\ adequate \\ intravascular \\ volume status, or \\ the need for \\ vasopressor to \\ maintain SBP \geq 90 \\ mm Hg or MAP \geq \\ 60 \mbox{ mm Hg} \end{array}$	$\begin{array}{l} Pao_2/Fio_2 \leq 250 \text{ in} \\ \text{the presence of} \\ \text{other organ} \\ \text{dysfunctions or} \\ \leq 200 \text{ if the} \\ \text{lung is the only} \\ \text{dysfunctioning} \\ \text{organ} \end{array}$	Urine output < 0.5 mL/kg for 1 hr despite adequate fluid resuscitation		Platelet count < 80,000/mm <sup>3</sup> or to have decreased by 50% in the 3 days preceding enrollment		$\begin{array}{l} pH \leq 7.3 \mbox{ or base} \\ deficit > 5.0 \\ mmol/L \mbox{ in association} \\ with a plasma \\ lactate > 1.5 \\ times the \\ upper limit of \\ normal for the \\ reporting \\ laboratory \end{array}$	At least 1
Warren et al, 2001 <sup>24</sup>	Antithrombin	2314	Body tempera- ture and white cell count. SIRS criteria (tachycardia and tachyp- nea criteria included in organ dysfunction criteria)	Clinical evidence of infection with a suspected source	SBP < 90 mm Hg despite sufficient fluid replacement or the need of vasoactive agents to maintain SBP ≥ 90 mm Hg	Tachypnea (>24/min) or mechanical ventilation because of septic indication	Urine output < 20 mL/hr despite adequate fluid replacement		Platelet count < 100 × 10 <sup>3</sup> /μL		Elevated lactate levels (above upper limit of normal range) or metabolic acidosis (pH < 7.3 or base excess $\leq -10$ mmol/L) not secondary to respiratory alkalosis	3 of 6 criteria (tachycardia, tachypnea, hypotension, oliguria, thrombocytopenia, raised lactate levels, or metabolic acidosis
Abraham et al, 2001 <sup>25</sup>	p55 TNF receptor fusion protein	1342	At least 3	Objective signs of infection	Hypotension requiring ≤ 4 hr vasopressor use within 24 hr of study entry	Hypoxemia	Oliguria		Thrombocytopenia or unexplained coagulopathy		Acidosis	At least 2 hypoperfusion abnormalities or signs of organ dysfunction
Albertson et al, 2003 <sup>26</sup>	Monoclonal antibody to Enterobacteriacea common antigen	826 Ie	Presence of temperature, tachycardia, and tachyp- nea compo- nents of SIRS criteria plus hypotension or dysfunc- tion of two end organs	Sepsis from pre- sumed or proven gram- negative infection	Hypotension (supine SBP $\leq$ 90 mm Hg; acute decrease in SBP $\geq$ 40 mm Hg despite adequate fluid administration and in the absence of antihypertensive agents or the requirement of vasopressors to maintain SBP $\leq$ 90 mm Hg or presence of hyperdynamic cardiovascular response (cardiac index > 4.0 L/min/m <sup>2</sup> with systemic vascular index < 1400 dyne/sec/m <sup>2</sup> /cm <sup>5</sup> or cardiac output > 7.0 L/min with	Hypoxia (Pao <sub>2</sub> ≤ 65 mm Hg or Pao <sub>2</sub> /Fio <sub>2</sub> ratio < 300 or Sao <sub>2</sub> < 90%) without overt preexist- ing cardiac or pulmonary disease	Acute oliguria (<0.5 mL/kg/ hr) despite adequate volume loading		Acute unexplained thrombocytopenia (<75,000 platelets/ mL or 50% decrease from baseline) and hypofibrinogen- emia (<250 mg/ dL)		Metabolic acidosis (pH ≤ 7.30; base deficit ≥ 5 mmol/L; plasma lactate greater than upper limits of normal)	Dysfunction of two end organs

## Table 35-1 SIRS and Organ Dysfunction Entry Criterion for Randomized Clinical Trials of New Therapeutic Interventions in Patients with Severe Sepsis—Cont'd

					ORGAN DYSFUNCTION DEFINITIONS FOR STUDY INCLUSION							
Study	Study Drug	No. of Patients	SIRS	Presence of infection								No. of Organ Dysfunctions Neces- sary for Inclusion
					Cardiovascular	Respiratory	Renal	Neurologic	Hematologic	Hepatic	Metabolic	
					systemic vascular resistance < 800 dyne/ sec/cm <sup>-5</sup> )							
Abraham et al, 2003 <sup>27</sup>	Recombinant tissue factor pathway inhibitor	1987	At least 2 criteria	Clinical evidence of infection								At least 2 (precise definitions not specified)
Panacek et al, 2004 <sup>11</sup>	Anti-TNF antibody F(ab') fragment	2634		Sepsis syndrome within a 24-hr period, micro- biological or clinical evi- dence of acute infection	SBP ≤ 90 mm Hg, or decrease in SBP of ≥ 40 mm Hg, or use of vaso- pressors for blood pressure support, despite a 500 mL fluid challenge	Pao <sub>2</sub> ≤ 75 mm Hg (corrected for altitude) while on room air or a Pao <sub>2</sub> /Fio <sub>2</sub> ratio ≤ 250 mm Hg in patients without overt pulmonary disease	Oliguria with a urine output ≤ 0.5 mL/kg/ hr for ≥2 continuous hr	Acute deterioration of mental status, not confounded by sedative hypnotic drugs or other therapeutic agents with CNS- depressive effects or evidence of intracranial injury or hemorrhage	Recent (within 24 hr) unexplained coagulation abnormalities (INR > 2, or prothrombin time $\geq 1.5$ times the control value, or partial thrombo-plastin time $\geq 1.2$ times the control value) or recent (within 24 hr) unexplained plate-let depression defined as $\leq 100,000$ plate-lets/µL or a decrease by $\geq 50\%$ from previously known baseline value		Metabolic acidosis (defined as a normalized hydrogen ion content [pH] of $\leq$ 7.3, or a base deficit of $\geq$ 5) or ele- vated plasma lactate levels (according to local laboratory)	Hypotension or evidence of dysfunction of 1 other end organ
López et al, 2004 <sup>28</sup>	Nitric oxide synthase inhibitor	797	2 or more criteria	Clinical evidence of infection and the intro- duction or change of sys- temic antimi- crobial therapy within the pre- vious 72 hr	MAP consistently < 70 mm Hg for at least 30 min (despite fluid resuscitation), or a requirement for vasopressor support	Pao <sub>2</sub> /Fio <sub>2</sub> < 300 in the absence of primary underlying pulmonary disease	Urine output < 0.5 mL/kg/ hr for at least 2 consecutive hr or a rise in serum creati- nine concen- trations ≥ 2 mg/dL within the previous 48 hr in the absence of primary underlying renal disease	Acute deteriora- tion in mental state not due to sedation or primary underlying CNS disease	Platelet count < 75,000 or an acute decrease of 50% within the previous 24 hr in the absence of pri- mary underlying bone marrow disease, disseminated intravascular coagulopathy	Serum bilirubin concentration > 2.5 mg/dL, serum alanine transaminase > 2× upper limit of normal range, prothrombin time > 1.5× the control value or INR > 1.5 in the absence of systemic anticoagulation	Lactate > 2 mmol/L or a base deficit > 5 mmol/L	At least 1
Opal et al, 2004 <sup>29</sup>	PAF acetylhydrolase	1425	At least 2 criteria	Known or probable source of	Sustained hypotension, after adequate	Tachypnea (respiratory rate $\geq 20$	$\begin{array}{l} \text{Urine output} \leq \\ 0.5 \text{ mL/kg/hr} \\ \text{for} \geq 2 \text{ hr that} \end{array}$	Glasgow Coma Scale score $\leq 11$	aPTT ≥ 1.5 times the upper limit of normal, platelet		pH ≤ 7.3, elevated lactate and	At least 1

				infection with need of systemic antimicrobial therapy	volume replacement: SBP $\leq$ 90 mm Hg determined by two or more measures $\geq$ 60 min apart or evidence that vasopressors were required to maintain blood pressure $\geq$ 60 min	breaths/min) or Paco <sub>2</sub> ≤ 32 mm Hg or mechanical ventilation for an acute process	persisted despite objective evidence of adequate volume replacement		$\begin{array}{l} \mbox{count} \leq 100 \times 10^3 \\ \mbox{cells/mm}^3 \end{array}$		base excess ( <u>BE</u> ) ≥ 5 mmol/L	
Zeiher et al, 2005 <sup>30</sup>	Inhibitor of group IIA secretory phospholipase A2	373	3 or 4	Suspected or proven infection	SBP < 90 mm Hg or MAP ≤ 70 mm Hg for at least 1 hr despite adequate fluid administration, or requiring vasopressors	Evidence of acute pulmonary dysfunction $(Pao_2/Fio_2$ ratio $\leq 250$ and a PAOP $< 18$ mm Hg (if measured), or, in setting of pneumonia or preexisting a lung disease, a PaO <sub>2</sub> /Fio <sub>2</sub> ratio $\leq 200$ and a PAOP $< 18$ mm Hg if measured	Low urine output (<0.5 mL/kg/ hr for 2 consecutive hr despite adequate fluid resuscitation) or a serum creatinine >2× upper laboratory limit		Platelet count < 100,000/mm <sup>3</sup> or 50% decrease in the platelet count over the 3 days immediately preceding screening		Plasma lactate > $1.5\times$ the upper limit of normal associated with a pH $\leq$ 7.3 or a base deficit of $\geq$ 5.0 mEq/l/hr	At least 2
Abraham et al, 2005 <sup>31</sup>	Drotrecogin alfa (activated)	2640	At least 3 criteria	Proven or suspected infection	SBP < 90 mm Hg or MAP < 70 mm Hg despite adequate fluid resuscitation, adequate intravascular volume status, or the need for vasopressor to maintain SBP > 90 mm Hg or MAP > 60 mm Hg	Pao <sub>2</sub> /Fio <sub>2</sub> < 250	Average urine output 0.5 mL/kg/hr for 1 hr, despite adequate fluid resuscitation		Platelet count < 80,000 or a 50% decrease from the highest value recorded over the past 3 days		Defined by (1) pH 7.30 or base deficit $> 5$ mEq/L and (2) plasma lactate level $> 1.5 \times$ the upper limit of normal for the reporting laboratory	At least 1
Werdan et al, 2007 <sup>32</sup>	Immunoglobulin G	653	4 of 9 sepsis criteria, 4 of which were the SIRS criteria	Positive blood cultures and clinical evidence of infection as 2 of the 9 sepsis criteria	MAP < 75 mm Hg	Respiratory rate > 28 breaths/ min or Fro <sub>2</sub> > 0.21	Renal failure	Delirium, coma, or other focal neurologic manifestation of pyemia or septicemia	Disseminated intravascular coagulation	Jaundice		A sepsis score <sup>33</sup> of 12-27; this includes 13 possible points related to organ dysfunction

CNS, central nervous system; INR, International Normalized Ratio; MAP, mean arterial pressure; PAF, platelet-activating factor; SBP, systolic blood pressure; TNF, tumor necrosis factor.

onset of the infection, its source, and the causative microorganism. Moreover, the immune response will be different in different patients and at different times in the same patient. The challenge is, therefore, to find a means to better define and classify the immune response in critically ill patients, so that potential new therapies can be appropriately targeted at those patients most likely to benefit.

To this end, the PIRO (predisposition, infection, response, organ dysfunction) system, broadly based on the concepts behind the tumor-node-metastasis system widely used for cancer diagnosis and staging, has been suggested.<sup>9</sup> Although further work is needed to validate PIRO, it has been proposed that points could be allocated such that a patient with sepsis could, for example, be staged as  $P_1I_2R_1O_0$ ,<sup>23</sup> depending on the features present for each of the four PIRO components. Such a system could be employed universally to assist diagnosis and follow progression of sepsis and to better characterize patients with sepsis for inclusion in clinical trials.

#### AUTHORS' RECOMMENDATIONS

- The SIRS criteria were developed as part of an attempt to standardize definitions of sepsis and in recognition of the fact that a systemic inflammatory response similar to that seen with sepsis can occur without the presence of infection.
- The SIRS criteria have been widely used to identify populations of patients for inclusion in clinical trials of new therapeutic agents in sepsis but create very heterogeneous groups because most patients, with varying pathologies, meet SIRS criteria at some point.
- MODS can be used to characterize patients with severe sepsis, using organ dysfunction scores to assess organ function over time.
- New concepts, such as PIRO, will help to better characterize sepsis patients for clinical trial inclusion so that more homogeneous and relevant populations can be targeted. Such staging systems could also potentially be used in clinical practice to help select more appropriate sepsis treatments and to follow the course of disease.

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## 36

## Is Sepsis-Induced Organ Dysfunction a Manifestation of a Prosurvival Adaptive Response?

Richard J. Levy

Organ dysfunction is a hallmark of sepsis.<sup>1</sup> Investigation during the past several years has focused on identifying potential causes of this component of the syndrome. The motivation for many researchers is the desire to pinpoint targets for therapeutic intervention. Although a variety of pathways and cellular systems are altered by sepsis and inflammation, no unifying or causative etiology has been uncovered. Historically, clinicians and investigators have viewed sepsis-induced organ failure as a pathologic process that is deleterious to the survival of the host.<sup>2</sup> Recently, an interesting alternative hypothesis has been proposed: Does organ dysfunction during sepsis represent an adaptive prosurvival response?<sup>3,4</sup> This concept is based on absence of histologic injury and reduced metabolism during sepsis that resembles a hibernating or suspended-animation state.<sup>1</sup>

In nature, hibernation, or torpor, is a protective adaptation to harsh environmental conditions and is a regulated seasonal response.<sup>5</sup> This response allows hibernating mammals to rapidly and dramatically reduce their metabolism to promote survival.<sup>5</sup> In this chapter, we review the striking similarities between organ function during sepsis and organ function during hibernation. Specifically, we (1) discuss the mechanisms that downregulate metabolism in both states and highlight the role of mitochondria, (2) focus on cardiac function during hibernation and assess similarities and differences with sepsis-induced myocardial depression, and (3) examine the evidence supporting the development of a hibernation-like state in during sepsis.

#### MITOCHONDRIA AS THE MEDIATOR OF METABOLIC DOWNREGULATION IN SEPSIS AND HIBERNATION

## Impaired Oxidative Phosphorylation in Sepsis

It has been proposed that an acquired defect in oxidative phosphorylation prevents cells from using molecular oxygen for adenosine triphosphate (ATP) production and potentially causes sepsis-induced organ dysfunction.<sup>6,7</sup> Most energy production in vertebrate cells occurs in the mitochondria and is generated by aerobic respiration.<sup>8</sup> This process, called *oxidative phosphorylation*, couples

oxidation of NADH (reduced nicotinamide adenine dinucleotide) and FADH<sub>2</sub> (flavin adenine dinucleotide) with phosphorylation of adenosine diphosphate (ADP) to form ATP.<sup>7,8</sup> Oxidative phosphorylation is accomplished by a series of enzyme complexes termed the *electron transport chain.*<sup>8</sup> Located on the mitochondrial inner membrane, these enzymes use energy released during transfer of electrons between complexes to actively pump protons from the mitochondrial matrix into the intermembrane space.<sup>7,8</sup> This proton motive force is used by ATP synthase (complex V) to synthesize ATP from ADP.<sup>8</sup>

Each mitochondrion contains 2 to 10 copies of a circular, double-stranded DNA called *mitochondrial DNA* (mtDNA). mtDNA encodes key subunits of the electron transport chain enzyme complexes while structural subunits arise from nuclear genes.<sup>9</sup> Thus, expression of genes that give rise to the protein complexes of the respiratory chain is under dual control. An acquired defect in gene expression or functional activity of any of the electron transport enzymes could impair oxidative phosphorylation and could lead to sepsis-induced organ dysfunction.<sup>6,7</sup>

When considering bioenergetic impairment in sepsis, investigators most commonly have focused on cytochrome oxidase (complex IV). This complex is composed of 13 subunits. Subunits 1, 2, and 3 make up the catalytic center and are encoded by mtDNA.<sup>8</sup> The other 10 subunits arise from nuclear DNA.<sup>8</sup> Subunit 1, the active site, houses the heme *aa*3 binuclear center.<sup>8</sup> Numerous studies have demonstrated abnormalities in expression and function of cytochrome oxidase during sepsis and in related models. For example, steady-state levels of cytochrome oxidase subunit I messenger RNA (mRNA) and protein were found to decrease in murine heart following cecal ligation and puncture (CLP) and in endotoxin-stimulated macrophages.<sup>10,11</sup> Subunit 1 mRNA half-life was markedly reduced in these macrophages.<sup>11</sup> Subunit 3 protein content and subunit 5A, 5B, and 6A message and protein decreased in the endotoxic diaphragm.<sup>12,13</sup> Cytochrome oxidase subunit 4 protein decreased in rat heart 18 hours after CLP.<sup>14</sup> Reductions in cytochrome oxidase message and protein result in reduced enzyme content and could affect the bioenergetic capacity of the cell.

Changes in mRNA and protein levels of key enzyme complex subunits are only functionally significant if they lead to or contribute to enzyme dysfunction. To this point, myocardial cytochrome oxidase activity decreased to 51% of baseline in baboons following *Escherichia coli* infusion.<sup>15</sup> In murine sepsis, myocardial cytochrome oxidase inhibition was reported after CLP.<sup>10</sup> This inhibition was competitive initially but became noncompetitive later. This change occurred at a time when cardiac function was markedly impaired and when mortality was quite high.<sup>10</sup> Cytochrome oxidase dysfunction also has been shown in septic liver and in the medulla of the endotoxemic rat.<sup>16,17</sup> Furthermore, reduced state 3 oxygen consumption has been demonstrated in the neonatal rat heart, feline liver, and rat diaphragm during endotoxemia.<sup>12,18,19</sup>

A reduced cytochrome *aa*3 redox state in the absence of tissue hypoxia indicates a defect in mitochondrial oxygen use and suggests impaired oxidative phosphorylation. A number of investigators have demonstrated reduced redox status during endotoxemia and gram-negative bacteremia in the heart, brain, skeletal muscle, and intestine in a variety of animals.<sup>20–24</sup> In addition, diminished heme *aa*3 content in heart and skeletal muscle has been shown in experimental sepsis.<sup>10,25</sup>

Bioenergetic failure as a potential cause of sepsisinduced organ failure is not a new concept. With regard to sepsis-associated myocardial depression, early investigation extensively evaluated oxygen delivery, global myocardial perfusion, and high-energy phosphate levels.<sup>26–32</sup> These studies clearly demonstrated that coronary blood flow and global cardiac perfusion were maintained and often increased during sepsis.<sup>26–28,33</sup> In addition, there was strong evidence to suggest that tissue oxygen tension was unchanged in the dysfunctional septic heart.<sup>30</sup> These findings argue strongly against decreased oxygen availability as a cause of myocardial depression in sepsis and support a defect in oxygen utilization.

The literature, however, is less clear regarding ATP availability. In many studies, preserved ATP levels were demonstrated in dysfunctional septic myocardium. Other investigations reported decreased high-energy phosphates in experimental sepsis and endotoxemia.14,29-32,34 Preservation of ATP does not indicate absence of mitochondrial dysfunction in sepsis.<sup>31,35</sup> During reduced oxygen delivery and cellular hypoxia, cells can adapt to maintain viability by downregulating oxygen consumption, energy requirements, and ATP demand.<sup>36,37</sup> Thus, although ATP content may remain unchanged, ATP utilization is decreased dramatically. In the heart, this response is called myocardial hibernation and classically occurs during myocardial ischemia.<sup>36</sup> This adaptive, prosurvival response results in cardiomyocyte hypocontractility with preserved cellular ATP.36 Thus, finding preserved ATP during sepsis reveals little about the integrity of oxidative phosphorylation and may support the notion of a similar prosurvival response, especially in the setting of cytochrome oxidase inhibition or impairment.

#### Cytochrome Oxidase Expression and Impaired Activity in Hibernation

Cytochrome oxidase I expression has been evaluated during hibernation in a variety of tissues of true hibernators such as the 13-lined ground squirrel.<sup>5</sup> Compared with euthermic controls, steady-state levels of both cytochrome oxidase I mRNA and protein were found to be relatively increased in the kidney during hibernation. This suggests upregulation.<sup>5</sup> Similar changes in cytochrome oxidase I message were seen in the heart and brown adipose tissue (BAT) of hibernators.<sup>5</sup> These changes stand in stark contrast to the observations reported in a variety of organs and tissues during sepsis. The reason for upregulation of cytochrome oxidase I during hibernation is unknown, but it has been hypothesized that such an increase in expression may limit cold and ischemic damage to the enzyme during torpor.<sup>5</sup>

Interestingly, failed upregulation and decreased steadystate levels have been demonstrated in kidney cytochrome oxidase I mRNA in squirrels that fail to hibernate.<sup>5</sup> This subset of animals has been termed *cold adapted* (probably a misnomer). It is unknown why these animals do not hibernate and why cytochrome oxidase I mRNA levels decrease. Further, it is also unknown if this response is maladaptive or if it is associated with death. Importantly, the response of cold-adapted squirrels is similar to that seen during sepsis with regard to cytochrome oxidase I mRNA. This begs the following question: Are the decreases in cytochrome oxidase mRNA and protein during sepsis adaptive or maladaptive? To answer this question, it may be more useful to compare changes in cytochrome oxidase activity during sepsis with changes seen during the adaptive, programmed state of hibernation.

Metabolic depression and downregulation that promote survival are crucial responses during true hibernation.<sup>5</sup> Central to this response are reduced oxygen consumption and cytochrome oxidase activity. In the hibernating frog, whole-body oxygen consumption decreases by 50% in normoxic 3°C water.<sup>38</sup> Whole-body oxygen consumption and respiration of isolated skeletal muscle mitochondria decreased further when hibernating frogs were placed in hypoxic cold water.<sup>38</sup> Further, cytochrome oxidase activity in frog skeletal muscle progressively decreases during different stages of hibernation.<sup>38</sup> In the hibernating ground squirrel, state 3 respiration decreased by almost 70% in liver mitochondria.<sup>39</sup> Thus, it is clear that reversible cytochrome oxidase inhibition and reduced activity are key to initiating and maintaining the hibernating phenotype in the hibernating mammal. Importantly, these reductions in cytochrome oxidase activity and mitochondrial respiration are similar to the changes seen during early sepsis.

### Cytochrome Oxidase Inhibition, Metabolic Downregulation, and Suspended Animation

Cytochrome oxidase adheres to first-order Michaelis-Menten kinetics.<sup>40</sup> Reversible enzyme inhibition may be competitive or noncompetitive.<sup>41</sup> The most recognized competitive inhibitor of cytochrome oxidase is nitric oxide, whereas noncompetitive inhibition is most notably caused by carbon monoxide, hydrogen sulfide, cyanide, azide, peroxynitrite, and lipid peroxidation.<sup>36,42–44</sup>

Cytochrome oxidase inhibition has been shown to induce a hibernation-like or suspended-animation state.<sup>45,46</sup> Reversible inhibition of cytochrome oxidase with carbon monoxide arrests embryogenesis in *Caenorhabditis elegans* embryos yet preserves their viability in hypoxic conditions.<sup>45</sup> In addition, noncompetitive cytochrome oxidase inhibition with inhaled hydrogen sulfide (H<sub>2</sub>S) induces a suspended-animation state in nonhibernating mice.<sup>46</sup> On exposure to H<sub>2</sub>S, mice dramatically reduce their core body temperature and metabolic rate in a dose-dependent and reversible manner.<sup>46</sup> At the cellular level, noncompetitive inhibition of cytochrome oxidase with sodium azide causes a rapid and reversible reduction in cardiomyocyte contraction and metabolic demand, mimicking myocardial hibernation.<sup>36</sup>

Importantly, cytochrome oxidase inhibition has been described during sepsis.<sup>10</sup> In the heart, for example, cytochrome oxidase was competitively inhibited during the early phase of sepsis and progressed to become noncompetitively inhibited during the late, hypodynamic phase.<sup>10</sup> A number of different inhibitors may be responsible for sepsis-induced cytochrome oxidase inhibition. The most likely offenders include nitric oxide, carbon monoxide, peroxynitrite, and reactive oxygen species. Certainly, all these are endogenously produced in a variety of tissues during sepsis.<sup>47–50</sup> The impairment in cytochrome oxidase activity during sepsis is notably similar to that seen during true hibernation, and this specific pattern of enzyme inhibition is known to induce metabolic downregulation and a suspended-animation state. Thus, sepsis-induced cytochrome oxidase inhibition may be an underlying mechanism of organ dysfunction during sepsis and, more importantly, may be related in some way to the adaptive response during true hibernation.

#### SEPSIS-ASSOCIATED MYOCARDIAL DEPRESSION SHARES SIMILARITIES WITH CHANGES SEEN IN CARDIAC FUNCTION DURING HIBERNATION

#### Sepsis-Associated Myocardial Depression

Cardiac dysfunction is an important but poorly understood characteristic of sepsis. The time course and progression of myocardial depression have been well described in humans.<sup>51–54</sup> Sepsis most often results in depressed myocardial contractility. With adequate volume resuscitation and increased preload, end-diastolic volume increases. This leads to biventricular dilation and enables stroke volume and cardiac output to be maintained in the face of reduced ejection fraction and myocardial dysfunction. Ultimately, reduced diastolic relaxation can lead to an inability of the heart to dilate, and cardiac output can decrease. This failure to dilate is often associated with death.

In canine sepsis, Natanson and colleagues found defects in cardiac performance similar to defects in humans.<sup>55</sup> With murine polymicrobial peritonitis induced by CLP, sepsis results in an early, hyperdynamic phase within 5 hours after CLP, when cardiac output and stroke volume increase. Early circulatory enhancement is superseded by a late, hypodynamic phase that is characterized by decreased cardiac output and stroke volume.<sup>56</sup> Tao and colleagues demonstrated that, despite maintained

cardiac output and stroke volume during the early, hyperdynamic phase, myocardial contractility and relaxation diminish progressively in septic mice within 6 hours of CLP.<sup>57</sup> Thus, CLP in the mouse results in cardiac depression similar to the human response.

#### **Cardiac Function During Hibernation**

Mammalian cardiac performance decreases dramatically during hibernation.<sup>58,59</sup> This is due largely to significant reductions in heart rate, ventricular ejection fraction, and stroke volume.<sup>58,59</sup> In the hibernating marmot, for example, heart rate decreases from 160 to 9 beats/minute.<sup>58</sup> In hibernating grizzly bears, the mean rate of circumferential left ventricular shortening and left ventricular ejection fraction decline significantly compared with the euthermic state.<sup>59</sup> Further, marmot cardiac index decreases from 61 to 7.6 mL/kg per minute during hibernation.<sup>58</sup> Thus, changes in systolic performance during hibernation are similar to those seen during sepsis. A key difference, however, is that there is enhanced diastolic relaxation and improved ventricular compliance during hibernation.<sup>59</sup> Hibernating grizzly bears, for example, demonstrate increases in mean mitral inflow ratio and isovolumic relaxation time compared with the active state.<sup>59</sup>

The similarities in cardiac function during hibernation and sepsis support the notion that sepsis-associated myocardial depression may represent a prosurvival adaptive change in ventricular function. However, the distinct differences in diastolic performance indicate that sepsisinduced organ dysfunction as a whole may represent something altogether different. One hypothesis that addresses both the similarities and differences is that organ failure during sepsis may initially represent an adaptive response. At some critical time point, the process becomes maladaptive and pathologic. It is possible that reduced performance in the septic heart initially reflects a decreased total-body need for oxygen as a substrate for ATP production (as in hibernation). However, when sepsis-induced mitochondrial and cellular defects become irreversible, the processes of metabolic downregulation and myocardial depression become irreversible, and a pathologic state of organ dysfunction manifests. If this is true, the challenges for the clinician will be to differentiate reversible adaptive organ "hibernation" from pathologic organ "failure," to recognize when this switch has occurred, and to intervene to prevent the alteration.

#### **Evidence of Hibernation in Sepsis**

The response of myocardium to ischemia is strikingly similar to sepsis-associated myocardial depression.<sup>31</sup> Hypoperfused myocardium, like septic myocardium, is hypocontractile yet viable with preserved cellular ATP.<sup>31,35,56,57</sup> Ischemia and hypoxia induce hibernation, whereby reversibly dysfunctional cardiomyocytes maintain viability by downregulating oxygen consumption, energy requirements, and ATP demand.<sup>36</sup> Myocardial hibernation has not been formally evaluated in other disease processes.

A key difference between sepsis-associated myocardial depression and ischemic myocardium is an impairment in

oxygen utilization and not in oxygen supply. During ischemia, hibernating cardiomyocytes undergo characteristic cellular and metabolic alterations.<sup>60–65</sup> To maintain viability, these cells rely on anaerobic glycolysis for ATP production and switch their primary substrate utilization from fatty acids to glucose.<sup>63</sup> Increases in the number of myocardial-specific glucose transporters (GLUT1 and GLUT4) enhance myocardial glucose uptake.<sup>62–64</sup> During ischemia and hypoxia, the more abundant transporter, GLUT4, translocates from intracellular vesicles to the plasma membrane and is upregulated.<sup>63–66</sup> In addition, in hibernating myocardium, there is increased glycogen deposition in the perinuclear region and between myofibrils.<sup>60</sup>

Recently, evidence of hibernation was demonstrated in the dysfunctional septic heart.<sup>33</sup> Studies were performed 48 hours after CLP in mice during the late hypodynamic phase of sepsis. Increased global myocardial glucose uptake was seen in vivo in septic mice using positron emission tomography.<sup>33</sup> Myocardial GLUT4 expression on the cell surface was noted, and characteristic glycogen deposits were visible in septic myocardium.<sup>33</sup> These changes occurred in the absence of hypoxemia and myocardial hypoperfusion and are consistent with the typical features of hibernating myocardium.<sup>33</sup>

#### CONCLUSION

Sepsis and hibernation have similarities that suggest that sepsis-induced organ dysfunction may represent an adaptive response. Mitochondrial dysfunction and cytochrome oxidase inhibition are likely central to the process. As in hibernation, it is possible that reversible cytochrome oxidase inhibition initiates metabolic downregulation during sepsis, leading to reduced organ function. Clinically, this manifests as organ failure. Although it is quite possible that the reduction in metabolism during sepsis may initially be adaptive, it is clear that the process can progress to become maladaptive and pathologic when sepsisinduced metabolic downregulation and organ dysfunction become irreversible. Future investigation will need to focus on the temporal nature of this process and attempt to identify the key mechanisms involved in the switch from reversible to irreversible mitochondrial inhibition and organ dysfunction. With further understanding, clinicians may be able to identify when and how to intervene at critical time points in the disease process in order to restore metabolic capacity of the cell. Thus, better understanding of how the human body acclimates and adapts to such life-threatening stimuli is required before we are truly able to improve survival during sepsis and other types of critical illnesses.

#### AUTHORS' RECOMMENDATIONS

 Sepsis and hibernation have similarities that suggest that sepsis-induced organ dysfunction may represent an adaptive response. Mitochondrial dysfunction and cytochrome oxidase inhibition are likely central to the process.

- Reversible cytochrome oxidase inhibition may initiate metabolic downregulation during sepsis, leading to reduced organ function. Clinically, this manifests as organ failure.
- The reduction in metabolism during sepsis may initially be adaptive. However, the process can progress to become maladaptive and pathologic when sepsis-induced metabolic downregulation and organ dysfunction become irreversible.
- Future investigation will need to focus on the temporal nature of this process and attempt to identify the key mechanisms involved in the switch from reversible to irreversible mitochondrial inhibition and organ dysfunction.

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# 7 Is Chronic Critical Illness a State of Endocrine Dysfunction?

# Clifford S. Deutschman

Our ability to manage patients in the intensive care unit (ICU) has led to a better understanding of the natural history of critical illness (Fig. 37-1). Initially, critical illness was viewed as a state of humoral excess. For unclear reasons, the inflammatory state initiated by injury or disease became prolonged.<sup>1</sup> Observed abnormalities were driven by activation of white blood cells and elaboration of proinflammatory mediators such as cytokines, perhaps provoked by persistent but unrecognized and untreated infection. This led to the hypothesis that blockade of inflammatory mediators would alter responses and improve outcome. Unfortunately, these approaches failed. More recently, our ability to support the patient has unmasked a later stage of critical illness. This is characterized by immune depression<sup>2</sup> and a syndrome best described as "stable severe organ dysfunction." That is, patients progress into a persistent state of impaired function of the heart, vasculature, lung, liver, kidney, gut, muscle, and peripheral nerves. In addition, there is a variable encephalopathy that has been attributed to "ICU psychosis" but may have an organic basis. Much of the dysfunction can be overcome using available technology. However, in addition to altered function, organ systems lose the ability to act in the organized, interactive manner that is found in the healthy organism.<sup>1</sup> They do not appear to be able to communicate with each other, a state that leads to functions in individual systems that are distinctly maladaptive (e.g., retention of fluid by the kidney despite the presence of severe pulmonary edema). Godin and Buchman have postulated that these discoordinated responses can be mathematically described as an uncoupling of biologic oscillators.<sup>3</sup> Although some patients recover both organ function and biologic coupling, in a significant number, the need for support continues, integrated function is not restored, and the situation becomes futile. The most common cause of death in these "chronic critically ill" patients is removal of life-support systems.

The biologic basis for the loss of organ-organ interaction is unknown. In general, communication is maintained by three systems: neural, humoral (primarily through white blood cells), and endocrine. Abnormalities in white cell function are well described,<sup>1,4</sup> whereas the potential contribution of altered central nervous system (CNS) function has not been explored. In contrast, a great deal is known about changes in endocrine activity over the course of critical illness. In this chapter, we explore the function of several components of the endocrine system. Changes in the acute phase of critical illness are contrasted with those observed over time. Our overarching hypothesis is that chronic critical illness is a state of severe compromise of endocrine systems with axes that originate in the hypothalamus. This failure contributes significantly to the intractable course of the syndrome.

## VASOPRESSIN

Vasopressin is produced in the magnocellular neurons of the hypothalamus and released from the posterior pituitary. Secretion is increased primarily in response to increases in osmolality and to a lesser extent by decreases in blood pressure. In the late 1990s, Landry and associates began to examine the effects of critical illness, and particularly distributive shock, on vasopressin synthesis and release.<sup>5</sup> These investigators found that serum levels decrease rapidly. In about 30% of patients, these abnormalities corrected. In most, however, including those with a protracted ICU course, circulating vasopressin levels remained depressed. Sharshar and coworkers demonstrated that the basis for this relative vasopressin deficiency lies in neurohypophyseal depletion.<sup>6</sup> Landry's studies also demonstrated that repletion of vasopressin using very modest (0.04 U/minute, a dose 1/10 of that used historically for variceal bleeding) made it possible to wean exogenous catecholamine support.7 Animal studies indicate that low-dose vasopressin does not alter blood flow in major vascular beds. Therefore, it has been proposed that the effect on blood pressure primarily involves altered baroreceptor reflexes.<sup>5</sup> The clinical use of vasopressin in the critically ill and the results of a recent randomized controlled trial are described in Chapter 32.

# **MINERALOCORTICOIDS**

Mineralocorticoids, principally aldosterone in humans, cause salt and water retention. The acute phase response to inflammation, whereby the body attempts to compensate for circulatory perturbations, is associated with a dramatic increase in serum aldosterone levels. This is driven, in part, by renin-angiotensin–mediated conversion of 18-hydroxycorticosterone to aldosterone. Importantly, aldosterone secretion also is modulated by endothelins, prostaglandins, serotonin, and atrial natriuretic factor and responsive to



**Figure 37-1.** Time course of responses in the critically ill. The x-axis represents time and the y-axis represents any of a number of physiologic, metabolic, or immunologic markers. The response to injury without complication is represented by the unbroken line: after a 3-7 increase, organ function/activity/marker levels return to baseline. Early critical illness is represented by the uniformly broken line: organ function/activity/marker levels remain elevated for up to 2 weeks and return to baseline. Chronic critical illness is represented by the intermittently broken line: organ function/activity/marker levels remain elevated for up to 2 weeks and return to baseline. Chronic critical illness is represented by the intermittently broken line: organ function/activity/marker levels become persistently depressed.

elevation of serum potassium ion and to the pituitary adrenocorticotropic hormone (ACTH).<sup>8</sup> The latter is best known for its role in controlling the secretion of glucocorticoids, most notably cortisol. However, the effects of ACTH on aldosterone are substantial and probably quite important in the chronic phase of critical illness. Du Cheyron and colleagues reported in 2003 that critically ill patients, over time, develop a deficiency of aldosterone.9 This is associated with salt and water wasting, prolonged ICU length of stay, and increased need for renal replacement therapy. This aldosterone deficiency is not predictive of poor overall outcome. Interestingly, this deficiency occurs despite high circulating levels of renin, suggesting that the defect lies in the biosynthesis of aldosterone in the adrenal cortex. As discussed later, Willenberg and colleagues have proposed that failure to appropriately increase serum cortisol levels in response to ACTH, even when very high at baseline, defines adrenal insufficiency in the critically ill.<sup>8</sup> They therefore postulate that chronic critical illness is associated with peripheral resistance to ACTH action. If this is the case, it is to be expected that secretion of aldosterone, as well as cortisol, would be impaired. In an interesting study, Manglik and associates found that a small subset of patients with severe sepsis did not increase serum aldosterone levels in response to an ACTH challenge.<sup>10</sup> All these patients also failed to increase cortisol levels after ACTH administration. Therefore, chronic critical illness is associated with aldosterone deficiency that may reflect resistance to the effects of ACTH.

# THYROID AXIS

The effects of thyroid hormones on peripheral tissue are under complex control (Fig. 37-2). At the most central level, cortical and peripheral signals stimulate the hypothalamus to produce thyrotropin-releasing hormone (TRH). TRH in



**Figure 37-2.** Changes in the thyrotropic axis induced by acute and chronic critical illness. Black arrows indicate stimulation of secretion; broken lines, inhibition. Early effects are indicated by Acute Critical Illness; late effects as Chronic Critical Illness. Arrows indicate direction and magnitude of change. TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone; T4, thyroxine; T3, triiodothyronine; rT3, reverse T3; T2, di-iodothyronine; X, inhibition.

turn provokes the secretion of thyroid-stimulating hormone (TSH), which leads to the release of thyroxine by the thyroid gland.<sup>11</sup> This form of thyroid hormone ( $T_4$ ) contains four iodide moieties and has limited activity. In peripheral tissue, deiodinases cleave one of the iodides.<sup>12</sup> Activity of the D1 and, to a lesser degree, D2 deiodinases leads to the formation of triiodothyronine ( $T_3$ ), the more potent form of thyroid hormone, whereas the D3 deiodinase stimulates production of the inactive reverse  $T_3$  (r $T_3$ ).

In the acute phase of critical illness, an unknown process blocks D1 and thus the peripheral conversion of T<sub>4</sub> to T<sub>3</sub>.<sup>13</sup> This increases the formation of rT<sub>3</sub> and limits the activity of thyroid hormones. In the more chronic phase of critical illness, a neuroendocrine component develops.<sup>14,15</sup> Studies by van den Berghe and associates have revealed a loss of the central (hypothalamic and pituitary) factors that activate a number of endocrine axes.<sup>14,15</sup> In addition, not only is the secretion of these central endocrine components diminished, but also the diurnal and hourly variability of release is lost.<sup>16</sup> With regard to the thyroid axis, TRH and TSH release falls.<sup>17</sup> As a result, T<sub>4</sub> secretion is diminished. This, in combination with inhibition of peripheral D1, results in a profound state of hypothyroidism. Interestingly, the effects of TRH are countered by dopamine, which blocks TSH release.<sup>18</sup> Although increased secretion of dopamine by the hypothalamus has not been demonstrated, the use of exogenous dopamine for cardiovascular support may enhance the hypothyroid state.<sup>18</sup> Administration of either T<sub>4</sub> or T<sub>3</sub> has produced variable results in animal models, whereas human trials of  $T_4$  have not shown benefit.<sup>14,15,17,19</sup> However, work by van den Berghe's group has examined infusion of TRH and a synthetic type 2 growth hormone-releasing peptide (GHRP-2) into animal

models and critically ill patients.<sup>20,21</sup> This TRH and GHRP-2 combination increased peripheral  $T_3$  and  $T_4$  but not  $rT_3$ . Further investigation clearly is warranted.

# SOMATOTROPIC AXIS

Muscle wasting is an important component of chronic critical illness and a major cause of post-ICU disability. Although a number of endocrine mediators effect muscle mass, growth hormone (GH) is an especially important factor. However, the effects of GH are both direct and indirect, and some examination of the involved pathways is required<sup>22,23</sup> (Fig. 37-3).

GH release from the somatotrope cells of the anterior pituitary is under the control of three hypothalamic factors. These are growth hormone-releasing hormone (GHRH), the inhibitor somatostatin, and the multifaceted protein ghrelin. The last is stimulated by a series of synthetic peptides and nonpeptide factors called GH secretagogues.<sup>24</sup> Included among the secretagogues are the GHRPs mentioned previously. Secreted GH can act directly on skeletal muscle and fat through a specific receptor. Activation of the GH receptor leads to lipolysis, enhanced amino acid uptake into skeletal muscle, and promotion of hepatic gluconeogenesis. However, the major effects of GH on skeletal muscle appear to be mediated through stimulated production of insulin-like growth factor-1 (IGF-1, also called somatomedin) by the liver. IGF stimulates skeletal muscle anabolism and, to lesser extent, lipolysis, through a different receptor-linked pathway than GH. IGF also is synergistic with the anabolic effects of insulin on skeletal muscle. IGF in 90% of patients circulates in a large complex bound primarily to IGF-binding protein-3 (IGFBP-3) and acidlabile subunit (ALS) and, on occasion, to IGFBP-5. IGF-1



**Figure 37-3.** Changes in the somatotropic axis induced by acute and chronic critical illness. Black arrows indicate stimulation of secretion; broken lines, inhibition. Early effects are indicated by broken arrow next to "Acute Critical Illness"; late effects by arrow next to "Chronic Critical Illness". Arrows indicate direction and magnitude of change. ALS, acid-labile subunit; GHRH, growth hormone–releasing hormone; GH, growth hormone; IGF, insulin-like growth factor; IGFBP, IGF-binding protein; broken lines, inhibition.

exerts feedback inhibition on its own response to GH in the liver and on the release of GH by the pituitary. In addition, IGF-1 may stimulate the hypothalamic release of somatostatin, further limiting GH release.

The acute phase response inhibits the somatotropic axis through the effects of cytokines on peripheral tissue.<sup>14,15</sup> As the process progresses into acute critical illness, however, several changes occur (see Fig. 37-3). GH receptor density decreases as expression is downregulated. This, in combination with a reprioritization of hepatic protein synthesis to accommodate the acute phase, increases GH secretion and decreases IGF-1 production by the liver, limiting feedback inhibition.<sup>25,26</sup> The resultant increases in GH levels and enhanced effects of GH on muscle do not, however, cause the indirect effects mediated by IGF-1. Thus, lipolysis is promoted, but skeletal muscle anabolism is limited. In addition, hepatic synthesis of ALS is diminished. Because IGFBP-3 is produced by many tissues, its concentration is more variable. With the transition to chronic critical illness, central adaptation, as described for the thyroid axis, occurs. Pulsatility is lost, and GH levels decline.<sup>20,27,28</sup> This further decreases IGF-1, IGFBP-3, and ALS production and adds to the decline in skeletal muscle anabolism. Severe wasting may result.

Based on the results of GH trials in GH-deficient disorders and small uncontrolled trials of GH in critical illness that focused on surrogate markers of outcome, Takala and associates conducted a randomized, prospective, doubleblind study of supraphysiologic doses of recombinant human GH in critically ill patients.<sup>29</sup> Although markers of GH activity such as IGF-1 and IGHBP-3 increased and nitrogen balance improved, mortality in the treatment group was elevated as a result of septic shock or multiple-organ failure. Importantly, most of the patients entered this study while in the chronic phase of critical illness.

In light of the results of the GH trial, focus has shifted to other agents that modulate the somatotropic axis. Treatment of chronic critically ill patients with GHRP or GHRH restored pulsatile GH secretion as well as the production of IGF-1, IGFBP-3, and ALS and feedback inhibition.<sup>20,27,28</sup> Analysis of data obtained from the Leuven Intensive Insulin Therapy (ITT) trial in chronically critically ill surgical patients revealed a restoration of GH levels but did not alter levels of IGF-1, IGFBP-3, or ALS.<sup>30</sup> Thus, ITT appeared to alter GH responses in chronic patients to a pattern that resembled the acute phase of the syndrome. A number of animal studies suggest that administration of IGF-1 may be valuable in sepsis. The use of IGF-1 as monotherapy, however, may be limited by the huge capacity of the IGFBPs. Studies by van den Berghe and colleagues using infusions of GHSH, GHRP-2, or a combination of the two have shown an increase in GH concentration, GH secretion, and GH pulsatility along with increases in IGF-1, IGFBP-3, and ALS.<sup>20,27</sup> Thus, it is reasonable to be optimistic regarding additional studies.

## HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

The adrenal response to critical illness has been the subject of intense investigation since the 1970s. Much of the data are reviewed in Chapter 73, but the importance of hypothalamic-pituitary-adrenal (HPA) axis dysfunction in the development of chronic critical illness requires further scrutiny. In the acute phase of critical illness cortisol levels rise. This occurs in response to increased release of corticotropin-releasing hormone (CRH) and ACTH.<sup>31</sup> Diurnal variation is lost; levels of cortisol-binding globulin (CBG), which binds more than 90% of circulating cortisol; and albumin, which binds much of the rest, decline, increasing free cortisol levels.<sup>32</sup> However, peripheral responses may vary because there is a change in glucocorticoid receptor number.<sup>14</sup> Feedback inhibition is altered by the presence of inflammatory cytokines that can alter secretion of CRH and ACTH. As the syndrome becomes chronic, circulating cortisol levels become extremely variable. However, levels of ACTH and CRH decline. The driving force for maintaining cortisol levels is unknown.

It has long been known that absolute adrenal insufficiency, that is, circulating levels of cortisol that are below "normal," are associated with high mortality from any inflammatory event (e.g., surgery, sepsis). In addition, clinical trials conducted in the late 1980s demonstrated that administration of high ("pharmacologic") doses of methylprednisolone to septic patients was detrimental.<sup>33</sup> However, recent work has generated a renewed interest in the use of "physiologic" doses of glucocorticoids. Annane and coworkers used a standard definition of adrenal insufficiency (absolute level  $< 8 \mu g/dL$ , change in response to 250  $\mu$ g of ACTH of < 9  $\mu$ g/dL) to examine the incidence of this disorder in patients with septic shock.<sup>34</sup> All patients were randomized to receive either 50 mg of hydrocortisone plus 50 µg of fludrocortisone, a mineralocorticoid, every 6 hours. The study demonstrated a statistically significant improvement in survival in patients who did not respond to ACTH stimulation. More recently, Sprung and associates conducted a randomized, prospective trial (the CORTICUS Trial) in a similar cohort of patients.<sup>35</sup> Entry criteria were less stringent, and patients received hydrocortisone only. In contrast to Annane's work, CORTICUS failed to show an outcome benefit in the entire cohort as well as in the cohort that met Annane's criteria for adrenal insufficiency. However, design concerns make these data somewhat problematic. The appropriate approach to management remains controversial. The topic is explored more fully in Chapter 73.

# **GONADOTROPIC AXIS**

Control of sex steroids is profoundly altered in critically ill patients (Fig. 37-4). The pattern differs in males and females, a finding that is consistent with both clinical and experimental findings, indicating lower mortality in women suffering from several types of critical illnesses.<sup>14,15</sup> Ultimate control of the gonadotropic axis lies with the hypothalamic gonadotropin-releasing hormone (GnRH) and to some extent dopamine. GnRH stimulates the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH stimulates androgen production by ovarian cells. These are aromatized to estrogens (primarily estradiol) under the modulation of FSH. In men, LH stimulates androgen (primarily testosterone) production by testicular Leydig cells, whereas FSH, in concert with testosterone, supports spermatogenesis by



**Figure 37-4.** Changes in the gonadotropic axis induced by acute and chronic critical illness. Black arrows indicate stimulation of secretion; broken lines, inhibition. Early effects are indicated by symbol, broken arrow next to "Acute Critical Illness"; late effects by symbol, arrow next to "Chronic Critical Illness". Arrows indicate direction and magnitude of change. GnRH, gonadotropin-releasing hormone; FSH, follicle stimulating hormone; LH, luteinizing hormone; X, inhibition.

Sertoli cells. Secretion of all gonadotropic hormones is pulsatile and subject to diurnal variation. Both androgens and estrogens exert feedback inhibition on GnRH, FSH, and LH.

In acute critical illness, serum levels of testosterone decrease rapidly despite elevated LH concentrations.<sup>36</sup> This suggests a loss of peripheral sensitivity in Leydig cells. With prolongation of the syndrome, testosterone levels drop to even lower levels and at times become undetectable. However, as is the case with other pituitary hormones, LH levels also decrease, and pulsatility is lost.<sup>14,15,36,37</sup> Total estradiol levels drop in both men and women, but a decrease in binding globulins indicates the bioavailability most probably is unchanged. The decrease in LH, coupled with the profound loss of testosterone, suggests that aromatization of androgens is enhanced.

Numerous studies in both humans and animal models indicate that estrogen is protective in many forms of critical illness and injury.<sup>38,39</sup> Findings suggest increased aromatization of androgens.<sup>14,15</sup> Although a recently published study demonstrated an association between estradiol concentrations and death, it is unclear whether estrogens cause death or levels rise to protect against a loss of peripheral activity.<sup>40</sup> A trial of GnRH in critically ill patients transiently restored LH pulsatility and led to a small but unsustained increase in serum testosterone concentrations.<sup>37</sup>

#### LACTOTROPHIC AXIS

Prolactin (PRL), produced by pituitary lactotrophic cells, is released in pulses and varies diurnally. Release is controlled by dopamine and several other factors. Apart from effects on lactation, PRL has immune-enhancing properties.

PRL rises in the acute phase of critical illness.<sup>14,15</sup> As in other pituitary hormones, pulsatility is lost and levels decline as the disorder becomes more chronic.<sup>16</sup> It has been postulated that this contributes to immunosuppression. As with other pituitary hormones, infusion of GHRH, GHRP-1, and TSH in critically ill patients restores pulsatility and increases levels.<sup>41,42</sup>

#### OTHER HORMONE SYSTEMS

Our hypothesis is focused on the impairment by critical illness of hormone systems that are regulated by an "axis" that involves the CNS. However, it is clear that other endocrine mediators are altered in ICU patients. For example, levels of the catecholamines norepinephrine and epinephrine increase acutely and then decrease in critically ill patients.<sup>43</sup> The initial phase is associated with peripheral resistance to catechol effects. This most likely reflects a downregulation of receptor expression and density as well as a failure of the G-coupled adenylate cyclase-cyclic adenosine monophosphate-protein kinase A pathway.<sup>44</sup> In the later phases of the syndrome, catechol levels fall. One could define an axis that originates in the sympathetic nuclei of the brainstem and extends through peripheral nerve endings (norepinephrine) to tissues or to the adrenal medulla (epinephrine). In that case, a case for early peripheral and late central dysfunction could be made. Similarly, it is intriguing to interpret recent studies involving insulin secretion and activity (see Chapter 72) within this paradigm. Certainly, early critical illness is accompanied by elevated serum levels, increased pancreatic secretion, and "insulin resistance" at the tissue level. In the later phase, islet  $\beta$ -cell function is impaired. The value of intensive insulin therapy in patients hospitalized in the ICU for more than 5 days could represent an approach to a syndrome of endocrine dysfunction in chronic critical illness. Thus, our hypothesis may be more applicable than proposed here. Importantly, in most of the axes described here, replacement of hormones has not improved outcome. Rather, a complex strategy involving modulation of several of the axes at once using a number of therapeutic agents appears to be required. This argues that the various components and axes that comprise the endocrine system may act in concert and perhaps synergistically. This raises concern about approaches to the insulin axis using insulin only.

# AUTHORS' RECOMMENDATIONS

- Critical illness involves three phases: initial (normal inflammation), early, and chronic.
- Chronic critical illness is characterized by organ dysfunction and a loss of organ-organ interaction.
- Under normal conditions, organ-organ interaction is maintained by neural, humoral, and endocrine connections.
- Critical illness alters the function of hormonal "axes," that is, feedback-controlled systems involving multiple hormones. These most often arise at the hypothalamus and connect to peripheral endocrine tissue through the pituitary.
- Early critical illness is characterized by an attenuation of hormonal activity in peripheral tissues.

- Chronic critical illness involves suppression of central (hypothalamic, pituitary) control of endocrine activity.
- Replacement of individual hormones does not appear to be sufficient to correct the defects.
- Therapy may require a complex approach involving multiple hypothalamic-pituitary mediators or synthetic secretagogues that affect multiple aspects of endocrine function.

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# How Does One Diagnose and Manage Severe Community-Acquired Pneumonia?

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Community-acquired pneumonia (CAP) is the major cause of infection-related death in developed countries and also is a common etiology of systemic sepsis and critical illness. The mortality rate in severe community-acquired pneumonia (SCAP) is about 30%. This is far higher than the mortality observed from pneumonia managed outside of the hospital or in the hospital but outside of the intensive care unit (ICU). Therefore, to ensure proper management and therapy, it is imperative to recognize this illness as soon as possible. Delays in recognizing severe forms of CAP can increase mortality. Indeed, a number of studies show that delayed management in the ICU is associated with a higher risk for death than when the disease is managed expectantly in the ICU, at the first signs of severe illness.<sup>1</sup>

There is no uniformly useful or accepted definition of SCAP, nor are there standard criteria for admission to the ICU. Current Infectious Diseases Society of America and American Thoracic Society (IDSA/ATS) guidelines define SCAP using major criteria such as respiratory failure (need for assisted ventilation) or septic shock requiring vasopressors.<sup>2</sup> Three additional minor criteria are used to diagnose SCAP: respiratory rate 30 breaths/minute or higher, Pao<sub>2</sub>/Fio<sub>2</sub> ratio 250 or less, multilobar infiltrates, confusion or disorientation, blood urea nitrogen (BUN) 20 mg/dL or higher, leukopenia (white blood cell count < 4000 cells/ mm<sup>3</sup>), thrombocytopenia (<100,000 platelets/mm<sup>3</sup>), hypothermia (temperature  $< 36^{\circ}$ C), and hypotension requiring aggressive fluid resuscitation. Other possible minor criteria that should affect the decision to admit the patient to the ICU include hypoglycemia (in nondiabetic patients), alcohol withdrawal, hyponatremia, unexplained metabolic acidosis or lactic acidosis, and asplenia.

Although there have been attempts to develop objective criteria for SCAP, most case series have defined this entity simply as CAP requiring admission to the ICU. In one study of a national database in the United Kingdom,<sup>1</sup> CAP accounted for 5.9% of all ICU admissions. Early admission appeared to be preferable in the setting of severe illness because the mortality rate was 46.3% in those admitted to the ICU within 2 days of hospital admission but rose to 50.4% in those admitted at 2 to 7 days and to 57.6% in those admitted more than 7 days after hospital admission. Other studies have shown improved outcomes in SCAP when initial therapy is appropriate. A 5-year retrospective French study<sup>3</sup> used multivariate analysis to demonstrate that the effectiveness of the initial therapy appeared to be the most significant prognostic factor. In fact, this was the only prognostic factor that constituted a modifiable medical intervention.

# WHO GETS SEVERE COMMUNITY-ACQUIRED PNEUMONIA?

## Risk Factors for Severe Forms of Community-Acquired Pneumonia

About 45% to 65% of patients with SCAP have coexisting illnesses. Conversely, patients who are chronically ill have an increased likelihood of developing a complicated pneumonic illness<sup>4</sup> (Table 38-1). The most common chronic illnesses in these patients are respiratory disease such as chronic obstructive lung disease (COPD), cardiovascular disease, and diabetes mellitus. In addition, certain habits, such as cigarette smoking and alcohol abuse, also are common in those with SCAP. Indeed, cigarette smoking has been identified as a risk factor for bacteremic pneumococcal infection.<sup>5</sup> Other common illnesses in those with CAP include malignancy and neurologic disorders (including seizures). Milder forms of pneumonia may be more severe on presentation if patients have not received antibiotic therapy before hospital admission. In addition, the ability to contain the infectious challenge, which may be related to genetic differences in the immune response, may predispose certain individuals to more severe forms of infection and adverse outcomes. This may be reflected in a family history of severe pneumonia or adverse outcomes from infection.<sup>6-14</sup> It appears likely that SCAP results when inflammation is either insufficient to contain the infection or so exuberant that the host response affects the uninvolved lung (leading to acute respiratory distress syndrome) or the systemic circulation (leading to severe sepsis).<sup>8</sup>

# PREDICTORS OF OUTCOME

The most commonly used predictors of outcome from pneumonia are two scoring systems, the Pneumonia Severity Index (PSI)<sup>15</sup> and the British Thoracic Society rule.<sup>16</sup>

#### Table 38-1 Risk Factors for Developing Severe Community-Acquired Pneumonia

- Advanced age (>65 yr)
- Comorbid illness: especially if decompensated
- Chronic respiratory illness (including chronic obstructive pulmonary disease), cardiovascular disease, diabetes mellitus, neurologic illness, renal insufficiency, malignancy
- Cigarette smoking (risk for pneumococcal bacteremia)
- Alcohol abuse
- Absence of antibiotic therapy before hospitalization, or inappropriate therapy
- Residence in a chronic care facility
- Poor functional status
- · Failure to contain infection to its initial site of entry
- Immune suppression (corticosteroids, other illnesses)
- Genetic polymorphisms in the immune response

The latter rule recently has been modified to the CURB-65 score. This is an acronym for the following: confusion, serum *u*rea nitrogen level higher than 19.6 mg/dL, respiratory rate 30 breaths/minute or higher, low systolic ( $\leq$ 90 mm Hg) or diastolic ( $\leq 60$  mm Hg) blood pressure, and age older than 65 years. These two scoring systems are valid in identifying patients at low risk for mortality. Each, however, has limitations. These limitations are most apparent when the systems are used to identify those with SCAP. Ideally, the two complement one another.<sup>17</sup> The PSI heavily weights age and comorbidity but does not necessarily measure the severity of acute illness, relying on vital sign abnormalities that fall either above or below a dichotomous variable threshold. Thus, it may overestimate severity of illness in older patients and underestimate severity in younger individuals without comorbid illness. Conversely, the CURB-65 criteria may not adequately consider the presence of comorbid illness, particularly those in which pneumonia has induced decompensation.

Several studies have compared both prognostic tools in the same population.<sup>16,18–22</sup> In one recent study, both the PSI and the CURB-65 were good at predicting mortality and identifying low-risk patients. However, the CURB-65 appeared to be more discriminating in defining mortality risk in the severely ill.<sup>20</sup> Another study by España and colleagues used both the PSI and the CURB-65 to evaluate a large number of inpatients and outpatients with CAP.<sup>21</sup> In this investigation, the CURB-65 (and its simpler CRB-65 version, which excludes measurement of BUN and thus can be used in outpatients) accurately predicted 30-day mortality, the need for mechanical ventilation, and perhaps the need for hospitalization. In addition, the CURB-65 criteria correlated with the time to clinical stability. Thus, a higher score predicted a longer duration of intravenous therapy and a longer length of hospital stay. The PSI predicted mortality. However, as demonstrated in other studies, the PSI was not good at predicting the need for ICU admission. España and colleagues found that the CURB-65 also could not predict the need for ICU admission reliably. However, other investigators found the CURB-65, although still limited, to be more accurate than the PSI for predicting need for ICU admission.<sup>19</sup>

In a study done in a tertiary care hospital in Spain,<sup>22</sup> most patients with the highest possible PSI category (risk class V) were treated on a medical ward, with only 20% treated in the ICU. The investigators found that when patients were admitted to the ICU, they tended to get more of their PSI points from acute rather than chronic illness. The reverse was true for those PSI class V patients who were not admitted to the ICU. Data from patients with CAP admitted to two tertiary hospitals in Texas<sup>23</sup> analyzed retrospectively demonstrated that, although the patients in the ICU had a higher PSI score than the ward patients, the ICU patient cohort (145 patients) included patients in all PSI classes, with 30% falling into low-risk PSI groups (classes I to III). These findings are similar to data reported by Ewig and associates,<sup>19</sup> indicating that the PSI was good for predicting CAP mortality but not for determining the need for ICU care. Prognostic tools used to identify the need for intensive care or to predict mortality are summarized in Table 38-2.<sup>16,18–21,24–30</sup>

Recently, España and colleagues tried to develop a more specific rule for ICU admission. They examined records from 1057 patients and determined that the need for ICU admission was defined by the presence of one of two major criteria: arterial pH less than 7.30 or systolic blood pressure less than 90 mm Hg.<sup>21</sup> In the absence of these criteria, SCAP also could be identified by the presence of two of six minor criteria. These included confusion, BUN greater than 30 mg/dL, respiratory rate greater than 30 breaths/minute, Pao<sub>2</sub>/Fio<sub>2</sub> ratio less than 250, multilobar infiltrates, and age at least 80 years. When these criteria were met, the tool was 92% sensitive for identifying those with SCAP and was more accurate than the PSI or CURB-65 criteria, although not quite as specific as the CURB-65 rule.<sup>21</sup>

A number of recent investigations have examined biomarkers in serum to measure CAP severity and to predict the outcome. These studies have focused on C-reactive protein (CRP), procalcitonin (PCT), and cortisol.<sup>31–36</sup>

In a study of 185 patients (144 inpatients and 44 outpatients) who had PCT measured within 24 hours of the diagnosis, CAP levels correlated with PSI score (higher in classes III to V than in I and II) and the development of complications (higher with empyema, mechanical ventilation, and septic shock). Levels also were increased in those who died compared with those who did not.<sup>33</sup> Serial measurements of PCT also have been used to define prognosis in SCAP patients. Investigators have reported that nonsurvivors have a significantly higher PCT level than survivors on day 1. With serial measurements, survivors had a decrease in PCT levels, whereas nonsurvivors had an increase by day 3.<sup>35</sup>

In a recent study of 278 patients presenting to an emergency department in Switzerland with pneumonia,<sup>36</sup> cortisol levels also could be used to predict severity of illness and outcome (death). Free and total cortisol levels correlated with severity of illness, as reflected by PSI score, with a level of total cortisol above 960 nmol/L having a sensitivity of 75% and a specificity of 71.7% for predicting mortality. These data should be viewed cautiously because some recent studies have questioned the reliability of serum cortisol levels in patients with acute septic illness.

Table 38-2 Cor	Table 38-2 Comparison of Studies for Prognostic Scores on Pneumonia Severity						
Study	No. of Patients	Outcome Predictor	Prediction Rule	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Farr B, 1991 <sup>24</sup>	245	Mortality	Original BTS rule 1	70	84	29	97
Karalus N, 1991 <sup>25</sup>	92	Mortality	Original BTS rule 1	83	80	23	99
Ewig, 1995 <sup>26</sup>	92	Mortality	Original BTS rule 1	65	73	21	95
			Original BTS rule 2	47	88	31	94
Neill A, 1996 <sup>27</sup>	122 deceased*	Mortality	Modified BTS (CURB $\geq 2$ ) <sup>†</sup>	95	71	22	99
			Original BTS rule 1	90	76	25	99
			Original BTS rule 2	90	88	33	97
Ewig S, 1998 <sup>28</sup>	395	Need for ICU admission	Modified ATS	78	94	75	95
Conte H, 1999 <sup>29</sup>	2356	Mortality	Original BTS rule 1 <sup>‡</sup>	50	70	NR	NR
Lim W, 2000 <sup>18</sup>	181 deceased*	Mortality	Modified BTS (CURB $\geq$ 2)	66	73	NR	NR
Lim W, 2003 <sup>16</sup>	1068	30-day mortality	Modified BTS (CURB-65 $\geq$ 3)	68.1	74.9	22.4	95.7
			Derivation cohort (718 pts) <sup><math>\dagger</math></sup>	75	74.7	23.4	96.7
			Validation cohort (214 pts)				
Ewig, 2004 <sup>19</sup>	696	30-day mortality	Modified ATS	94 (95% CI, 82.5-98.7)	93 (95% CI, 90.6-94.7)	49 (95% CI, 38.2-59.7)	99.5 (95% CI, 98.5-99.9)
			Modified BTS (CURB $\geq$ 2)	51 (95% CI, 35.5-67.1)	80 (95% CI, 76.3-83.1)	16 (95% CI, 10.1-23.3)	96 (95% CI, 93.4-97.3)
Aujesky D, 2005 <sup>20</sup>	3181	Mortality	$\text{PSI} \geq 4$	79 (95% CI, 71-85)	70 (95% CI, 68-72)	13 (95% CI, 11-17)	99 (95% CI, 98-99)
			$\text{CURB} \geq 2$	47 (95% CI, 39-55)	85 (95% CI, 84-87)	13 (95% CI, 11-17)	97 (95% CI, 96-98)
			CURB-65 $\geq$ 3	45 (95% CI, 37-53)	87 (95% CI, 86-88)	14 (95% CI, 11-18)	97 (95% CI, 96-98)
España, 2006	1057	Mortality, need for mechanical ventilation and/ or septic shock	SCAP prediction rule <sup>†§</sup>	92.1	95.97	21.4	99.2
			Modified ATS	51.3	95.9	49.4	96.2
			CURB-65 $\geq$ 3	68.4	86.8	28.6	97.3
			$\text{PSI} \geq 4$	94.7	68.1	18.7	99.4
			Adjusted PSI (classes I-III with oxygen desaturation and PSI ≥ IV)	97.4	57.5	15.1	99.7

\*Indicates derivation studies.

<sup>\$</sup>9/20 Variables also present in PSI + multi-lobar chest radiograph.

ATS, American Thoracic Society; BTS, British Thoracic Society; CI, confidence interval; CURB, confusion, serum urea, respiratory rate, blood pressure; ICU, intensive care unit; NPV, negative predictive value; NR, not reported; PPV, positive predictive value; PSI, Pneumonia Severity Index; SCAP, severe community-acquired pneumonia.

<sup>&</sup>lt;sup>†</sup>Case-control studies.

<sup>&</sup>lt;sup>\*</sup>All patients  $\geq$  65 yr or older.

# DIAGNOSTIC TESTING

# **History and Physical Examination**

History should focus on the presence of symptoms suggesting respiratory infection (fever, cough, purulent sputum, pleuritic chest pain, dyspnea) along with information suggesting serious illness. The history should thus focus on the presence of comorbid illness, recent hospitalization, and recent antibiotic therapy. In addition, there are certain clinical conditions associated with specific pathogens in patients with CAP, and these associations should be evaluated when obtaining a history (Table 38-3).<sup>2</sup> For example, if the presentation is subacute, following contact with birds, rats, or rabbits, the possibility of psittacosis, leptospirosis, tularemia, or plague should be considered. Coxiella burnetii (Q fever) is a concern with exposure to parturient cats, cattle, sheep, or goats; Francisella tularensis is a concern with rabbit exposure; hantavirus with exposure to mice droppings in endemic areas; Chlamydia psittaci with exposure to turkeys or infected birds; and Legionella species with exposure to contaminated water sources (saunas). After influenza superinfection with pneumococcus, Staphylococcus aureus (including methicillin-resistant S. aureus [MRSA]) and Haemophilus influenzae should be considered. With travel to endemic areas in Asia, the onset of respiratory failure after a viral illness should lead to suspicion of a viral pneumonia, which could be severe acute respiratory syndrome (SARS) or avian influenza. Endemic fungi (coccidioidomycosis, histoplasmosis, and blastomycosis) occur in well-defined geographic areas and may present acutely with symptoms that overlap with acute bacterial pneumonia.

Physical findings of pneumonia include tachypnea, crackles, rhonchi, and signs of consolidation (egophony, bronchial breath sounds, dullness to percussion). Patients should also be evaluated for signs of pleural effusion. In addition, extrapulmonary findings should be sought to rule out metastatic infection (arthritis, endocarditis, meningitis) or to add to the suspicion of an "atypical" pathogen such as Mycoplasma pneumoniae or Chlamydophila pneumoniae that can lead to such complications as bullous myringitis, skin rash, pericarditis, hepatitis, hemolytic anemia, or meningoencephalitis. An attentive physical examination may help identify patients with severe pneumonia. One study<sup>37</sup> showed that in elderly patients, elevation of the respiratory rate can be the initial presenting sign of pneumonia, preceding other clinical findings by as much as 1 to 2 days. Indeed, tachypnea is present in more than 60% of all patients, being found more often in elderly than in younger patients with pneumonia. In addition, the counting of respiratory rate can identify the patient with severe illness, who commonly have a rate higher than 30 breaths/minute.

# **Recommended Diagnostic Testing**

In addition to a constellation of suggestive clinical features, a diagnosis of CAP can only be made with the finding of a

Condition	Commonly Encountered Pathogens
Alcoholism	Streptococcus pneumoniae (including drug-resistant S. pneumoniae), anaerobes, gram-negative bacilli, tuberculosis
Chronic obstructive pulmonary disease; smoker	S. pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Legionella species
Nursing home residency	S. pneumoniae, gram-negative bacilli, H. influenzae, Staphylococcus aureus, anaerobes, Chlamydia pneumoniae, tuberculosis
Poor dental hygiene	Anaerobes
Epidemic legionnaires disease	Legionella species
Exposure to bats	Histoplasma capsulatum
Exposure to birds	Chlamydia psittaci, Cryptococcus neoformans, H. capsulatum
Exposure to rabbits	Francisella tularensis
Travel to southwest United States	Coccidioidomycosis
Exposure to farm animals or parturient cats	Coxiella burnetii (Q fever)
Influenza active in community	Influenza, S. pneumoniae, S. aureus, H. influenzae
Suspected large-volume aspiration	Anaerobes, chemical pneumonitis, obstruction
Structural disease of lung (e.g., bronchiectasis, cystic fibrosis)	Pseudomonas aeruginosa, Pseudomonas cepacia, S. aureus
Injection drug use	S. aureus, anaerobes, tuberculosis, Pneumocystis carinii
Endobronchial obstruction	Anaerobes
Recent antibiotic therapy	Drug-resistant pneumococci, P. aeruginosa

# Table 38-3 Epidemiologic Conditions Related to Specific Pathogens in Patients with Community-Acquired Pneumonia

new radiographic lung infiltrate. These findings are not specific for pneumonia and generally cannot help define an etiologic pathogen. Thus, microbiologic data are needed.<sup>4</sup> Although chest radiographic patterns generally are not useful for identifying the etiology of CAP, certain findings such as pleural effusion (pneumococcus, H. influenzae, M. pneumoniae, pyogenic streptococci) and cavitation (Pseudomonas aeruginosa, S. aureus, anaerobes, MRSA, tuberculosis) can suggest certain groups of organisms. It often is difficult to define the etiologic pathogens in patients with CAP because up to half of such patients have no identified etiology even with extensive diagnostic testing that includes cultures of blood and sputum. Although there is controversy about the value of diagnostic testing in patients with CAP, extensive routine testing is recommended for those admitted to the ICU.<sup>2</sup> Several studies have shown that establishing an etiologic diagnosis does not improve the outcome of SCAP and that outcome is only improved if empirical and broad-spectrum early therapy is given, targeting the likely etiologic pathogens. However, diagnostic testing may have value for the purpose of narrowing and focusing therapy and for guiding management in the patient who is not responding to empirical therapy.<sup>38</sup>

When collecting samples for diagnostic testing, it is important to start empirical antibiotics because delays in therapy have been associated with increased mortality. In addition to a chest radiograph, all SCAP patients should have blood and lower respiratory tract (sputum, endotracheal aspirate, bronchoalveolar lavage, or bronchoscopic specimen) cultures, arterial blood gas analysis,<sup>39</sup> and routine hematologic and blood chemistry testing. If the patient has a moderate-sized pleural effusion, this should be tapped and the fluid sent for culture and biochemical analysis. The yield of a positive culture of pleural fluid is low, but the information acquired when the cultures are positive have a substantial effect on the management, not only for antibiotic choice, but also for the indications for drainage.<sup>2</sup> Patients with SCAP should have two sets of blood cultures,<sup>2,4,40</sup> and these are more likely to be positive if the patient has not received antibiotics at the time of sampling or if there are signs of liver disease, hypotension, fever or hypothermia, tachycardia (pulse > 125 beats/minute), elevated BUN, serum sodium level less than 130 mEq/L, and white cell count lower than 5000 cells/ $\mu$ L or higher than 20,000 cells/ $\mu$ L.<sup>40</sup> The presence of bacteremia may not worsen prognosis but does allow identification of drug-resistant organisms, although most positive blood cultures in CAP reveal pneumococcus.

Sputum culture should be accompanied by Gram stain to guide interpretation of the culture results but not to focus initial antibiotic therapy. In some situations, Gram stain can be used to broaden initial empirical therapy by enhancing the suspicion for organisms that are not covered by routine empirical therapy (such as *S. aureus*, suggested by clusters of gram-positive cocci, especially during a time of epidemic influenza). Routine serologic testing is not recommended. However, in patients with severe illness, the diagnosis of *Legionella* species infection can be made by urinary antigen testing because this is the test most likely to be positive at the time of admission. One shortcoming is that this test is specific only for serogroup I infection.<sup>2</sup> Examination of concentrated urine for pneumococcal antigen also may be valuable. In cases in which viral etiology is suspected, influenza direct fluorescent antibody testing can be performed, and the result is usually available in few hours. For other respiratory viruses, testing might be of use, particularly in the setting of outbreaks.<sup>4</sup> Bronchoscopy is not indicated as a routine diagnostic test but may be needed in some patients with severe forms of CAP to establish an etiologic diagnosis in order to focus the initially broad-spectrum empirical therapy to a simpler regimen.<sup>2</sup>

#### BACTERIOLOGY

# Identifying Patients with Health Care-Associated Pneumonia

Some patients with severe pneumonia are admitted to the hospital after outpatient contact with the health care environment and thus do not have traditional CAP; rather, the diagnosis is health care-associated pneumonia (HCAP). These patients are admitted from a nursing home or extended care facility, have been in the hospital sometime during the past 90 days, have undergone hemodialysis, or are receiving ongoing wound care. Because of contact with the hospital environment, these patients are at risk for infection with multidrug-resistant (MDR) gramnegative pathogens and MRSA. Thus, they need a differ-ent approach to therapy.<sup>41,42</sup> In the 2005 IDSA/ATS Nosocomial Pneumonia guidelines, HCAP was considered a form of nosocomial infection,<sup>43</sup> and Medicare has exempted such patients from therapy that is compliant with CAP "core measures." We have chosen to include HCAP in the discussion of CAP because these are the patients who develop severe illness and are at risk for infection with enteric gram-negative bacteria and MRSA. However, patients admitted from a nursing home still may have infections caused by atypical pathogens and Legionella species.44,45 Some patients with HCAP have pathogens similar to SCAP, whereas others have pathogens similar to severe nosocomial pneumonia. Therapy varies accordingly. Some examples of HCAP patients at high risk for MDR pathogens are those with prior antibiotics exposure (within the past 3 to 6 months), those with poor functional status, and those with recent hospitalization.46-48

## **Common Pathogens**

The most common cause of SCAP is pneumococcus (*Streptococcus pneumoniae*).<sup>4</sup> This organism accounts for two thirds of bacteremic pneumonia and are the most frequent cause of lethal CAP.<sup>2,49</sup> At least 40% of cases are resistant to penicillin or other antibiotics, leading to the term *drugresistant S. pneumoniae* (DRSP). Currently, most penicillin resistance in the United States is of the "intermediate" type (penicillin minimum inhibitory concentration, or MIC, of 0.1 to 1.0 mg/L) rather than the high-level type (penicillin MIC of 2.0 or more).<sup>50</sup> Pneumococcal resistance to other antibiotics, including macrolides and trimethoprim-sulfamethoxazole, also is common, but the clinical relevance

and effect on outcome of these in vitro findings are uncertain. One study, corroborated by the opinion of many experts, found that only organisms with a penicillin MIC higher than 4 mg/L were associated with an increased risk for death.<sup>51</sup> In a prospective international study of 844 patients with pneumococcal bacteremia,<sup>52</sup> in vitro resistance to βlactams was associated with little in the way of clinical impact. Discordant therapy with penicillins, cefotaxime, and ceftriaxone did not result in a higher mortality. However, discordant therapy with cefuroxime led to a worse clinical outcome than if the organism were sensitive to this agent. Although DRSP is common, quinolone resistance is unusual. Doern and associates<sup>50</sup> observed that, although penicillin resistance was present in 34.2% of pneumococci, quinolone resistance was rare. However, 21% of organisms had a single first-step mutation (par C) that did not confer resistance but could predispose to clinical resistance in the presence of a second mutation (gyr A). This situation mandates close observation.

All patients with SCAP should be considered at risk for DRSP. In addition, those admitted to the ICU can have infection with atypical pathogens that can account for up to 20% of infections, either as primary infection or as copathogens. The identity of these organisms varies with time and geography. In some areas, Legionella species is a common cause of SCAP, whereas in others, C. pneumo*niae* or *M. pneumoniae* infection predominates.<sup>4</sup> Other important causes of SCAP include H. influenzae, S. aureus, MRSA (especially after influenza), and enteric gramnegative bacteria (including P. aeruginosa). Risk factors for gram-negative bacteria include underlying COPD (especially with corticosteroid therapy), recent hospitalization, prior antibiotics, bronchiectasis, and the presence of HCAP.47 The specific risks for P. aeruginosa include the presence of structural lung disease (bronchiectasis), COPD, treatment with broad-spectrum antibiotics within 7 days of presentation, chronic steroid use, malignancy, and malnutrition.<sup>2,47</sup> Rapid radiographic spread of the disease is also a clue to the presence of P. aeruginosa infection. In a multicenter Spanish study of 529 patients with SCAP, 15 of 20 patients (75%) with P. aeruginosa had rapidly progressive illness because antimicrobial treatment at admission was inadequate.<sup>53</sup>

Recently, a toxin-producing strain of MRSA has been described in patients with CAP after influenza and other viral infections. This community-acquired MRSA is biologically and genetically distinct from the MRSA that causes nosocomial pneumonia. It is more virulent and necrotizing and is associated with the production of the Panton-Valentine leukocidin (PVL).<sup>54,55</sup> Viruses can be a cause of SCAP. Culprits include influenza virus as well as parainfluenza virus and epidemic viruses such as coronavirus (which causes SARS) and avian influenza.<sup>2,56</sup> Viral pneumonia (SARS and influenza) can lead to respiratory failure, and occasionally tuberculosis or endemic fungi can result in severe pneumonia.

Unusual etiologies should be considered in patients who have epidemiologic risk factors for specific pathogens, as discussed previously. In addition, the presence of certain "modifying factors" increases the likelihood of CAP caused by DRSP and gram-negative bacteria.<sup>47,57</sup> The risk factors for DRSP include  $\beta$ -lactam therapy in the

past 3 months, alcoholism, age older than 65 years, immune suppression, multiple medical comorbidities, and contact with a child in day care.<sup>57,58</sup> The risk factors for gramnegative bacteria were mentioned previously and include the presence of HCAP. In addition, aspiration is more commonly associated with gram-negative pneumonia than with anaerobic infection in the institutionalized elderly population.<sup>59</sup>

#### TREATMENT

For ICU-admitted CAP, initial therapy should be directed at DRSP, Legionella species, and other atypical pathogens, enteric gram-negative bacteria (including P. aeruginosa), and other selected organisms. Drug selection should be based on appropriate historical and epidemiologic data. Therapy is stratified depending on whether the patient is at risk for P. aeruginosa (based on the risk factors listed previously). In all treatment algorithms, no ICU-admitted CAP patient should receive empirical monotherapy, even with one of the new quinolones.<sup>57</sup> This recommendation is based on the fact that the efficacy (especially for meningitis complicating pneumonia), effective dosing, and safety of any single agent, including quinolone monotherapy, has not been established for ICU-admitted CAP patients. In one recent study comparing high-dose levofloxacin to a β-lactam-quinolone combination, the singleagent regimen was overall effective. However, patients in septic shock were excluded, and there was a trend to a worse outcome with monotherapy for individuals treated with mechanical ventilation.<sup>60</sup> In another study of SCAP, the use of a  $\beta$ -lactam-macrolide combination had a survival advantage compared with quinolone monotherapy.<sup>61</sup>

If the patient has no pseudomonal risk factors, therapy should be limited to a selected intravenous  $\beta$ -lactam (cefotaxime, ceftriaxone, ertapenem, or a  $\beta$ -lactam- $\beta$ -lactamase inhibitor combination) combined with either an intravenous macrolide or an intravenous antipneumococcal quinolone (levofloxacin or moxifloxacin). For patients with pseudomonal risk factors, therapy can be with a two-drug regimen, using an anti-pseudomonal  $\beta$ -lactam (imipenem, meropenem, piperacillin-tazobactam, cefepime) plus ciprofloxacin (the most active antipseudomonal quinolone) or levofloxacin (750 mg daily). Alternatively, a three-drug regimen involving an antipseudomonal β-lactam plus an aminoglycoside plus either an intravenous and antipneumococcal quinolone (levofloxacin or moxifloxacin) or a macrolide<sup>2,57,62</sup> can be used. One of the justifications for being familiar with these recommendations is the finding that if patients are treated with these types of regimens, outcomes are improved.<sup>53,63</sup> Several studies have shown that guideline compliance can improve outcome and that nonadherence can lead to a delay in clinical resolution.63-6

All these regimens have alternatives, and it is not clear whether one regimen is better than another. However, in the selection of an empirical therapy regimen, it is necessary to know what antibiotic the patient has received within the past 3 months and to choose an agent that is in a different class. Indeed, repeated use of the same class of antibiotic may drive resistance to that class, especially if the pathogen is pneumococcus. In one study, use of a penicillin, cephalosporin, trimethoprim-sulfa, or levofloxacin in the 3 months preceding pneumococcal bacteremia led to an increased likelihood that the bacteremic pathogen would be resistant to the recently used therapeutic agent.<sup>68</sup>

In addition to choosing antibiotic therapy, as discussed previously, it is important to give the first dose of antibiotic as soon as possible after the diagnosis is established. For all patients with CAP, timely administration of antibiotics reduces mortality. This is especially true if the first dose is given within 4 to 6 hours, but even more rapid administration is necessary for those with severe illness. For example, in patients with sepsis, each hour of delay in the start of antibiotic therapy increases mortality by 7.6%.<sup>69</sup>

The antibiotic regimens discussed previously all cover for atypical pathogens using either a macrolide or a quinolone. Data indicate that such an approach reduces mortality, especially in those with severe illness.<sup>70–72</sup> Even in patients with pneumococcal bacteremia, the use of combination therapy (generally with the addition of a typical pathogen coverage to pneumococcal coverage) has been associated with reduced mortality relative to monotherapy.<sup>72</sup> In one study, the benefit of adding a second agent applied to those pneumococcal bacteremia patients who were critically ill but not to other populations.<sup>73</sup> Rodriguez and colleagues found a benefit to adding a second agent for all patients with SCAP and shock.<sup>4</sup> This benefit applied if the agent added was either a macrolide or a quinolone.

Certain adjunctive therapies should be considered, although the recommendations on these strategies have less supportive evidence. These include oxygen, chest physiotherapy (in those with at least 30 mL of sputum daily and a poor cough response), aerosolized bronchodilators, and corticosteroids (if hypotension and possible relative adrenal insufficiency is suspected).<sup>75–77</sup> Analysis of the use of activated protein C for patients with septic shock demonstrated that 35% of the patients in the pivotal clinical trial had underlying CAP and that activated protein C was most effective for CAP patients with an Acute Physiology and Chronic Health Evaluation (APACHE) II score higher than 25, a PSI class of IV or V, and a CURB-65 score of at least 2. There was also benefit in those with pneumococcal infection and with inadequate therapy, although the benefit was minimal in those treated with adequate therapy.<sup>75</sup>

Corticosteroids may be helpful in SCAP because of their immunomodulating effect. One randomized controlled trial of 48 patients comparing hydrocortisone infusion (240 mg/day) to placebo found that steroid therapy reduced mortality, length of stay, and duration of mechanical ventilation.<sup>76</sup> Another recent study involved a retrospective analysis of 308 patients with SCAP (based on PSI score), some of whom had received systemic corticosteroids for reasons other than pneumonia while being treated for CAP.<sup>77</sup> Therapy with systemic corticosteroids was found to be independently associated with decreased mortality. Large randomized controlled studies are needed to make recommendations on the routine use of

corticosteroids in SCAP, but the data suggest that steroid use is not dangerous if this therapy is needed for other reasons in patients with SCAP.<sup>78</sup>

There are few data on the proper duration of therapy in patients with CAP, especially in those with severe illness. Even in the presence of pneumococcal bacteremia, short durations of therapy may be possible. It also may be possible to rapidly switch from intravenous to oral therapy in responding patients. Generally, S. pneumoniae can be treated for 5 to 7 days if the patient is responding rapidly and has received accurate empirical therapy at the correct dose. The presence of extrapulmonary infection (e.g., meningitis and empyema) and the identification of certain pathogens (e.g., bacteremic S. aureus and P. aeruginosa) may suggest a need for a longer durations of therapy. Treatment of Legionella pneumophila pneumonia may require 14 or more days of therapy. Recent data, however, suggest that quinolone therapy may the best approach to management and that treatment for as little as 5 days with levofloxacin, 750 mg, may be effective.<sup>79</sup> The switch to oral therapy, even in severely ill patients, may be facilitated by the use of quinolones because these agents are highly bioavailable and achieve the same serum levels with oral therapy as with intravenous therapy.

There is controversy about the need for empirical therapy directed against community-acquired MRSA. Most experts recommend that this organism be targeted with empirical therapy only in patients with severe necrotizing CAP following a viral illness, particularly influenza. Optimal therapy has not been defined. Vancomycin alone may not be sufficient and has led to clinical failure, presumably because it is not active against the PVL toxin that accompanies community-acquired MRSA. For that reason, it may be necessary to add clindamycin to vancomycin or to use linezolid (with rifampin in severe illness) because both these latter agents can inhibit toxin production.<sup>55</sup>

#### **Nonresponding Pneumonia**

Overall, 6% to 15% of patients hospitalized with CAP do not respond to initial therapy.<sup>4</sup> Mortality is increased for these nonresponders.<sup>80</sup> In patients admitted to the ICU, the risk for failure to respond is high, and as many as 40% of the patients experience deterioration even after initial stabilization in the ICU.<sup>81</sup> Because pneumonia is a clinical syndrome, not all patients with this diagnosis actually have lung infection. Indeed, some may be infected with an unusual or nonsuspected pathogen. In addition, some patients can develop complications of the illness or its therapy, and all these situations may lead to an apparent nonresponse to therapy.

Nonresponding patients should be evaluated for alternative diagnoses (inflammatory lung disease, atelectasis, heart failure, malignancy, pulmonary hemorrhage, pulmonary embolus, nonpneumonic infection), a resistant or unusual pathogen (including tuberculosis and fungal infection), pneumonia complication (empyema, lung abscess, drug fever, antibiotic-induced colitis), or a secondary site of infection (central line infection, intraabdominal infection) (Table 38-4). The search for a specific etiologic agent has been evaluated. In one study, a change in the antibiotic regimen based on microbiologic studies,

# Table 38-4 Factors Present in Patients with Nonresponding Pneumonia

#### NONINFECTIOUS DIAGNOSIS

- Inflammatory lung disease: bronchiolitis obliterans, pulmonary fibrosis
- Atelectasis
- Heart failure
- Respiratory malignancy
- Pulmonary hemorrhage: Goodpasture syndrome, granulomatous vasculitis, systemic lupus erythematosus
- Pulmonary emboli with infarction
- PATHOGEN RELATED
  - Resistant bacteria
  - Unusual pathogen (unsuspected): fungus, *Mycobacterium tuberculosis*

#### COMPLICATIONS OF PNEUMONIC PROCESS

- Empyema
- Lung abscess
- Metastatic infection: bacterial endocarditis, intra-abdominal infection

#### COMPLICATIONS OF TREATMENT WITH INTRAVENOUS ANTIBIOTICS

- Drug-induced fever
- Central line infection
- Antibiotic-induced colitis

as opposed to empirical changes, did not alter the mortality in nonresponders.<sup>82</sup>

Although most patients respond to therapy rapidly,<sup>83</sup> those with severe pneumonia tend to have a more protracted course.<sup>84</sup> The evaluation of a nonresponding patient should be individualized but may include computed tomography of the chest, pulmonary angiography, bronchoscopy, and occasionally open-lung biopsy. Bronchoscopy may be valuable in immunocompromised and immunosuppressed patients to help identify the presence of *Pneumocystis* species, viruses, fungi, and mycobacterial infection.

#### **AUTHORS' RECOMMENDATIONS**

- Recognition of SCAP at the earliest possible time point improves outcome.
- There is no uniformly accepted definition of SCAP, and prognostic scoring systems such as the PSI and CURB-65 are decision support tools only.
- Diagnostic testing for SCAP should focus on historical data increasing the risk for infection with specific pathogens and on obtaining a chest radiograph, blood cultures, sputum culture, and urinary antigen testing for *Legionella* and *Pneumococcus* species.
- All patients with SCAP need therapy for drug-resistant pneumococcus and atypical pathogens (including *Legionella* species), and consideration of risk factors for enteric gramnegative bacteria, including *P. aeruginosa*. Some patients, especially those diagnosed with influenza, are at risk for MRSA. Patients who come from nursing homes have HCAP and may be at risk for drug-resistant organisms.

- All patients with SCAP require combination therapy that is based on whether the patient is at risk for *P. aeruginosa*. No patient should receive empirical monotherapy.
- Adjunctive therapy for SCAP includes chest physiotherapy and consideration of corticosteroids (as immune modulators) and activated protein C.

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# How do I Diagnose and Manage Catheter-Related Blood Stream Infections?

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This chapter looks at a particular complication of critical care, one that has been the focus of many quality improvement initiatives: catheter-related bloodstream infection (CRBSI). They are a major, and largely preventable, cause of mortality, morbidity, and increased health care costs.<sup>1</sup>

#### EPIDEMIOLOGY

Bloodstream infections, the presence of actively proliferating bacteria in serum, account for 14% of nosocomial infections in the United States.<sup>2</sup> Most occur in patients who have central venous catheters (CVCs) in situ: they are "catheter related."

CRBSIs are the fourth most common cause of nosocomial sepsis after urinary tract infection, surgical site infection, and pneumonia. In the United States, 36 million acute care patients annually spend 18 million days in ICU.<sup>3</sup> CVCs are in place for 54% to 83% of this time (9.7 to 15 million days).<sup>1,3–5</sup> As late as 2004, these catheters were responsible for 48,600 to 80,000 CRBSIs (i.e., 5 per 1000 catheter-days). The attributable mortality has been estimated at 0% to 17%.<sup>1,6-8</sup> According to studies of death certificates, bloodstream infections (BSIs) are the 10th leading cause of death in the United States,9 and a 78% increase in BSI-related deaths has occurred over the past 20 years, although not all are catheter related.<sup>10</sup> Additionally, each CRBSI is estimated to cost \$11,971,<sup>1,11</sup> although costs of up to \$56,000 have been reported depending on the population studied.<sup>3</sup> CRBSIs increase the duration of intensive care unit (ICU) stay (2.41 days) and in-hospital length of stay (7.54 days).<sup>11</sup> However, simple and cost-effective measures can be undertaken to reduce their incidence.

# DEFINITIONS

In practice, two types of definitions are used: *surveillance* criteria and *clinical* criteria. The surveillance criteria published by the Centers for Disease Control and Prevention (CDC) are defined as the presence of all BSI in a patient with a CVC in the absence of an alternative documented source of sepsis.<sup>2</sup> This is similar to that provided by the Infectious Diseases Society of America (IDSA): a CRBSI is a bacteremia or fungemia in a patient with an intravascular

device in place, with one or more positive blood cultures obtained by peripheral vein, and clinical manifestations of sepsis in the absence of any source of sepsis apart from the device.

One of the following should be present: (1) a semiquantitative (>15 cfu) or quantitative (> $10^2$  cfu) culture from a catheter segment, with the same organism obtained by peripheral culture; (2) paired quantitative cultures; or (3) differential time difference to positive cultures by 2 hours or more in samples from the CVC compared with the peripheral samples (both discussed later).<sup>12</sup>

In the nosocomial setting, 70% to 90% of BSIs are catheter related.<sup>3</sup> The remaining are due to alternative undocumented sources of sepsis, such as lung, wound, or urinary tract. Therefore, the surveillance definition overestimates the incidence of CRBSIs. In clinical practice, local and systemic infections should be differentiated (Table 39-1).

Removal of a central catheter from a febrile patient with subsequent defervescence is accepted as indirect evidence of a CRBSI. Most episodes of line sepsis develop through one of two pathologic processes: (1) extraluminal colonization of the device that usually originates in the skin (much more rarely due to hematogenous seeding from the catheter tip); or (2) intraluminal colonization of the hub and lumen.

#### INCIDENCE

Maki and colleagues undertook a meta-analysis of 200 studies on the incidence of CRBSI up to 2006.<sup>13</sup> This represents the best available recent evidence. The lowest incidence of device-related BSI was observed with peripherally inserted cannulas (0.5 per 1000 catheter-days). Noncuffed, untreated CVCs were associated with a much higher incidence of BSI (2.7 per 1000 catheter-days, although less than the 5.3 per 1000 catheter-days for this device type published by the National Nosocomial Infection Surveillance [NNIS] report<sup>4</sup>). Surgically tunneled, cuffed catheters had a much lower CRBSI incidence of 1.6 per 1000 catheter-days, as did antimicrobial impregnated lines. Units caring for subspecialties such as pediatric and burn patients had higher rates of CRBSI compared with cardiac surgical patients. Although often overlooked, arterial lines had an infection rate of 1.7 per 1000 catheter-days.

#### Table 39-1 Local versus Systemic Catheter-Related Bloodstream Infections

#### LOCAL INFECTIONS

- Colonization
- Insertion site infection
- Phlebitis
- Reservoir infection
- Tunnel infection

#### SYSTEMIC INFECTIONS\*

- Isolation of the same organism from the catheter as well as from two sequential peripheral blood cultures
- · Clinical examination that fails to reveal another source
- Negative infusate culture (rarely a source, but outbreaks have occurred with red blood cell culture)

\*Systemic infections include bloodstream infections, septic thrombophlebitis, and distant infective metastases (cerebral abscesses, infective endocarditis).

#### INFECTING ORGANISMS

Table 39-2 provides a summary of organisms responsible for CRBSIs in the United States published by the NNIS.<sup>2</sup> The increasing prevalence of gram-positive organisms observed over time correlates with evolving trends since the 1960s and 1970s, when gram-negative organisms were dominant. Additionally, empirical antimicrobial therapy has become more difficult for all common pathogens with the emerging resistance patterns. The Surveillance and Control of Pathogens of Epidemiologic Importance (SCOPE) project examines 49 hospitals geographically dispersed throughout the United States and constitutes the largest nongovernmental surveillance program in the area of BSI.<sup>14</sup> According to this report,<sup>14</sup> the most common organisms in the ICU in 2004 were coagulase-negative staphylococci (35.9%), Staphylococcus aureus (16.8%), enterococci (9.8%), and Candida species (10.1%). Gram-negative organisms accounted for a smaller proportion of isolates;

Table 39-2 Organisms Responsible for Catheter-Related Bloodstream Infection

Pathogen	1986- 1989 (%)	1992- 1999 (%)	2004 <sup>14</sup> (%)
Coagulase-negative staphylococci	27	37	35.9
Staphylococcus aureus	16	12.6	16.8
Enterococcus species	8	13	9.8
Gram-negative bacilli	19	14	
Escherichia coli	6	2	3.7
Enterobacter species	5	5	4.7
Pseudomonas aeruginosa	4	4	4.7
Klebsiella pneumoniae	4	3	4.0
Candida species	8	8	10.1

Escherichia coli (3.7%) and Klebsiella (4.0%), Pseudomonas (4.7%), Enterobacter (4.7%), Serratia (2.1%), and Acinetobacter (1.6%) species accounted for most of these. Overall, 87% of BSIs were monomicrobial. More recent data from the National Healthcare Safety Network (NHSN) are consistent with these findings, although some changes to the rank order of pathogens was observed.<sup>15</sup> Coagulase-negative staphylococci remained the most prevalent organism, followed respectively by enterococci, candida, and S. aureus. The infecting organism may be responsible for adverse outcomes. The SCOPE authors found that the crude mortality rates in the ICU for coagulase-negative staphylococci and Klebsiella species were 26% and 34%, respectively. This contrasts with the mortality rates for Pseudomonas (48%) and Candida (47%). For polymicrobial infections, the crude mortality rate was 32%.<sup>14</sup>

Antimicrobial resistance is increasing. The SCOPE authors found that the proportion of S. aureus infections resistant to methicillin increased from 22% in 1995 to 57% in 2002. Vancomycin resistance was detected in 2% of Enterococcus faecalis and 60% of Enterococcus faecium isolates. Among gram-negative organisms, relatively high levels of resistance were encountered to treatment with ampicillin, piperacillin, and cephalosporin. Higher levels of susceptibility to aminoglycosides and carbapenems were found. However, clusters of carbapenemase-producing Klebsiella species have recently emerged, notably in the New York area.<sup>15</sup> Finally, neutropenic patients are significantly more susceptible to infections with candida, enterococci, and viridans group streptococci, and empirical treatment of these patients should defeat these organisms. Finally, although the NNIS did not report a rise in candidemia, the SCOPE authors reported an incidence of 12%, and this is similar to the NHSN study (11%). Leroy and colleagues reported that nonalbicans species are responsible for about half of cases of candidemia.<sup>16</sup> Reduced susceptibility to fluconazole was observed in 17.1% of cases in this study.

#### DIAGNOSIS

Appropriate and timely diagnosis and treatment of CRBSI reduces patient mortality, morbidity, and associated costs. Diagnosis is based on microbiologic confirmation of the catheter as the source of the BSI. Catheter removal based solely on clinical suspicion as being the source of a BSI, but which subsequently proves to be sterile, occurs in more than 70% of cases<sup>17</sup>; this inappropriate removal has a potential morbidity resulting from the interruption of treatment, including chemotherapy, and the cost and practical difficulties of replacement of the catheter, particularly tunneled devices. Catheter-sparing diagnosis of CRBSI is possible.<sup>18</sup> An appropriate diagnostic strategy uses evidence-based microbiologic tools, the accuracy of which increases with improved pretest clinical probability (Table 39-3).<sup>19</sup>

The clinical features of a CRBSI can be systemic and include any or all of the spectrum of features that vary from systemic inflammatory response syndrome (SIRS) to septic shock with or without multiorgan failure; in this regard, CRBSI does not distinguish itself from other

Sensitivity (%)	Specificity (%)	Reference	Comment
96	92	10	Morphologic identification of bacteria possible; not widely used
89-90	72-87	3	Blood cultures positive from catheter ≥2 hr before peripheral cultures indicates catheter as likely source of infection
93	97-100	3	Most accurate test; expensive, complex, time-consuming; not widely available
95	84	11	Useful if blood not obtainable from catheter; risks embolization of bacteria
	Sensitivity (%) 96 89-90 93 95	Sensitivity (%)         Specificity (%)           96         92           89-90         72-87           93         97-100           95         84	Sensitivity (%)         Specificity (%)         Reference           96         92         10           89-90         72-87         3           93         97-100         3           95         84         11

Table 39-3 MICIODIOIOUIC TOOIS IO DIAUTIOSE Catheter-Related Diooustream mile	Table 3	39-3	Microbiologic	Tools to Diagnose	Catheter-Related B	Bloodstream Infection
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sources of a BSI. Given that the most common etiology of infection is extraluminal catheter colonization from local skin contamination, local signs of infection may be evident at the catheter insertion site. However, such local signs are not a reliable predictor of a CRBSI.<sup>20</sup> Conversely, local infection may exist at a peripherally inserted central catheter (PICC) site without a CRBSI.<sup>21</sup>

The nonspecific nature of many of the clinical features represents a diagnostic challenge—a rational microbiologic approach that proves that the catheter is the source of the CRBSI is required. For example, when a BSI occurs in a patient with a catheter, a CRBSI should be suspected if there is no other apparent BSI source. A 2005 meta-analysis of techniques for diagnosis of intravascular device-related BSI concluded that all catheter-sparing diagnostic tests have a sensitivity and specificity greater than 75% and a negative predictive value of 99%.<sup>19</sup> Blood for culture should be taken simultaneously from the catheter and from a peripheral source. At least 10 mL of blood should be drawn for each culture. If blood is drawn from every lumen of the catheter, the diagnostic yield is improved.<sup>19,22–24</sup> Paired quantitative blood cultures produce the most accurate diagnosis.<sup>19</sup> The IDSA regards the catheter as being the source of the BSI when the colony count for the blood cultures drawn from the catheter is at least 5 times the peripherally drawn blood culture colony count. However, this test is expensive, and availability is limited; a reasonable first-line approach is to use the differential time to positivity with an automated radiometric blood culture system. This is a simple, widely available system with high sensitivity and specificity.<sup>22</sup> If the blood cultures drawn from the catheter become positive 2 hours or more before a simultaneously drawn peripheral blood culture, a CRBSI is likely. Catheters should not be routinely cultured in the absence of clinical suspicion of CRBSI.<sup>19</sup> A variety of non-catheter-sparing diagnostic techniques are also available.

# PREVENTION

#### Hygiene and Aseptic Technique

The single most important strategy in prevention of CRBSI is the process of catheter placement. A multicenter collaborative cohort study was undertaken in a wide variety of ICUs totaling 1625 beds in Michigan over an 18-month period.<sup>25</sup> This involved implementation of five evidencebased, CDC-recommended interventions that were identified for their impact on reduction of CRBSI (Table 39-4). Clinicians were educated about the positive effects of these interventions and the negative consequences for CRBSI of noncompliance with them in their entirety.

A properly equipped central line cart was made available; a third party monitored operator compliance with infection-control practices during insertion and could mandate abandonment of the procedure for violation. Daily rounds involved discussion on catheter removal.

A total of 103 units reported data in the study. The analysis included 1981 ICU-months of data and 375,757 catheter-days. CRBSI rates, as defined by the NNIS, were measured throughout the study period. The median rate of CRBSI per 1000 catheter-days decreased from 2.7 infections at baseline to 0 at 3 months after implementation of the study intervention (P < .002), and the mean rate per 1000 catheter-days decreased from 7.7 at baseline to 1.4 at 16 to 18 months of follow-up (P < .002). The regression model showed a significant decrease in infection rates from baseline, with incidence-rate ratios continuously decreasing from 0.62 (95% confidence interval [CI], 0.47 to 0.81) at 0 to 3 months after implementation of the intervention to 0.34 (95% CI, 0.23 to 0.50) at 16 to 18 months.

Thus, a sustained reduction of up to 66% was observed. This study demonstrated that these uncomplicated interventions that were implemented without additional ICU staffing or expensive technology could have a significant effect on CRBSI.

#### Table 39-4 Evidence-Based Preventative Measures

- Handwashing
- Full barrier protection during catheter insertion
- Use of 2% chlorhexidine solution to disinfect the skin, with air drying of skin before insertion
- Avoidance of the femoral site
- · Prompt removal of unnecessary catheters

Data from Pronovost P, Needham D, Berenholtz S, et al. An intervention to decrease catheter-related bloodstream infections in the ICU. N Engl J Med. 2006;355:2725-2732.

#### Antimicrobial-Coated Central Venous Catheters

CVCs in vivo develop a biofilm—a film of material that may include fibrin, fibronectin, fibrinogen, collagen, elastin, thrombospondin, laminin, vitronectin, and von Willebrand factor. This biofilm provides an ideal growth medium for infection. Antibiotic-coated CVCs were developed to prevent development of biofilms and hence to decrease colonization rates and CRBSIs. Many different types of coated catheters exist. They may be externally or internally coated.

Universal use of coated catheters has not occurred; there are concerns regarding cost-effectiveness, hypersensitivity reactions, and antimicrobial resistance.

Silver has broad-spectrum antimicrobial activity with greater antimicrobial activity against gram-negative than gram-positive organisms. Silver-impregnated devices include first-generation chlorhexidine–silver sulfadiazine (CSS), second-generation CSS, and iontophoretic silver. Benzalkonium chloride is an antiseptic and antimicrobial. It is a quaternary ammonium compound that inhibits membrane function and DNA replication. Antibiotic minocycline-rifampicin– or rifampicin-miconazole–coated CVCs are also used.

The CDC guidelines comment on CSS and minocyclinerifampicin catheters. The CDC recommends that their use be restricted to patients in settings in which the risk for CRBSI is high despite adherence to other preventive strategies.

A 2008 meta-analysis by Casey and colleagues<sup>26</sup> concurred with the CDC guideline recommendations for the use of these antibiotic-impregnated lines only when baseline incidence of CRBSI is above institutional goals despite adherence to basic infection prevention measures. The first-generation CSS CVCs reduced colonization (odds ratio [OR], 0.51 [95% CI, 0.42 to 0.61]) and CRBSI (OR, 0.68 [0.47 to 0.98]), as did the minocycline-rifampicin CVCs (OR, 0.39 [0.27 to 0.55] and OR, 0.29 [0.16 to 0.52], respectively). The minocycline-rifampicin CVCs outperformed the first-generation CSS CVCs in reducing colonization (OR, 0.34 [0.23 to 0.49]) and CRBSI (OR, 0.18 [0.07 to 0.51]). The authors concluded that the overall methodologic quality of studies involving coated CVCs has been poor and therefore limits the observations that can be made. There was substantial heterogeneity between the clinical groups. There was an overall reduction in colonization and CRBSIs when these devices were used; however, this varied with the device. Benzalkonium does not appear to reduce the risk for infection.<sup>27</sup>

One prospective trial<sup>28</sup> analyzing the efficacy of rifampicin-miconazole in 223 patients demonstrated a reduction of colonization (OR, 0.14 [0.07 to 0.27]) and no cases of CRBSI.

Minocycline-rifampicin may be useful in the more long-term setting because one trial showed a reduction in CRBSIs when the catheters were left in situ for a mean of 66 days.<sup>29</sup> This may indicate that their appropriate use lies outside the ICU setting.

In a meta-analysis, Hockenhull and associates<sup>30</sup> looked at cost-effectiveness in 32 trials of antibiotic-impregnated CVCs. They found that two thirds of the trials were commercially funded, with many having serious design flaws. They concluded, however, that the use of these catheters can lead to a reduction in CRBSI and decreased medical costs. Similar conclusions were reported by Niel-Weise and colleagues.<sup>31</sup>

In vivo resistance to chlorhexidine or CSS CVCs has not been reported. However, reduction of minocyclinerifampicin and rifampicin-miconazole activity against *Candida albicans, Pseudomonas aeruginosa, Enterobacter* species, and *E. coli* has been demonstrated in vitro.<sup>32</sup> In vitro resistance of gram-positive cocci to minocycline and rifampicin has been demonstrated.<sup>33–35</sup> Two studies<sup>33,36</sup> have noted a significant increase in *Candida* species colonization rates with minocycline-rifampicin CVCs. In the only clinical study evaluating this to date, there was no resistance to rifampicin-miconazole.<sup>28</sup>

In summary, these catheters appear to have a limited role in critical care: they should be reserved for units whose baseline CRBSI rates are elevated.

## **Insertion Site**

The CDC guidelines, based on long-term epidemiologic data, currently recommend that the subclavian site be preferred for infection control purposes when the access device is not to be used for hemodialysis or pheresis. Other factors, such as operator experience, patient factors, and relative risk for mechanical complications, should also be taken into account.

It is widely believed that femoral CVCs are more commonly infected, and one study of 300 CVCs demonstrated a higher rate of colonization, although not infection of femoral lines.<sup>37</sup>

A review from  $2002^{38}$  found that at least six studies demonstrated that placement in an internal jugular (OR, 1.0 to 3.3) or femoral (OR, 3.3 to 4.83), rather than subclavian (OR, 0.4 to 1.0), vein was associated with significantly increased risk.

Lorente and colleagues undertook a single-center 3-year prospective observational study<sup>39</sup> of 2018 patients and 2595 CVCs. CRBSI incidence density was statistically higher for femoral than for jugular (8.34 versus 2.99; P = .002) and subclavian (8.34 versus 0.97; P < .001) accesses, and higher for jugular than for subclavian access (2.99 versus 0.97; P = 0.005).

Deshpande and colleagues<sup>40</sup> prospectively examined the incidence of CRBSI at different sites in critically ill patients. There was standardization of the line insertion technique, with strict sterile measures observed. Data were collected on 831 CVCs in 657 patients over 4735 days. The incidence of infection was as follows: subclavian, 0.881 infections/1000 catheter-days (0.45%); internal jugular, 0/1000 (0%); and femoral, 2.98/1000 (1.44%; P = .2635). There was no statistically significant difference in the incidence of infection and colonization or duration of catheters (P = .8907) among the insertion sites.

Gowardman and colleagues<sup>41</sup> found that devices inserted in the subclavian vein were significantly less likely to be colonized than those inserted in the femoral (Hazard Ratio [HR], 5.15; 95% CI, 1.82 to 14.51; P = .004) or internal jugular (HR, 3.64; 95% CI, 1.32 to 10.00; P = .01) sites.<sup>41</sup> Factors associated with increased risk for colonization (a reasonable surrogate for infection) were placement in a site other than subclavian vein, device insertion in the ICU or operating room rather than emergency room, and female gender.

In summary, many of the published data suggest that subclavian access has the lowest rates of colonization and CRBSI. None of the studies reported significantly greater complications of line insertion at this location. In experienced hands and with strict adherence to asepsis and maintenance, internal jugular has lower rates of infection than femoral and should be a second choice.

#### Scheduled Line Replacement

There are no data to support the changing of CVCs after a fixed time for infection prevention.

The evidence against routine line changing is well established. Cobb and colleagues,<sup>42</sup> in 1992, randomized 160 patients to routine replacement (after 3 days, either at a separate site or over a guidewire) or to replacement when clinically indicated, again either at a new site or over a guidewire. There was no decrease in infection rates in the catheters routinely replaced. The lowest rate of CRBSI was in the group in whom catheters were changed when indicated at a new site. Patients randomly assigned to guidewire-assisted exchange were more likely to have bloodstream infection after the first 3 days of catheterization (6% versus 0%; P = .06). Insertions at new sites were associated with more mechanical complications (5% versus 1%; P = .005).

Castelli and associates performed a prospective, singlecenter randomized controlled trial examined 898 CVCs over 3 years,<sup>43</sup> looking at new site versus guidewire exchange. They were unable to demonstrate an increased risk for infection when guidewire exchange was used; the study, however, appears underpowered. Similar data were reported in a previous systematic review.<sup>44</sup>

There are some data to suggest that first CVCs in critically ill patients have a lower rate of infection than replaced catheters. Badley and colleagues reported a prospective study of 2470 patients that showed a statistically significantly lower rate of infection in de novo catheters than those replaced over a wire or in a new site.<sup>45</sup>

In summary, current evidence available suggests that routine changing of CVCs is not beneficial. There should be meticulous adherence to asepsis on insertion, daily checks and replacement on clinical suspicion of infection, and earliest possible removal. Replacement over a guidewire should be undertaken only in the case of mechanical difficulty should be preferred.

#### Total Parenteral Nutrition and Central Venous Catheters

Total parenteral nutrition (TPN) is a hyperosmolar glucosecontaining lipid emulsion that provides an ideal medium in which bacteria can thrive. Much of the evidence regarding the administration of TPN through CVCs dates from the 1970s and 1980s and is well established. Assimilating these data, the CDC guidelines from 2002 state that if a multilumen catheter is used to administer parenteral nutrition, a single, specifically designated lumen should be used. Administration sets should be changed every 96 hours,<sup>46</sup> although a more frequent changing should be considered with lipid emulsions.

Kemp and colleagues retrospectively studied 192 patients with 3334 catheter-days over 6 months.<sup>47</sup> They found that femoral catheters were significantly more likely to become infected if multilumen (but not single lumen) and used for TPN. Likewise, Ishizuka and colleagues,<sup>48</sup> looking at 423 catheters in 350 surgical patients who had catheters and had undergone colorectal surgery, found that the use of a femoral venous catheter was an independent risk factor for catheter-related bloodstream infection (OR, 3.175; 95% CI, 1.103 to 9.139; P = .0322).

Single-lumen catheters used solely for TPN were compared with multiuse catheters (i.e., used for fluids, pressors, antibiotics) in 260 critically ill inpatients. The result was a fivefold lower risk for infection (HR, 0.19; 95% CI, 0.04 to 0.83).<sup>49</sup> This was a single-lumen catheter used only for TPN placed only in the subclavian vein and cared for by a dedicated multidisciplinary team.

This result demonstrates that TPN need not increase risk when other known risk factors are modified (Table 39-5).

#### **Biopatch Device**

The chlorhexidine gluconate–impregnated hydrophilic polyurethane foam dressing (Biopatch, Johnson & Johnson Medical, Arlington, TX) has been investigated as a means of reducing CRBSI and colonization rates. The patch should be covered with a transparent polyurethane dressing to suppress cutaneous colonization. It has been demonstrated to reduce cutaneous colonization and colonization of percutaneous epidural catheters.<sup>50</sup> It has been shown to significantly decrease cutaneous colonization rates of CVCs in one prospective randomized trial; however, CRBSI was not examined in this study.<sup>51</sup>

One multicenter randomized controlled trial in 705 neonates<sup>52</sup> has shown decreased colonization rates (15.0% versus 24.0%; relative risk [RR], 0.6; 95% CI, 0.5 to 0.9) when the Biopatch was used and replaced weekly. The Biopatch was compared with cutaneous disinfection, with 10% povidone-iodine and redressing the site every 3 to 7 days. It was as effective for preventing CRBSI and BSI without a source. The use of Biopatch, however, was complicated by local dermatitis in 15.8% of low-birthweight infants (<1000 g).

Another pediatric randomized study<sup>53</sup> compared transparent polyurethane dressings and chlorhexidineimpregnated sponges covered with polyurethane dressing in 145 patients. Significantly lower rates of colonization and lower rates of CRBSI ensued.

# Table 39-5 Guidelines for Central VenousCatheters Used for Total Parenteral Nutrition

- 1. A single lumen catheter should be used when possible.
- 2. When multilumen, have a single lumen designated for total parenteral nutrition.
- 3. The subclavian vein is the optimal site.
- 4. The femoral vein should be avoided.
- 5. The line should be inserted and cared for by a trained multidisciplinary team using the guidelines in Table 39-4.

# TREATMENT

The basic principles of treatment of CRBSI are common to all patients with severe sepsis: supportive assistance of vital organ functions, source control (usually catheter removal), and administration of empirical broad-spectrum antibiotics, pending results from the previously drawn blood cultures that are then used in rationalizing therapy.<sup>12</sup> Several additional points require consideration:

- 1. How unstable is the patient's clinical condition? Are prosthetic heart valves in situ?
- 2. What is the patient's underlying diagnosis?
- 3. What is the likely organism?
- 4. Is there evidence of distal organ involvement endocarditis, septic thrombophlebitis, metastatic septic spread?

Knowledge of common nosocomial organisms and their antibiotic sensitivities are important in selecting empirical treatment. A close relationship with laboratory microbiology and infection control at the institutional level is extremely important. Antimicrobial resistance is increasing. Ibrahim and colleagues revealed that failing to initially select appropriate antimicrobials for CRBSI doubled the in-hospital mortality rate from 30% to 60%.<sup>54</sup> Vancomycin is good empirical choice in countries with a high level of methicillin-resistant S. aureus (MRSA), in additional to providing cover for coagulasenegative staphylococci. The coadministration of an antigram-negative agent until these pathogens have been excluded is also appropriate depending on the clinical context. Because the prevalence of Candida is increasing, empirical antifungal therapy may be considered in atrisk patients. Risk factors include prolonged previous antibiotic therapy (>6 days), multiple antibiotics (more than three), prolonged ICU stay, presence of central access device, recent upper gastrointestinal surgery, and dialysis requirement. For most patients, antibiotic therapy should continue 10 to 14 days.<sup>12</sup> Complications, such as endocarditis or osteomyelitis, require a much longer duration of treatment (4 to 6 weeks). In cases of fungemia, treatment should continue until 2 weeks after the last positive blood culture.<sup>12</sup>

In most cases, the catheter is removed for source control. However, this might be waived in settings in which (1) the patient has a coagulase-negative *Staphylococcus*, is otherwise well and stable, and has no secondary infective complications; and (2) the patient has a tunneled device (i.e., access is a premium) but is systemically well.<sup>12</sup> Local erythema and purulence mandate immediate catheter removal. Infection with S. aureus has been reportedly associated with a high incidence of infective endocarditis. Therefore, transesophageal echocardiography (TEE) is routinely recommended (unless contraindicated) in patients in whom this organism is isolated. A retrospective cohort study of mixed ICU patients suggested that very elderly ICU patients (>75 years old) are less likely to develop CRBSI than moderately old (65 to 74 years) or middle-aged (45 to 64 years) patients, but the condition is more lethal in the very elderly group.<sup>5</sup>

# ANTIBIOTIC LOCKS

Antibiotic locks are left in the catheter lumen for 12 hours, combined with systemic antibiotics, in order to decrease local infection. Their use has shown to be effective in pediatric studies<sup>56</sup> involving long-term parenteral nutrition and oncology in long-term tunneled or totally implanted central venous access devices, particularly in gram-positive infections. One small pilot study<sup>57</sup> has shown benefit in catheter salvage in those with CRBSI with a catheter in place for more than 10 days; however, no randomized controlled trial has shown benefit, and it is not recommended that treatment with antibiotic locks be substituted for removal of catheter when appropriate in a patient with CRBSI in the ICU.

#### **AUTHORS' RECOMMENDATIONS**

- CRBSIs remain a frequent cause of nosocomial infection in the ICU. They are associated with increased costs and lengths of ICU and in-hospital stays and increased mortality.
- The current evidence is that most CRBSIs can be prevented.
- Strict adherence to hand hygiene practices and adherence to aseptic techniques are the most effective preventative strategies.
- Antimicrobial- and antibiotic-impregnated catheters are expensive. Their use should be limited to high-risk patients and units in which there is a high incidence of CRBSI despite adherence to best practice asepsis.
- Consideration should be given to placing surgically tunneled catheters for access required for longer periods, such as dialysis or apheresis.
- Use the subclavian vein for placement of nontunneled, uncuffed CVC lines when possible. Avoid the femoral route if at all possible.
- Treatment of CRBSI follows the same general principles as management of sepsis. Selection of appropriate empirical antibiotics should be based on knowledge of local pathogens and resistance patterns. Inappropriate empirical antibiotic selection increases mortality. Risk factors for fungal infections should be identified.

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# What is the Epidemiology of Anti-Microbial Resistance in the Intensive Care Unit?

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Antimicrobial resistance in the intensive care unit (ICU) continues to be an important determinant of patient outcomes and is associated with increasing resource use. According to the Centers for Disease Control and Prevention (CDC), about 1.7 million patients developed health care-associated infections in 2002. Of these, almost 100,000 died.<sup>1</sup> More than 400,000 cases occurred in adult ICUs. Resistance to many of the most common nosocomial pathogens is increasing. Examples include methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant enterococci (VRE), and Pseudomonas aeruginosa, Acinetobacter baumannii, and Enterobacteriaceae such as Klebsiella species and Escherichia *coli* producing extended-spectrum  $\beta$ -lactamases (ESBLs). Particularly worrisome is the increasing incidence and increased mortality due to Clostridium difficile-associated disease (CDAD). Thus, physicians are faced with a conundrum when treating critically ill patients with suspected infections. Critical care physicians must walk a fine line between the need for aggressive broad-spectrum antibiotic therapy, often without knowledge of the infecting organism, and avoiding excessive and inappropriate antibiotic use that can lead to the development and dissemination of antibiotic resistance. Greater than 60% of ICU patients receive broadspectrum antibiotics at some time during their hospitalization. Yet it is estimated that up to 60% of antibiotic use in hospitals is inappropriate or unnecessary.<sup>2,3</sup> The potential for cross-transmission of resistant organisms, either by the hands of health care personnel or the environment, potentiates the problem of antibiotic resistance. The purpose of this review is to discuss the epidemiology of antibiotic resistance in the ICU and to propose potential strategies for management.

# OUTCOMES ASSOCIATED WITH INCREASED ANTIBIOTIC RESISTANCE

Infections caused by antibiotic-resistant organisms have been associated with higher mortality rates and longer lengths of ICU and hospital stay.<sup>4–6</sup> A meta-analysis conducted in 2003 found that patients with VRE bacteremia had a case-fatality rate 2.57 times higher than patients with bacteremia due to vancomycin-susceptible enterococci (relative risk [RR], 2.57; 95% confidence interval [CI], 2.27 to 2.91). The attributable excess length of hospital stay and cost due to VRE bacteremia were found to be 17 days and \$81,208 respectively.<sup>6</sup> Similar findings have been shown with bacteremia due to MRSA and *Acinetobacter* species.<sup>4,7</sup> This occurs, in part, because infection with a resistant organism is associated with the risk for receiving initially inappropriate antibiotics (i.e., antibiotics to which the organism is not susceptible based on *in vitro* antibiotic susceptibility testing). This, in turn, has been shown to be an important determinant of hospital mortality in seriously ill patients.<sup>8–10</sup> Moreover, multiple studies confirm that modification of an initially inappropriate antibiotic regimen based on microbiology results does not improve mortality.<sup>11–14</sup> The total cost of antimicrobial resistance to U.S. society has been estimated at nearly \$5 billion annually.<sup>15</sup>

# TRENDS IN ANTIBIOTIC RESISTANCE IN THE INTENSIVE CARE UNIT

Antibiotic resistance among nosocomial pathogens continues to rise at an alarming rate and has been classified as a public health disaster by both the Institute of Medicine and the CDC. Surveillance systems developed to longitudinally track antibiotic resistance rates provide the practitioner with vital information regarding the likely activity of an antibiotic compared with a specific pathogen. According to data from the National Nosocomial Infections Surveillance (NNIS) system, managed by the National Centers for Infectious Diseases, the most common resistant bacteria found in the ICU are MRSA, VRE, and quinolone-resistant *P. aeruginosa* (Table 40-1).<sup>16</sup>

MRSA has become a significant public health problem worldwide and is the leading cause of health careacquired infections, including bacteremia, surgical wound infection, and pneumonia. Within hospitals, the highest concentration of MRSA is in the ICU, with almost 60% of all staphylococcal infections being due to MRSA.<sup>17</sup> Colonized and infected patients are the main source of MRSA in health care facilities with the main mode of patient-topatient transmission by the hands of health care workers. Depending on the type of ICU studied, the prevalence of MRSA colonization at ICU admission has been shown to vary from 5% to 21% (mean, 12%). Medical ICUs were found to have a 37-fold higher odds of having an MRSA admission prevalence higher than 10% compared with surgical ICUs. However, the monthly incidence of MRSA was highest among surgical ICUs.<sup>18</sup>

Table 40-1 Antibiotic Resistance Rates of Clinically Relevant Bacteria in the Intensive Care Unit According to the National Nosocomial Infections Surveillance System<sup>16</sup>

Pathogen	Resistance Rate, 1998-2002 (%)	Resistance Rate, 2003 (%)	Increase in Resistance, 2003 vs. 1998-2002 (%)
Vancomycin-resistant enterococci	25.4	28.5	12
Methicillin-resistant Staphylococcus aureus	53.6	59.5	11
<i>Pseudomonas aeruginosa</i> Fluoroquinolone resistant Imipenem resistant	27 18.3	29.5 21.1	9 15
Klebsiella pneumonia TGC resistant	14	20.6	47
Escherichia coli TGC resistant	5.8	5.8	0

TGC, third-generation cephalosporin.

*P. aeruginosa* is the leading gram-negative organism associated with nosocomial infection and is the second leading cause of pneumonia. *P. aeruginosa* is particularly challenging for the critical care physician owing to its intrinsic resistance to antibiotics and its ability to rapidly acquire resistance during treatment. Of increasing concern is the rapid emergence of multidrug-resistant *P. aeruginosa*, defined as resistance to three or more antibiotic classes. From 1993 to 2004, the prevalence of multidrug-resistant *P. aeruginosa* causing infections in U.S. ICUs increased from 1.7% to 9.3%.<sup>19</sup>

Other organisms of increasing importance include ESBL-producing Enterobacteriaceae, multidrug-resistant Acinetobacter species, and infections due to C. difficile. According to data from the MYSTIC (Meropenem Yearly Susceptibility Test Information Collection) program, a global antibiotic surveillance program, the prevalence of ESBL-producing E. coli increased fivefold in Europe between 1997 and 2004 from 2.1% to 10.8%; ESBL-producing *Klebsiella* species increased from 9% to 13.6%.<sup>20</sup> In the United States, 4.4% of Klebsiella species were found to be ESBL-producing in 2004. ESBL-mediated resistance is not always detectable using routine antibiotic susceptibility tests even with current guidelines from the Clinical Laboratory Standards Institute. Difficulties in detection may delay initiation of appropriate therapy, with the potential for increased morbidity and mortality. Currently, carbapenems (i.e., imipenem and meropenem) are considered the drugs of choice in the treatment of serious infections due to ESBL-producing organisms.

Multidrug-resistant *A. baumannii* has become an important cause of infections in the ICU. Characteristics that make *Acinetobacter* species difficult to treat include their ability to rapidly develop resistance to multiple antibiotics and a hardiness that allows them to survive for prolonged periods in the hospital environment, facilitating person-to-person transmission. Outbreaks with multidrug-resistant *Acinetobacter* species have been reported worldwide and are considered endemic in many geographic regions.<sup>21</sup> According to the NNIS system,

*Acinetobacter* organisms were the only gram-negative pathogens associated with consistently increasing proportions of hospital-acquired pneumonia, skin and skin structure infections, and urinary tract infections between 1986 and 2003.<sup>22</sup> Carbapenems had been considered the drugs of choice for infections due to these resistant organisms. However, the development of carbapenem-resistant strains and the lack of new antibiotics active against gram-negative bacteria have led to the revival of colistin for the treatment of serious multidrug-resistant infections.

Of recent concern are the reports of outbreaks of CDAD due to a hypervirulent strain of C. difficile associated with more severe disease, increased relapse rate, and increased mortality. This strain, BI/NAP1, has been shown to produce the two toxins of C. difficile, toxin A and B, in substantially greater quantities than historical strains.<sup>23</sup> Risk factors for CDAD include the use of broad-spectrum antibiotics that results in the disruption of the normal intestinal microflora, host factors (age > 65 years, impaired immune status, or severe underlying illness), and prolonged hospital stay. Pepin and associates found a 4.5-fold increase in the incidence of C. difficile-associated diarrhea in hospitalized patients in Ouebec, Canada, between 2003 and 2005 (156,3/ 100,000) compared with 1991 (35.6/100,000). This was associated with a fivefold increase in mortality (4.5% in 1991 versus 22% in 2004).<sup>24</sup> In the United States, the rate of CDAD in acute care hospitals increased by 26% in 2001 compared with 1998 to 2000.<sup>25</sup> Although oral vancomycin is the only drug approved by the U.S. Food and Drug Administration (FDA) for the treatment of CDAD, multiple organizations recommend metronidazole as the preferred first-line therapy because the two drugs were similar in early comparative studies, oral metronidazole is less expensive than oral vancomycin, and there is concern that use of oral vancomycin will select for VRE in the gastrointestinal tract.<sup>26</sup> Treatment failure, however, has been reported with metronidazole, particularly in seriously ill patients.<sup>27</sup>

## STRATEGIES FOR MANAGEMENT OF ANTIBIOTIC RESISTANCE IN THE INTENSIVE CARE UNIT

Despite the seemingly relentless growth of antimicrobial resistance in the ICU, clinicians are not helpless against this advance. Measures can be taken to slow the acceleration of antimicrobial resistance or to reduce the level of resistance institution-wide or within an ICU. These strategies may sometimes be at odds with individual clinician practices and infringe on physician autonomy, increase staff workload, and engender feelings of stigmatization in patients. Thus, these measures must be implemented in a sensitive manner and always within the context of doing what is best for patients.

#### Identifying Local Resistance Problems

When considering implementing strategies to deal with antimicrobial resistance in an ICU, it is important to understand local patterns of resistance. At a minimum, a hospital's microbiology laboratory should be able to produce a yearly antibiogram, that is, a chart describing the percentage of isolates from major clinically important species that tested susceptible to the major formulary antimicrobials. Guidelines for appropriate reporting of antibiograms are available.<sup>28</sup> For larger hospitals, consideration can be given to designing unit-specific antibiograms (i.e., descriptions of the antimicrobial susceptibility restricted to pathogens isolated in a particular ICU).<sup>29</sup> These unit-specific antibiograms can be helpful in identifying resistance issues that are particularly problematic in ICU compared with ward patients or between different ICUs.<sup>30</sup> A limitation, however, is the smaller number of isolates on which the ICU estimates are based, leading to a potential for overstating ICU resistance problems based on a small sample of resistant isolates. Guidelines for antibiograms suggest reporting only resistance among organisms for which there are at least 30 isolates over the time period of interest.<sup>28</sup>

# Strategies for Reducing or Reversing Resistance

Figure 40-1 presents a conceptual model of the acquisition and transmission of antimicrobial resistance and illustrates where various intervention strategies can be brought to bear on the cycle. These interventions can be broadly divided into infection-control strategies and antimicrobial stewardship strategies. In general, infection-control strategies are aimed at preventing the acquisition and spread of resistant organisms already present in the environment, whereas antimicrobial stewardship activities attempt to reduce the initial selection pressure for resistant organisms. However, there often is overlap in their effects if not in their methods. Guidelines for infection-control measures endorsed by the CDC are listed in Table 40-2. Antimicrobial stewardship interventions that may be applicable to the ICU setting with illustrative examples from the



Figure 40-1. Interventions to prevent antimicrobial resistance in the intensive care unit (ICU).

Table 40-2 Published Guidelines in the Prevention and Management of Drug-Resistant Infections in the Intensive Care Unit

Guideline	Organization(s)	Latest Edition	Location
INFECTION CONTROL			
Transmission of infectious agents	Centers for Disease Control and Prevention	2007	http://www.cdc.gov/ncidod/ dhqp/guidelines.html
Preventing health care-associated pneumonia	Centers for Disease Control and Prevention	2003	http://www.cdc.gov/ncidod/ dhqp/guidelines.html
Management of multidrug- resistant organisms	Centers for Disease Control and Prevention	2006	http://www.cdc.gov/ncidod/ dhqp/guidelines.html
Hand hygiene in health care settings	Centers for Disease Control and Prevention	2002	http://www.cdc.gov/ncidod/ dhqp/guidelines.html
Prevention of intravascular device-related infections	Centers for Disease Control and Prevention	2002	http://www.cdc.gov/ncidod/ dhqp/guidelines.html
ANTIBIOTIC STEWARDSHIP			
Antibiotic stewardship	Infectious Diseases Society of America	2007	http://www.idsociety.org → Practice Guidelines
MANAGING INTENSIVE CARE	UNIT INFECTIONS		
Treatment of health care- associated pneumonia	Infectious Diseases Society of America/ American Thoracic Society	2006	http://www.idsociety.org → Practice Guidelines
Sepsis	Society of Critical Care Medicine and Others	2008	http://www.survivingsepsis.org

literature are discussed later. It is important to recognize that many interventions were not studied in isolation but as a component of a larger underlying strategy. Thus, extrapolating from the literature to estimate the effectiveness of an individual intervention, or of an intervention paired with other interventions that were not originally employed, is speculative.

## Antimicrobial Stewardship

Formulary and restriction strategies dictate which antimicrobials are available for clinicians to use. The formulary component usually involves selecting one or more drugs from a particular group of antimicrobials that are available for use. Although cost is usually the primary consideration for selection among similar drugs for formulary addition, some data suggest that certain antimicrobials may have less potential to select for resistant isolates. Rice and associates showed that ceftriaxone was selective for colonization with VRE, whereas piperacillin-tazobactam was protective against colonization.<sup>31</sup> Empey and associates attempted to put these concepts into practice at a tertiary care medical center by redesigning their formulary, reducing third-generation cephalosporin use, and encouraging the use of cefepime, a fourth-generation cephalosporin, and piperacillin-tazobactam.<sup>32</sup> Resistance decreased among gram-negative pathogens, although interestingly the rate of VRE increased. Restriction refers to the selective release of formulary antimicrobials based on individual patient criteria; for example, linezolid may be restricted for use only in patients with documented VRE infections. White and colleagues instituted a program requiring prior approval from infectious disease specialists for certain antimicrobials and demonstrated an increase in antimicrobial susceptibility hospitalwide.<sup>33</sup> A potential unintended consequence of formulary and restriction strategies is "squeezing the balloon," that is, substituting one resistance problem for another. For example, in response to an outbreak of ESBL-producing gram-negative organisms, Rahal and coworkers instituted strict restrictions on cephalosporin use.<sup>34</sup> The rate of ESBL-producing organisms decreased, but imipenem resistance in *P. aeruginosa* increased because imipenem, a carbapenem, was used in the place of cephalosporins.

An offshoot of formulary and restriction strategies is the idea of "antibiotic cycling." This approach aims to modulate selective pressure on organisms in the hospital environment by rotating the antibacterial class used as the drug of primary choice. For example, during the first period of the cycle, a broad-spectrum cephalosporin (e.g., ceftazidime) would be the core drug for empirical therapy, followed by a fluoroquinolone, then a carbapenem, then a broad-spectrum penicillin. For practical purposes, most recent cycling studies have been performed in ICUs or other defined patient care areas (e.g., bone marrow transplantation units). Early studies suggested cycling might slow the development of resistance in ICUs,<sup>35</sup> despite mathematical studies suggesting cycling could amplify resistance.<sup>36</sup> However, more recent studies, including early reports of CDC-sponsored trials, are not as encouraging.<sup>37</sup> Thus, antibiotic cycling approaches, if undertaken, should be performed in the context of a clinical trial rather than as an established intervention.

Although formulary and restriction strategies target the initial prescribing of antimicrobials, audit and feedback strategies aim to guide the selection of definitive therapy. The process involves regular review of the use of targeted antimicrobials and assessment of their appropriateness for the particular patient. If there is concern that the drug is not being used appropriately, the prescriber is contacted, and alternative regimens are discussed. Audit and feedback mechanisms can be used to encourage de-escalation or streamlining of therapy (using the most narrowspectrum drug appropriate for the infection), to truncate excessive durations of therapy, to switch from the intravenous to the oral route when appropriate, and to adjust dosages. An example of audit and feedback strategies applied in an ICU environment is a study by Micek and colleagues.<sup>38</sup> Their group instituted a protocol for empiric therapy for ventilator-associated pneumonia (VAP) and then randomized VAP patients to physician-dictated continuation therapy (control) or to feedback regarding choice and duration of therapy from a clinical pharmacist and physician team (intervention). The intervention arm demonstrated a significant reduction in days of antimicrobial use relative to the controls with equivalent outcomes in terms of days of ventilation, ICU and hospital stay, and hospital mortality.

The increasing digitalization of the health care environment can be exploited in the design and execution of the antimicrobial stewardship strategies described previously. For example, procedures for obtaining authorization for restricted agents can be built into computerized physician order entry systems, and database query tools can streamline the audit and feedback process by automatically flagging orders for follow-up. Shojania and associates performed a trial in which prescribers entering orders into a computerized physician order system were randomized to encounter a "justification screen" when entering or renewing orders for vancomycin.<sup>39</sup> The prescribers in the intervention group had to enter the appropriate justification (based on CDC guidelines for vancomycin use) in order to proceed with the order. This simple step reduced the number of initial and renewal orders for vancomycin in the intervention group. The most advanced computerassisted interventions incorporate "expert systems" that can integrate data from multiple sources, apply prespecified decision rules, and create patient-specific suggestions for therapy. The group at Latter-Day Saints Hospital performed a trial in their ICU comparing antimicrobial prescribing and outcomes before and after implementation of a point-of-care expert system.<sup>40</sup> In the intervention period, there was a reduction in excess antimicrobial days, organism-drug susceptibility mismatches, adverse effects, and drug acquisition costs. A number of such systems are now commercially available, albeit requiring substantial financial and infrastructure investment.

An often-overlooked component of minimizing antimicrobial resistance is selection of the correct dosage and duration of therapy. Current recommendations for duration of therapy are based largely on experience, anecdote, and convention (e.g., 10 to 14 days of therapy) rather than an understanding of the biologic interplay among host, drug, and pathogen. Although an insufficient duration of therapy is considered to predispose patients to treatment failure, overlong courses of therapy apply unnecessary selective pressure and can contribute to resistance. Data are becoming available to define adequate courses of therapy for different infections based on clinical studies. Chastre and associates randomized patients who were treated with initially appropriate antimicrobial therapy for VAP to receive 8 or 15 days of total antibacterial therapy.<sup>41</sup> Mortality and recurrence of VAP were similar in both groups, and fewer resistant pathogens were recovered among patients in the 8-day group who had recurrences. In vitro and animal research on the role of antimicrobial pharmacodynamics in preventing selection of resistant organisms is beginning to reach clinical application. The concept of a mutant prevention concentration, an antibiotic dose at which the selection for drug-resistant mutants is minimized, has guided the development of optimal dosing for the fluoroquinolones.<sup>42</sup> For β-lactam drugs, prolonged or continuous infusions provide the most optimal pharmacodynamic exposure and may become increasingly used in the ICU setting for critically ill patients.<sup>43</sup> Future studies are likely to lead to a complete overhaul of current standards for the dose and duration of antimicrobials used in clinical practice, with potentially beneficial effects both for patients and the microbial environment.

#### AUTHORS' RECOMMENDATIONS

- Antibiotic resistance continues to increase in the ICU, and antibiotic-resistant infections are becoming increasingly difficult to treat with currently available antibiotics.
- Infection with an antibiotic-resistant organism has been shown to significantly affect morbidity and mortality and increases cost to the health care system.
- Knowledge of local resistance patterns is key in managing antimicrobial resistance in the ICU. Antibiograms describing the susceptibility of key pathogens for the ICU and hospital should be developed and updated regularly.
- Infection control measures and antimicrobial stewardship programs should be implemented and regularly enforced. The primary recommended modes of antimicrobial stewardship are restricting the use of certain antimicrobials and regular audit of antimicrobial prescribing with feedback to providers when antimicrobial therapy can be improved.
- Other antimicrobial stewardship strategies that may be considered when resources are available include the use of computer programs providing decision support for selection of antimicrobials and implementation of protocols to optimize the dose and duration of antimicrobials used in the ICU.

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# 1 Is Selective Decontamination of the Digestive Tract Useful?

Sean A. Nix, Craig M. Coopersmith

Selective decontamination of the digestive tract (SDD) was first described by Stoutenbeek and colleagues in 1984 as a means of decreasing endogenous bacteria in critically ill patients.<sup>1</sup> In theory, SDD both prevents secondary colonization and preemptively treats infection (regardless of whether it is suspected on intensive care unit [ICU] admission) caused by either respiratory flora or commensal gut flora. In turn, this should decrease the incidence of pneumonia and bacteremia. It has been hoped that this approach would decrease mortality in ICU patients. Since its first description, the use of SDD has been controversial. Proponents tout more than 40 randomized trials and numerous meta-analyses (Tables 41-1 and 41-2) showing decreased pneumonia and bacteremia rates. Many of these studies also demonstrate decreased mortality in patients receiving SDD. Opponents stress the concern for the development of resistant organisms, especially in ICUs that have a significant number of resistant organisms at baseline. This dichotomy has led to widely disparate geographic practice patterns with minimal use of SDD in the United States and significantly greater use in Europe. This chapter reviews the available evidence on this highly studied, yet highly contentious, practice.

#### INTERVENTIONS

The term SDD is a misnomer in most cases because most protocols use enteral nonabsorbable antibiotics but also include a 4-day course of parenteral antibiotics. Some protocols also give antibiotics as a paste to decontaminate the oral cavity. This can make interpreting the literature confusing; in some studies, SDD can refer to enteral antibiotics only, whereas in others, it may involve a combination of enteral and parenteral antibiotics or a combination of oral, enteral, and parenteral antibiotics. To further complicate the matter, selective oropharyngeal decontamination (SOD) using oral antibiotics alone may well prevent ventilatorassociated pneumonia. Thus, SOD may or may not be considered as distinct from SDD. Because oral, enteral, and parental antibiotics can have distinct effects, this chapter will attempt to distinguish the routes of antibiotic administration for all studies quoted.

SDD regimens typically target aerobic gram-negative bacteria, *Staphylococcus aureus*, and enteric fungus. An attempt is made to maintain anaerobic intestinal flora through selective use of antibiotics without anaerobic coverage and by discouraging the use of parenteral antibiotics with anaerobic coverage.<sup>1,2</sup> The most common enteral and oral antibiotics given include polymyxin E or colistin, tobramycin, and amphotericin B. The most common parenteral antibiotic used is cefotaxime. However, the marked variability in antibiotic choice can limit the generalizability of individual SDD studies.

# OUTCOMES

There have been more than 40 randomized controlled trials and 10 meta-analyses of SDD.<sup>1–55</sup> Most show that SDD confers benefit in at least one of the outcomes measured. The most common of these variables are pneumonia and mortality. Other outcomes measured in either primary or subgroup analyses include overall infection rates, specific types of infection (e.g., gram-negative, resistant organisms) rates, bloodstream infection rates, tracheobronchitis, anastomotic leakage, and organ dysfunction. Details for each study regarding (1) primary and secondary outcomes, (2) treatment protocol used, (3) control arm, and (4) size of patient population examined are listed in Tables 41-1 and 41-2.

Three meta-analyses published after the year 2000 demonstrate decreased mortality in patients receiving SDD.<sup>51,53,55</sup> The most recent of these, published in 2007, examined 51 trials between 1987 and 2005 and included more than 8000 patients who received oropharyngeal or enteral antibiotics with or without parenteral antibiotics.<sup>53</sup> SDD decreased overall mortality in 30 evaluable studies with an odds ratio of 080 (0.60 to 0.90). SDD was also associated with decreased overall bloodstream infections and gram-negative bloodstream infections without altering gram-positive bloodstream infections. Of note, a subgroup analysis that examined 16 trials with 3331 patients who received "standard" SDD (including both parenteral and enteral antibiotics) demonstrated a 26% decrease in overall mortality with an odds ratio of 0.74 (0.61 to 0.91). Decreases in bloodstream infections and gram-negative bloodstream infections also were noted. A follow-up metaanalysis from the same group examining 9473 patients demonstrated a marked decrease in gram-negative respiratory tract infections (odds ratio, 0.11 [0.06 to 0.20]) as well as a modest decrease in gram-positive respiratory tract infections (odds ratio, 0.52 [0.34 to 0.78]).<sup>54</sup> A subgroup analysis of 11 studies containing 1231 patients

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Study	No. of Subjects (Treatment/Control)	Patient Population (Medical, Surgical, Trauma, Liver, Mixed)	Treatment (Polymyxin E [PE], Tobramycin [T], Amphotericin B [AB])	Control	Outcomes
Abele-Horn, 1997 <sup>3</sup>	88 (58/30)	Surgical	Oral decontamination only: PE, AB, T	Placebo	SDD vs. control Primary pneumonia: 0% vs. 33% ( $P < .05$ ) Mortality: 19% vs. 17% ( $P > .05$ )
Aerdts, 1991 <sup>4</sup>	56 (control groups) Group 1: 18 Group 2: 21 Study group: 17	Mixed	PE, AB, norfloxacin Cefotaxime parenterally	Standard antibiotics therapy	Lower respiratory tract infections: Group 1: 78% Group 2: 62% Study group: 6% ( $P = .0001$ )
Arnow, 1996 <sup>5</sup>	69 (34/35)	Liver transplantation	Routine prophylaxis and PE, T, AB Cefotaxime and ampicillin IV	Cefotaxime and ampicillin	Overall rates of infections Control: 42% Study: 39% AGNB infections SDD: 0% vs. control 7% ( $P < .05$ )
Barret, 2001 <sup>6</sup>	23 (11/12)	Pediatric Burn	PE, T, AB	Placebo	No difference in pneumonia or sepsis
Bergmans, 2001 <sup>7</sup>	226 Oral decontamination: 87 Control in same ICU: 78 (group A) Control different setting: 61 (group B)	Mixed	Oral decontamination only: PE, gentamicin, and vancomycin	Placebo: One group in same ICU and one group in different ICU	VAP SDD: 10% Group A: 31% Group B: 23% ( $P = .001$ and $P = .04$ ) No difference in mortality or length of stay
Blair, 1991 <sup>8</sup>	256 (126/130)	Mixed	PE, AB, T Cefotaxime IV	Placebo	<ul> <li>SDD vs. control</li> <li>Nosocomial infection: 16.7% vs. 30.8% (P = .008)</li> <li>Mortality in patients with APACHE II scores: 10-19</li> <li>8 of 76 SDD vs. 15 of 70 controls (P = .03)</li> </ul>
Camus, 2005 <sup>9</sup>	515 Control: 126 PE and T: 130 Mupirocin nasally and chlorhexidine: 130 Both : 129	Mixed	PE and T only Mupirocin and chlorhexidine wash	Placebo	Infections Both regimens: OR, 0.44 (95% CI: 0.26-0.75; P = .003) No difference between two treatments
Cerra, 1992 <sup>10</sup>	46 (23/23)	Surgical	Norfloxacin suspension with nystatin	Placebo	SDD vs. control Total infections: 22 vs. 44 ( $P = .002$ ) Mortality: 13 vs. 10 ( $P = NS$ )

Cockerill, 1992 <sup>11</sup>	150 (75/75)	Mixed	PE, gentamicin, nystatin Cefotaxime IV	Placebo	Infections: 36 vs. 12 ( $P = .04$ ) No significant difference in mortality or length of stay
de Jonge, 2003 <sup>12</sup>	934 (466/468)	Surgical	PE, T, AB Cefotaxime IV ×4 days	Standard treatment	Treatment vs. control ICU mortality: 15% vs. 23% ( $P = .002$ ) Hospital mortality: 24% vs. 31% ( $P = .02$ ) Resistant gram-negative: 16% vs. 26% ( $P = .001$ ) VRE: 1% vs. 1% ( $P = 1.01$ ) MRSA: No incidence observed
De la Cal, 2005 <sup>13</sup>	107 (53/54)	Burn	PE, T, AB	Placebo	Treatment vs. control Mortality: 9.4% vs. 27.8% RR, 0.25 (95% CI, 0.08-0.76) Hospital mortality: RR, 0.28 (95% CI, 0.10-0.8) Pneumonia: 17/1000 ventilation days vs. 30.8/1000 ventilation days, ( $P = .03$ )
de Smet, 2009 <sup>2</sup>	5939 Control: 1990 Oral decontamination: 1904 SDD: 2405 (cluster randomization)	Mixed	<ul><li>SDD: PE, AB, T, and cefotaxime IV</li><li>SOD: antibiotics given for oral decontamination only</li></ul>	Standard treatment	28-day mortality compared with standard of care SOD: OR, 0.86 (95% CI, 0.74-0.99) SDD: OR, 0.83 (95% CI, 0.72-0.97) Gram-negative infections: NIs SOD: OR, 0.49 (95% CI, 0.27-0.87) SDD: OR, 0.43 (0.24-0.77)
Ferrer, 1994 <sup>14</sup>	80 (39/41)	Mixed	PE, AB, T Cefotaxime IV	Placebo Cefotaxime IV	SDD vs. control NI: OR, 0.66 (NS) Pneumonia: OR, 0.7 (NS) Mortality: OR, 1.21 (NS)
Flaherty, 1990 <sup>15</sup>	107 (51/56)	Cardiac surgery	PE, gentamicin, nystatin	Sucralfate	SDD vs. control infections: 12% vs. 27% ( $P = .04$ ) Mortality: No significant difference
Gastinne, 1992 <sup>16</sup>	445 (220/225)	Mixed	PE, AB, T	Placebo	SDD vs. control Mortality: 34% vs. 30% ( $P = .37$ ) Pneumonia: 33% vs. 26% ( $P = .42$ )
Hammond, 1992 <sup>17</sup>	239 (114/125)	Mixed	AB, PE, T Cefotaxime IV	Placebo	Control vs. study Infection: 26% vs. 34% ( $P = .22$ ) Length of stay: 16.2% vs. 16.8% Mortality: 18% vs. 17%
Hellinger, 2002 <sup>18</sup>	80 (37/43)	Liver transplantation	PE, nystatin, gentamicin	Nystatin	No difference in outcome Infection: 32.4% vs. 27.9% Death: 5.4% vs. 4.7%

Table 41-1	Randomized Controlled Trials on Selective Decontamination of the Digestive Tract—Cont'd					
Study	No. of Subjects (Treatment/Control)	Patient Population (Medical, Surgical, Trauma, Liver, Mixed)	Treatment (Polymyxin E [PE], Tobramycin [T], Amphotericin B [AB])	Control	Outcomes	
Kerver, 1988 <sup>19</sup>	96 (49/47)	Mixed	PE, AB, T Cefotaxime IV	Placebo	Control vs. study group Infection: 39% vs. 81% ( <i>P</i> < .001) Mortality: 28.5% vs. 32% ( <i>P</i> < .05)	
Koeman, 2006 <sup>20</sup>	385 Placebo: 130 Chlorhexidine: 127 Chlorhexidine Polymyxin E: 128	Mixed	Oral only Group 1: chlorhexidine Group 2: chlorhexidine and PE	Placebo	VAP Group 1: hazard ratio, 0.352 (95% CI, 0.160-0.791; <i>P</i> = .012) Group 2: hazard ratio, 0.454 (95% CI, 0.224- 0.925; <i>P</i> = .30) No difference in mortality	
Korinek, 1993 <sup>21</sup>	123 (63/60)	Neurosurgical	PE, AB, T Vancomycin added to oral solution	Placebo	SDD vs. control Pneumonia: 15% vs. 25% ( $P < .01$ ) Mortality: 3% vs. 7% ( $P < .01$ )	
Krueger, 2002 <sup>22</sup>	527 (265/262)	Surgical	PE, gentamicin Ciprofloxacin IV ×4 days	Placebo IV and PO	Treatment vs. control Total infection: OR, 0.477 (95% CI, 0.367-0.620; P < .001) Pneumonia: 6% vs. 29% ( $P = .007$ ) BSI: 14% vs. 36% ( $P = .007$ ) Organ dysfunction: 63% vs. 96% ( $P = .0051$ ) Mortality in ICU: 28% vs. 51% ( $P = .058$ )	
Laggner, 1994 <sup>23</sup>	67 (33/34)	Mixed	Gentamicin to oropharynx only	Placebo	Oral decontamination vs. placebo Pneumonia: 3% vs. 12% Mortality: 27% vs. 41% Differences not significant	
Lingnau, 1997 <sup>24</sup>	310 Control: 148 Treatment group 1: 83 Treatment group 2: 82	Trauma	Group 1: PE, T, AB Ciprofloxacin ×4 days Group 2: PE, AB Ciprofloxacin ×4 days	Placebo Ciprofloxacin ×4 days IV	No difference observed in rates of pneumonia, sepsis, organ dysfunction, or mortality	
Luiten, 1995 <sup>25</sup>	102 (50/52)	Pancreatitis	PE, AB, enteral norfloxacin	Standard	SDD vs. control Mortality: 22% vs. 35% ( $P = .048$ )	
Pneumatikos, 2002 <sup>26</sup>	61 (30/31)	Trauma	PE, AB, T (subglottic decontamination only)	Placebo	SDD vs. placebo Pneumonia: 16.6% vs. 51.6% No difference in mortality 16% vs. 23% ( $P = NS$ )	
Pugin, 1991 <sup>27</sup>	79 (38/41)	Trauma Surgical	Oral decontamination only: polymyxin B, neomycin, vancomycin	Placebo	SDD vs. control Pneumonia: 16% vs. 78% ( $P < .0001$ ) No difference in mortality	

Quinio, 1996 <sup>28</sup>	148 (76/72)	Trauma	PE, AB, gentamicin	Placebo	<ul> <li>SDD vs. control</li> <li>19 infections vs. 37 (P &lt; .01)</li> <li>No change in ICU days, duration of ventilation, or mortality</li> </ul>
Rayes, 2002 <sup>29</sup>	95 (32/63)	Liver transplantation		Fiber containing tube feeding and live lactobacillus 299	SDD vs. fiber + lactobacillus 43% vs. 13% ( $P = .017$ ) Mortality and other end points not statistically significant
Rocha, 1992 <sup>30</sup>	101 (47/54)	Mixed	PE, T, AB, cefotaxime	Placebo	Overall infection: 26% vs. 63% ( $P < .001$ ) Pneumonia: 15% vs. 46% ( $P < .001$ ) Mortality: 21% vs. 44% ( $P < .01$ )
Rodriguez- Roldan, 1990 <sup>31</sup>	28 (15/13)	Mixed	PE, T, AB	Placebo	SDD vs. control Tracheobronchitis: 3% vs. 3% ( $P < .001$ ) Pneumonia: 0% vs. 11% ( $P < .001$ ) Mortality: 30% vs. 33%
Rolando, 1993 <sup>32</sup>	104 (49/52)	Hepatic failure	PE, AB, T, cefuroxime IV or Cefuroxime IV	Standard	Infections: 34% vs. 61% ( $P = .005$ ) No significant difference in mortality
Rolando, 1996 <sup>33</sup>	108 (47/61)	Hepatic failure	Ceftazidime and flucloxacillin IV Enteral PE, T, AB	Ceftazidime and flucloxacillin IV Enteral AB	Infections: 21% vs. 20% ( $P = NS$ ) Mortality: 21% vs. 27% ( $P = NS$ )
Ruza, 1998 <sup>34</sup>	226 (116/110)	Pediatric	PE, T, nystatin	Standard care	Infections: 44% vs. 43% Mortality: 5.2% vs. 4.5% ( $P = NS$ )
Sanchez- Garcia, 1998 <sup>35</sup>	271 (131/140)	Trauma	PE, AB, gentamicin Orally and enterally Ceftriaxone IV ×4 days	Placebo	Treatment group vs. control VAP: 11% vs. 29.3% ( $P < .001$ ) Other infection: 19.1% vs. 30.% ( $P < .04$ ) Cost: \$11,926 vs. \$16,296 Mortality: 38.9% vs. 47.1% ( $P < .57$ )
Schardey, 1997 <sup>36</sup>	205 (102/103)	Surgical gastrectomy	Polymyxin B, AB, T, and oral vancomycin All received cefotaxime for 2 days	Placebo	SDD vs. control Anastomotic leak: 2.9% vs. 10.6% ( $P = .0492$ ) Pulmonary infections: 8.8% vs. 22.3% ( $P = .02$ ) Mortality: 4.9% vs. 10.6% ( $P = .1$ )
Smith, 1993 <sup>37</sup>	36 (18/18)	Pediatric Liver transplantation	PE, AB, T Standard perioperative antibiotics	Perioperative antibiotics	SDD vs. control Gram-negative infections: 11% vs. 50% ( $P < .001$ ) No significant differences in mortality

Table 41-1	Randomized Control				
Study	No. of Subjects (Treatment/Control)	Patient Population (Medical, Surgical, Trauma, Liver, Mixed)	Treatment (Polymyxin E [PE], Tobramycin [T], Amphotericin B [AB])	Control	Outcomes
Stoutenbeek, 1984 <sup>1</sup>	181 (122/59)	Trauma	PE, T, AB, cefotaxime	(Retrospective)	16% infection rate in treatment group versus 81% in control group
Stoutenbeek, 2007 <sup>38</sup>	401 (200/201)	Trauma	PE, T, AB Cefotaxime ×4 days	Standard care	Treatment vs. control Mortality: 20.9% vs. 22% Late mortality: 16% vs. 13% OR, 0.75 (95% CI, 0.40-1.37) Respiratory infection: 30.9% vs. 50% ( $P < .01$ ) Pneumonia: 9.5% vs. 23% ( $P < .01$ ) BSI, AGNB: 2.5% vs. 7.5% ( $P = .02$ ) Organ dysfunction: No difference
Tetteroo, 1990 <sup>39</sup>	114 (56/58)	Surgical, esophageal	PE, AB, T Cefotaxime IV	Standard antibiotic prophylaxis	SDD vs. control Infections: 18 vs. 58
Unertl, 1987 <sup>40</sup>	39 (19/20)	Long-term ventilated patients	PE, AB, gentamicin	Standard care	SDD vs. control Respiratory infections: 1% vs. 14% ( $P < .001$ ) No change in mortality
Verwaest, 1997 <sup>41</sup>	660 Control group A: 220 Group B: 195 Group C: 200	Mixed	Group B: AB, ofloxacin enteral and IV ×4 days Group C: PE, T, AB Cefotaxime IV	Group A: conventional treatment	<ul> <li>No change in mortality in all comparisons</li> <li>B vs. A: OR for infection, 0.27 (95% CI, 0.27-0.64)</li> <li>Respiratory infections: OR, 0.47 (95% CI, 0.26-0.82)</li> <li>Group C vs. A</li> <li>Resistant organism: 83% vs. 55% (<i>P</i> &lt; .05)</li> <li>Gram-positive bacteremias: OR, 1.22 (95% CI, 0.72-2.08)</li> </ul>
Wiener, 1995 <sup>42</sup>	61 (30/31)	Mixed	PE, AB, gentamicin	Placebo	No significant difference observed in: NIs Pneumonia Mortality
Winter, 1992 <sup>43</sup>	Treated: 91 Historical: 84 Contemporaneous: 92	Medical	PE, T, AB, ceftazidime	Standard of care	32 infections in contemporary controls vs. 27 in the historical and only 3 infections in the treated group ( $P < .01$ ) No difference in mortality
Zobel, 1991 <sup>44</sup>	50 (25/25)	Pediatric	PE, AB, gentamicin Cefotaxime IV	Standard	SDD vs. control NIs: 8% vs. 36% ( $P < .025$ ) No difference in mortality
Zwaveling, 2002 <sup>45</sup>	55 (26/29)	Liver transplantation	PE, AB, T	Placebo	Infections: SDD 84.5% vs. control 86% $(P = NS)$

Table 11 1

AGNB, aerobic gram-negative bacilli; APACHE, Acute Physiology and Chronic Health Evaluation; BSI, bloodstream infection; CI, confidence interval; ICU, intensive care unit; MRSA, methicillin-resistant Staphylococcus aureus; NIs, nosocomial infections; NS, not significant; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk; SOD, selective oropharyngeal decontamination; SDD, selective decontamination of the digestive tract; VRE, vancomycin-resistant enterococcus.
Table 41-2 Meta-Analyses on Selective Decontamination of the Digestive Tract							
Study	No. of Trials	No. of Subjects (Intervention/No Intervention)	Intervention (Polymyxin E [PE], Tobramycin [T], Amphotericin B [AB]	Control	Outcomes		
SDD Trialists' Group, 1993 <sup>46</sup>	22	4142 (2047/2095)	PE, T, AB, and enteral cefotaxime Some received quinolone and gentamicin	Placebo	<ul> <li>SDD vs. control</li> <li>Respiratory tract infection: OR, 0.37 (95% CI, 0.31-0.43)</li> <li>Mortality: OR, 0.9 (95% CI, 0.79-1.04)</li> <li>Mortality in trials giving parenteral and enteral treatment: OR, 0.8 (95% CI, 0.67-0.97)</li> </ul>		
Kollef, 1994 <sup>47</sup>	16	2270 (1105/1165)	Most studies PE, T, AB, and cefotaxime IV	Placebo	SDD vs. control Mortality rate: 0.262 vs. 0.243; $P = .291$ Pneumonia: 0.074 vs. 0.219 Gram-positive pneumonia: 0.033 vs. 0.033 ( $P = .933$ )		
Heyland, 1994 <sup>48</sup>	25	Not given	PE, T, AB, and cefotaxime IV	Placebo	SDD vs. control Mortality: RR, 0.87 (95% CI, 0.79-0.97; $P = .55$ ) Pneumonia: RR, 0.46 (95% CI, 0.39-0.56; $P = .01$ )		
D'Amico, 1998 <sup>49</sup>	16	3361	PE, T, AB, and enteral antibiotic	Placebo	SDD vs. control Pneumonia: OR, 0.29 (95% CI, 0.29-0.41) Mortality: OR, 0.80 (95% CI, 0.69-0.93)		
	17	2366	PE, T, and AB for most	Placebo	Pneumonia: OR, 0.56 (95% CI, 0.46-0.68) Mortality: OR, 1.01 (95% CI, 0.84-1.22)		
Nathens, 1999 <sup>50</sup>	11 RCTs for surgical	Not given	PE, T, AB, and cefotaxime	Placebo	Mortality: OR, 0.70 (95% CI, 0.52-0.93) Pneumonia: OR, 0.19 (95% CI, 0.15-0.26)		
	10 RCTs for medical	Not given	Standard PE, T, AB, and cefotaxime	Placebo	Mortality: OR, 0.91 (95% CI, 0.71-1.18) Pneumonia: OR, 0.45 (95% CI, 0.33-0.62)		
Van Nieuwenhoven, 2001 <sup>51</sup>	32	4804 (2400/2404)	Varied	Placebo	RRR for pneumonia: 0.57 (95% CI, 0.49-0.65) RRR for mortality: 0.12 (95% CI, 0.04-0.32)		
Safdar, 2004 <sup>52</sup>	14 Liver transplantation	201 (treated vs. control not given)	Varied	Placebo	Overall infection: RR, 0.88 (95% CI, 0.07-1.1) Gram-negative infection: 0.16 (95% CI, 0.07-0.37) No mortality benefit observed		
Silvestri, 2007 <sup>53</sup>	51	8065 (4079/3986)	PE, T, AB, and cefotaxime IV	Placebo	Mortality: OR, 0.80 (95% CI, 0.69-0.94) BSI: OR, 0.73 (95% CI, 0.59-0.90) Gram-negative BSI: OR, 0.39 (95% CI, 0.24-0.63) Gram-positive BSI: OR, 1.06 (95% CI, 0.77-1.47)		
	31 (subgroup analysis for BSI)	4753 (2453/2300)			BSI: OR, 0.73 (95% CI, 0.59-0.90)		
	30 (subgroup analysis for mortality)	4527 (2337/2190)			Mortality: 20% reduction OR, 0.80 (95% CI, 0.69-0.94; <i>P</i> = .0064)		
	16 (subgroup analysis)	3331 (1645/1686)	Parenteral and enteral		Mortality: 26% reduction OR, 0.74 (95% CI, 0.61-0.91) BSI: OR, 0.63 (95% CI, 0.46-0.87)		

Continued

Table 41-2 Meta-Analyses on Selective Decontamination of the Digestive Tract-Cont'd							
Study	No. of Trials	No. of Subjects (Intervention/No Intervention)	Intervention (Polymyxin E [PE], Tobramycin [T], Amphotericin B [AB]	Control	Outcomes		
Silvestri, 2008 <sup>54</sup>	54	9473 (4672/4801)	Standard SDD treatment/ varied	Placebo	Gram-negative bacteria Overall infection: OR, 0.17 (95% CI, 0.10-0.28) BSI: OR, 0.35 (95% CI, 0.21-0.67) Respiratory tract infection: OR, 0.11 (95% CI, 0.06-0.20) Gram-positive bacteria Lower respiratory tract infections: OR, 0.52 (95% CI, 0.34-0.78) Gram-positive BSI: OR, 1.03 (95% CI, 0.75-1.41)		
Liberati, 2004 <sup>55</sup>	36	6922	Standard SDD treatment/ varied	Placebo			
	17	4295	Topical and systemic antibiotic		Respiratory tract infections: OR, 0.35 (95% CI, 0.29-0.41) Mortality: OR, 0.78 (95% CI, 0.68-0.89)		
	17	2664	Topical antibiotics only		Respiratory tract infections: OR, 0.52 (95% CI, 0.43-0.63) Mortality: OR, 0.97 (95% CI, 0.81-1.16)		

BSI, bloodstream infection; CI, confidence interval; OR, odds ratio; RR, relative risk; RRR, relative risk reduction; SDD, selective decontamination of the digestive tract.

who received "standard" SDD also demonstrated a marked decrease in lower respiratory tract infections with an odds ratio of 0.07 (0.04 to 0.13).

These findings were consistent with a 2004 Cochrane meta-analysis on the same topic. This included 36 trials involving 6922 patients and included a subset of 17 trials of 4295 patients that tested both topical and systemic antibiotics.<sup>55</sup> In trials using standard SDD, mortality was decreased with an odds ratio of 0.78 (0.68 to 0.89). Respiratory infection also was markedly decreased with an odds ratio of 0.35 (0.29 to 0.41).

Only one meta-analysis published in the past decade failed to show benefit from SDD. This, however, examined only patients who received the therapy after liver transplantation.<sup>52</sup> It covered four randomized trials that included 259 patients. Three of these trials contained mortality data and did not show a positive effect. Overall the infection rate was unchanged (odds ratio, 0.88 [0.7 to 1.1]). However, there was an 84% relative risk reduction in gram-negative infections in patients treated with SDD (odds ratio, 0.16 [0.07 to 0.37]). A subgroup analysis of a meta-analysis published in 1999 showed a reduction in mortality in surgical patients in 11 trials (odds ratio, 0.70 [0.52 to 0.93]) but did not show a reduction in mortality in medical patients in 10 trials (odds ratio, 0.91 [0.71 to 1.18]).<sup>50</sup>

Although these meta-analyses combine all trials on SDD, the weight of an individual study is determined by the number of patients enrolled. As such, we believe it is important to consider the only four studies comparing standard SDD to control that investigated more than 400 patients. Importantly, a recent 6000-patient study comparing SDD to SOD to control showing a mortality benefit to both SDD and SOD is described later but has not yet been incorporated into a meta-analysis.

Perhaps the most widely quoted of these large trials is a prospective randomized controlled unblinded study by de Jonge and associates.<sup>12</sup> This trial compared 466 patients given standard SDD (4 days of parenteral antibiotics with oral and enteral antibiotics) to 468 control patients in a mixed ICU (60% surgical, 40% medical) in Amsterdam. ICU mortality decreased from 23% to 15% in the SDD group, and in-hospital mortality decreased from 31% to 24%.

In contrast, the other three studies did not demonstrate a clear mortality benefit for SDD. A prospective randomized trial of 546 patients in a predominantly surgical and trauma ICU examined the effect of SDD on late deaths (>5 days after admission).<sup>22</sup> A total of 28 patients receiving SDD and 51 control patients died in the surgical ICU (odds ratio, 0.64 [0.402 to 1.017]). In addition, overall mortality including early deaths (52 versus 75, respectively) was not statistically different. Subset analysis demonstrated a mortality benefit in patients receiving SDD if their Acute Physiology and Chronic Health Evaluation (APACHE) II score was between 20 and 29 on admission (odds ratio, 0.508 [0.295 to 0.875]). Of note, patients receiving SDD developed fewer pneumonias, bloodstream infections, urinary tract infections, and severe organ dysfunction than control patients. Similar results were found in a 2007 prospective randomized trial of 401 trauma patients with an injury severity score greater than 16.<sup>38</sup> Late mortality was 13.4% for patients randomized to SDD compared with 17.2% in control patients (odds ratio, 0.75 [0.40 to 1.37]). However, patients in the SDD group had a lower incidence of both lower airway infection and gram-negative bloodstream infection. A final study by Verwaest and associates of 660 patients compared two different SDD regimens (both with cefotaxime treatment but different enteral antibiotics) with controls.<sup>41</sup> Mortality was nearly identical in the three groups, with mortality rates in the two SDD groups of 15.5% and 17.6% compared with 16.8% in control patients.

# CONCERNS

Despite multiple studies and meta-analyses showing the efficacy of SDD, it is not commonly performed in the United States. This reflects concerns about the development of resistant organisms. Additionally, the efficacy of SDD in ICUs with high baseline rates of multidrug-resistant organisms has not been well documented. These issues have resulted in SDD not being recommended in guidelines to prevent ventilator-associated pneumonia and for the treatment of sepsis.<sup>56,57</sup>

The question of whether SDD generates resistant organisms has been studied extensively. Results are conflicting. Two recently published meta-analyses by Silvestri and colleagues do not support the notion that treatment with SDD is associated with an increase in resistant organisms.<sup>53,54</sup> The Cochrane meta-analysis<sup>55</sup> stated that the only study that "appropriately explored" this issue was that of de Jonge and associates, which did not support the development of resistance. This study showed that colonization with resistant gram-negative bacteria was significantly lower in the SDD group (16%) compared with the control group (26%). Additionally, colonization with vancomycin-resistant enterococcus occurred in 1% of each group. No patient in either group was colonized with methicillin-resistant *S. aureus*.

These data indicate that SDD is effective in ICUs with low endemic rates of vancomycin-resistant enterococcus, methicillin-resistant S. aureus, and multidrug-resistant gram-negative bacteria (such as occurs in many European countries). Nonetheless, it is possible that SDD might lead to enhanced selection of these organisms in ICUs where they are endemic.<sup>58</sup> A study supporting this concern was performed by Lingnau and coworkers in a surgical ICU in Austria.<sup>59</sup> During a 5-year period in which SDD was practiced, the incidence of oxacillin resistance in S. aureus isolates increased from 17% to 81%. Similarly, the threearm study described previously by Verwaest and associates demonstrated increased resistance to S. aureus (83%) versus 55%), Enterobacteriaceae (48% versus 14%), and ofloxacin-resistant nonfermenters (81% versus 52%) in patients treated with SDD.<sup>41</sup> Although anecdotal, an additional study documented the isolation of multidrugresistant Escherichia coli and Klebsiella pneumonia in four patients in Amsterdam undergoing SDD who were not known to be carriers of these strains before ICU admission.<sup>60</sup> These isolates had identical plasmids with extended-spectrum  $\beta$ -lactamase genes and were resistant to tobramycin, gentamicin, and ciprofloxacin and had intermediate sensitivity to polymyxin E.

# A COMPARISION OF SELECTIVE DECONTAMINIATION OF THE DIGESTIVE TRACT AND SELECTIVE OROPHARYNGEAL DECONTAMINATION

The data on the effectiveness of standard SDD (parenteral and enteral antibiotics) compared with SOD (no parenteral antibiotics) is mixed. A subgroup analysis of 17 studies using topical antibiotics alone in the Cochrane meta-analysis showed no mortality benefit to using this treatment (odds ratio, 0.97 [0.81 to 1.16]).<sup>55</sup> Topical antibiotics alone, however, decreased respiratory tract infections (odds ratio, 0.52 [0.43 to 0.63]). In addition, the most recent meta-analysis by Silvestri and colleagues indicated that parenteral and enteral antibiotics were superior to enteral antibiotics in reducing overall infections, respiratory infections, and bloodstream infections due to gram-negative bacteria.<sup>54</sup>

In contrast, a 2009 study of nearly 6000 patients that is, by far, the largest study of the treatments to date found that SOD was as effective as SDD.<sup>2</sup> This cluster randomization trial compared SDD with SOD to standard care in 13 ICUs. Each of the three regimens was applied in random order in each ICU over 6 months. Overall crude mortality rates in the groups were 26.9%, 26.6%, and 27.5%, respectively. However, when accounting for age, gender, APACHE II score, intubation status, and medical specialty, SDD reduced mortality by 3.5%, and SOD reduced mortality by 2.9%, compared with control patients. The cost for each treatment was \$12 per day for SDD and \$1 per day for SOD. Neither SDD nor SOD was associated with the emergence of antibiotic-resistant microorganisms or with increased rates of *Clostridium difficile* infection over the length of the study. Thus, SDD and SOD decreased mortality to a similar degree with the same mortality benefit. Theoretically, however, SOD minimized the risk for developing long-term antibiotic resistance, owing to the absence of systemic antibiotics and lower volume of topical antibiotics used. It also was less expensive. Therefore, the authors concluded that SOD may be preferable to SDD.

# CONCLUSION

Despite a significant body of literature on the topic, SDD continues to be highly controversial. Proponents point to multiple meta-analyses demonstrating a marked decrease in pneumonia and bloodstream infections, with a more modest, but still meaningful, decrease in ICU mortality. Opponents point to concerns about development of resistant organisms and lack of efficacy data in ICUs where multidrug-resistant organisms are endemic. This is highlighted by a nominal group vote in the latest Surviving Sepsis Campaign, in which nine votes were "weak for use," four votes were "neutral," eight votes were "weak for not using," and one vote was "strong for not using."<sup>57</sup> These differing opinions are reflected in the fact that SDD is almost never practiced in the United States where resistant organisms are common but is used with some frequency in many European countries where resistant organisms are less common. Most data indicate that SDD using both parenteral and enteral antibiotics is superior to use of enteral antibiotics alone. However, a 6000-patient study showing similar decreases in mortality with both SDD and SOD calls this conclusion into question. Unless definitive studies in the future demonstrate that SDD reduces mortality in ICUs with high baseline levels of resistant organisms without altering long-term resistance patterns, SDD is unlikely to become a widely used therapy in ICUs in the United States.

# **AUTHORS' RECOMMENDATIONS**

- SDD reduces pneumonia and bloodstream infections in ICUs that have low rates of multidrug-resistant organisms.
- SDD likely reduces mortality in ICUs with low rates of multidrug-resistant organisms.
- The impact of SDD on the development of resistant organisms is uncertain.
- The utility of SDD in ICUs with high rates of multidrugresistant organisms is uncertain.
- Most analyses demonstrate that SDD (parenteral antibiotics for 4 days plus enteral antibiotics) is superior to SOD. A recent 6000-patient study showing equivalent mortality benefit of both regimens calls this conclusion into question.

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# What Is the Evidence That Supports Current Resuscitation Guidelines for Cardiac Arrest?

Ramakrishnan Subramaniam, Noel M. Flynn

New guidelines for cardiopulmonary resuscitation (CPR) of adults and children were introduced at the end of November 2005 by the American Heart Association (AHA). The new CPR guidelines evolved from evidence-based resuscitation studies, and the evaluation process included the input of 281 international resuscitation experts who evaluated hypotheses, topics, and research over a 36-month period. The process included evidence evaluation, review of the literature, and focused analysis.<sup>1</sup> A new cycle of evidence evaluation has begun and is expected to be completed in 2010 with the publication of new and revised treatment recommendations.<sup>2</sup>

It is difficult to perform clinical trials in CPR science because of the low survival rate of out-of-hospital and in-hospital cardiac arrest, ethical issues, and the logistics of obtaining informed consent. The greatest challenge is to complete trials with sufficient power to be able to demonstrate impact on long-term or short-term outcomes. In the past, end-point criteria were for the patient to survive to hospitalization and be neurologically intact by hospital discharge. These trials were small, underpowered, and not randomized, and had interventions that made it hard to demonstrate a benefit. Informed-consent regulations in Europe<sup>3</sup> and North America<sup>4</sup> also made it challenging.

There are four major changes to the previous guidelines concerning CPR and sudden cardiac arrest. The most significant changes in the CPR guidelines are concerning the following:

- Compression-to-ventilation (C/V) ratio
- Compression first versus shock first for ventricular fibrillation (VF) in sudden cardiac arrest
- One-shock versus three-shock sequence for attempted defibrillation
- Vasopressors, antiarrthymics, and sequence of actions during treatment of cardiac arrest

# CARDIOPULMONARY RESUSCITATION

# **Compression-to-Ventilation Ratio**

The first major recommendation relates to first exposure to an unresponsive, pulseless, and nonbreathing victim. The recommendation is a 30:2 ratio for victims of all ages (except newborn infants). The old recommendation was for a ratio of 15:2. The 30:2 ratio is based on circulatory studies showing that, over time, blood flow increases with a greater amount of chest compressions.<sup>5</sup> If interrupted, as in the old 15:2 with two rescue breaths, blood flow decreases, causing less perfusion of tissues. The 30:2 ratio of compressions to ventilation is based on a consensus opinion rather than derived from evidence. Mathematical and animal models demonstrated that matching of pulmonary blood flow and ventilation might be more appropriate at C/V ratios higher than 15:2.<sup>6,7</sup> This increased ratio of chest compressions to breaths is thought to reduce hyperventilation of the patient, minimize interruptions of compressions, and simplify teaching to health care professionals and lay people.

Animal<sup>5</sup> and human<sup>8,9</sup> studies support a chest compression rate of greater than 80 compressions per minute to achieve optimal forward blood flow during CPR. The guidelines recommend a compression rate of about 100 compressions per minute (class IIa).

There are no reliable human data to identify the optimal C/V ratio for CPR in any age group. Two human studies of different C/V ratios have also been published since the 2005 guidelines were released. The first instituted a continuous compression (no ventilation) protocol and compared outcomes with those from 3 years prior. The results were significantly better, with a 57% survival rate compared with 20% before protocol implementation (P = .001).<sup>10</sup> A prospective, multicenter, observational trial conducted in Japan found that in patients with apnea, cardiac-only resuscitation (no ventilation) resulted in a higher percentage of patients with favorable neurologic outcomes (6.2%) compared with patients receiving conventional CPR (3.1%; P = .0195).<sup>11</sup>

# Compression First versus Shock First for Ventricular Fibrillation in Sudden Cardiac Arrest

Recent data challenge the standard practice of providing defibrillation first to every victim with VF, particularly when more than 4 to 5 minutes have elapsed from collapse to rescuer intervention. In two studies of out-ofhospital arrest, when the interval between the call to the emergency medical services (EMS) and delivery of the initial shock was 4 to 5 minutes or longer, a period of CPR before attempted defibrillation improved survival rates.<sup>12,13</sup> One randomized study<sup>14</sup> showed equivalent survival rates when either CPR or defibrillation was performed first for any EMS call-to-shock interval.

The data were insufficient to determine<sup>1</sup> whether this recommendation should be applied to in-hospital cardiac arrest,<sup>2</sup> the ideal duration of CPR before attempted defibrillation<sup>3</sup> or the duration of VF at which rescuers should switch from defibrillation first to CPR first.

In animal studies of VF lasting more than 5 minutes before treatment, providing CPR before defibrillation improved hemodynamics and survival rates.<sup>15–19</sup> In a human observational before-after study, a significant increase in survival was seen when EMS provided 90 seconds of CPR before defibrillating, rather than defibrillating without providing CPR (odds ratio [OR], 1.42; 95% confidence interval [CI], 1.07 to 1.90; P = .02).<sup>20</sup> A randomized controlled trial compared an EMS protocol providing 3 minutes of CPR before defibrillation to a protocol focused on immediate defibrillation and found no difference between the protocols when defibrillation was provided within 5 minutes; however, when the time from collapse exceeded 5 minutes, survival to hospital discharge was significantly greater in patients assigned to the CPR-first protocol (OR, 6.79; 95% CI, 1.42 to 31.4; P = .01.<sup>21</sup> One randomized trial that did not factor delay time into the analysis found no benefit to CPR first when 90 seconds of predefibrillation CPR was compared with immediate defibrillation.<sup>22</sup>

Although both animal and human data suggest that a protocol incorporating CPR before defibrillation will improve survival in certain circumstances, the most effective approach has not yet been established.

# One-Shock versus Three-Shock Sequence for Attempted Defibrillation

The latest recommendation is for only one shock of 150 or 200 J (manufacturer variation), using a biphasic defibrillator, or 360 J if using a monophasic defibrillator. This takes the place of the three stacked shocks at 200, 300, and 360 J, as were previously recommended in the Advanced Cardiac Life Support (ACLS) guidelines.<sup>23</sup>

The three-shock recommendation was based on the low first-shock efficacy of monophasic damped sinusoidal waveforms and efforts to decrease transthoracic impedance with delivery of shocks in rapid succession. Modern biphasic defibrillators have a high first-shock efficacy (defined as termination of VF for at least 5 seconds after the shock), averaging more than 90%,<sup>24,25</sup> so that VF is likely to be eliminated with one shock.

The evidence concerning the interruption of chest compressions reducing coronary perfusion pressure was sufficiently strong for the International Committee to make the one-shock strategy a recommendation during cardiac arrest.

After VF is terminated,<sup>26–28</sup> most victims demonstrate a nonperfusing rhythm (pulseless electrical activity or asystole) for several minutes; the appropriate treatment for such rhythms is immediate CPR. Yet in 2005, the rhythm analysis for a three-shock sequence performed by commercially available automated external defibrillators (AEDs) resulted in delays of 29 to 37 seconds or more between delivery of the first shock and the beginning of the first postshock compression.<sup>28,29</sup> This prolonged interruption in chest compressions cannot be justified for analysis of a rhythm that is unlikely to require a shock.

Providers should give one shock rather than three shocks, because of the high success rate for biphasic defibrillators<sup>30</sup> and fewer interruptions of CPR.

There is no direct evidence to suggest that one shock is superior to three stacked shocks. The rationale for single shocks is based on three major findings. First, the rhythm analysis used by AEDs after each shock results in an average delay of 37 seconds before the delivery of the first postshock chest compression.<sup>31,32</sup>

As discussed previously, this delay results in low cerebral perfusion pressure (CPP) and is a predictor of poor survival.<sup>33,34</sup> Second, with a first-shock efficiency of 90% for biphasic defibrillators, stacked shocks provide little incremental value and unduly delay chest compressions.<sup>31,32,35,36</sup> In cases in which the first shock fails, resumption of CPR confers greater benefit than further defibrillation.<sup>36</sup> Third, even when a shock eliminates VF, it may take several minutes for a heart rhythm to establish and even longer to achieve perfusion. Chest compressions can provide coronary and cerebral perfusion during this period.

The current recommendation for AED use is to provide CPR for 2 minutes before use of an AED. A large prospective, community-based, multicenter clinical trial was conducted with 19,000 volunteer responders from 993 community units in 24 North American regions. The community units were randomly assigned to a structured and monitored emergency response system involving lay volunteers trained in CPR alone or in CPR plus the use of AEDs. The study found more survivors to hospital discharge in the units assigned to volunteers trained in CPR plus AEDs (relative risk, 2.0; 95% CI, 1.07 to 3.77; P = .03).<sup>37</sup>

# Vasopressors, Antiarrhythmics, and Sequence of Actions during Treatment of Cardiac Arrest

A meta-analysis of five randomized out-of-hospital trials showed no significant differences between vasopressin and epinephrine for return of spontaneous circulation, death within 24 hours, or death before hospital discharge.<sup>38</sup> A proposal to remove all recommendations for vasopressors was considered but not approved in the absence of a placebo versus vasopressor trial and the presence of laboratory evidence documenting the beneficial physiologic effects of vasopressors on hemodynamics and short-term survival.

A number of animal studies and early human trials found that the use of vasopressin in cardiac arrest improved return of spontaneous circulation (ROSC), increased CPP, and improved neurologic outcomes.<sup>39,40</sup> Stiell and associates<sup>41</sup> performed a prospective, tripleblind, randomized, controlled trial evaluating vasopressin in hospitalized patients with cardiac arrest. Patients experiencing VF, pulseless electrical activity (PEA), or

asystole (n = 200) were randomized to receive a single intravenous dose of either epinephrine, 1 mg, or vasopressin, 40 units. Successful resuscitation was achieved in 39% of the vasopressin-treated group and 35% of the epinephrinetreated group; there was no significant difference in success rates between the two groups. Rates of survival to hospital discharge also did not significantly differ between the vasopressin-treated group (12%) and the epinephrine-treated group (14%). Wenzel and associates<sup>42</sup> conducted a prospective, double-blind, randomized controlled trial of 1219 patients with out-of-hospital VF, PEA, or asystolic cardiac arrest. Patients were randomly assigned to receive epinephrine, 1 mg intravenously, or vasopressin, 40 units intravenously. If spontaneous circulation was not restored within 3 minutes, a second dose of the same agent was administered.

Overall, there was no significant difference in survival to hospital admission (36.3% with vasopressin versus 31.2% with epinephrine) or survival to hospital discharge (9.9% for both groups). There was also no difference in either end point in the subgroup populations of VF and PEA; however, a difference was found in patients with asystole. Asystolic patients treated with vasopressin had a survival to hospital admission rate of 29.0%, compared with 20.3% in patients treated with epinephrine (P = .02). There was also a significant difference in survival to hospital discharge that occurred in 4.7% and 1.5% in the vasopressinand epinephrine-treated groups, respectively (P = .04). Gueugniaud and associates<sup>43</sup> conducted a prospective,

double-blind, randomized controlled trial of 2894 patients with out-of-hospital VF, PEA, or asystolic cardiac arrest. Patients were assigned to receive epinephrine, 1 mg intravenously, and vasopressin, 40 units intravenously, or epinephrine, 1 mg intravenously alone. If spontaneous circulation was not restored within 3 minutes, a second dose of the same regimen was administered. Overall, there was no significant difference between the combination therapy and the group receiving epinephrine alone in survival to hospital admission (20.7% versus 21.3%, respectively) or survival to hospital discharge (1.7% versus 2.3%, respectively). In this study, 83% of the patient population were enrolled after an asystolic arrest, refuting the suggestion by Wenzel and colleagues<sup>42</sup> that vasopressin may be beneficial in this patient population. The current evidence for the use of vasopressin in cardiac arrest is indeterminate.44 Given the similarly equivocal evidence of efficacy for epinephrine, either drug can be considered a first-line agent in cardiac arrest. Placebo-controlled, appropriately powered studies are needed to evaluate meaningful clinical outcomes (e.g., survival to hospital discharge).

There is no evidence that routine administration of any antiarrhythmic drug during human cardiac arrest increases the rate of survival to hospital discharge. One antiarrhythmic, amiodarone, improved short-term outcome (i.e., survival to hospital admission), but did not improve survival to hospital discharge when compared with placebo<sup>45</sup> and lidocaine.<sup>46</sup>

The Amiodarone in Out-of-Hospital Resuscitation of Refractory Sustained Ventricular Tachycardia (ARREST) trial<sup>45</sup> compared an amiodarone hydrochloride 300-mg intravenous bolus injection with placebo in patients with out-of-hospital cardiac arrest (OOHCA) who had received

three or more precordial shocks, had no pulse, and had VF or ventricular tachycardia.<sup>45</sup> More patients in the amiodarone group had admission to the hospital with successful resuscitation than the placebo group (44% versus 34%, respectively; OR, 1.5; 95% CI, 1.04 to 2.10; P = .03). Patients who received amiodarone and had a transient or sustained return of spontaneous circulation (ROSC) had a lower blood pressure and heart rate and required more vasopressor support (59% versus 48%; P = .04) and more treatment for bradycardia (41% versus 25%; P = .004) than patients who received placebo. The study found no significant difference in the rates of survival to hospital discharge between the amiodarone treated group (13.4%) and patients who received placebo (13.2%).

The Amiodarone versus Lidocaine in Prehospital Ventricular Fibrillation Evaluation (ALIVE) compared amiodarone hydrochloride administered as a 5-mg/kg intravenous bolus injection with lidocaine hydrochloride administered as a 1.5-mg/kg intravenous bolus injection in patients with out-of-hospital VF resistant to three shocks from an external defibrillator, at least one dose of epinephrine, and a fourth shock.<sup>46</sup> More patients in the amiodarone group (22.8%) had successful survival to hospital admission than in the lidocaine group (12.0%; OR, 2.17; 95% CI, 1.21 to 3.83; P = .009). There was no significant difference in the rates of vasopressor use for hypotension (7% versus 4%) or atropine use for bradycardia (24% versus 23%) between the amiodarone and lidocaine groups, respectively. The study found no significant difference in the rates of survival to hospital discharge between the amiodarone (5.0%) and lidocaine (3.0%) groups.

The results of both the ARREST and ALIVE trials may support the 2005 guidelines' recommendation to use amiodarone as the first-line antiarrhythmic agent in cardiac arrest. The guidelines recommend amiodarone hydrochloride as a 300-mg intravenous bolus injection followed by one dose of 150 mg given intravenously for VF or paroxysmal ventricular tachycardia (PVT) unresponsive to CPR, shock, and a vasopressor.<sup>4,5</sup> However, as reported, there are few data that support the contention that antiarrhythmics improve survival.

In summary, the 2005 AHA guidelines for CPR and emergency cardiac care (ECC) recommend that rescuers resume CPR beginning with chest compressions *immediately* after a shock, without an intervening rhythm (or pulse) check. Vasopressors or antiarrhythmics should be administered during CPR, as soon as possible after a rhythm check. The drug will be circulated by the CPR performed while the defibrillator charges or by the CPR that follows the shock.

Studies have shown that a reduction in the interval between compression and shock delivery by as little as 15 seconds can increase the predicted shock success.<sup>47,48</sup> The most important part of the sequence is high-quality chest compressions with minimal interruptions.

# POSTRESUSCITATION CARE

The appropriate management of cardiac arrest victims after ROSC is paramount to optimize outcomes. The 2005 guidelines highlight the shift from primary rhythm-based therapies and resuscitation to a focus on neurologic outcomes. An important advance in the care of cardiac arrest patients is induced hypothermia. Central neuron tissues are sensitive to a reduction in perfusion as a result of cardiac arrest, and cerebral malfunction occurs within seconds. Patients often sustain cerebral damage after cardiac arrest, and, until recently, therapies that improve neurologic outcome have been unsuccessful. However, two studies randomized comatose patients resuscitated from out-of-hospital VF or PVT to mild induced hypothermia compared with standard care.49,50 In these trials, all patients received standard postresuscitation supportive care, including ventilation and cardiovascular support in an intensive care setting. Patients randomized to induced hypothermia had surface cooling initiated within 6 hours of ROSC and then a core temperature of 32° to 34°C maintained for 12 to 24 hours, after which they were allowed to return to normothermia, and the sedation and paralysis medication were removed. Bernard and associates<sup>49</sup> and the Hypothermia after Cardiac Arrest (HACA) study group<sup>50</sup> demonstrated improved survival rates in patients who were cooled compared with those who received standard care (49% versus 26% [P = .046] and 55% versus 39% [P = .009], respectively). Improvement in neurologic outcomes was also demonstrated in patients treated with induced hypothermia in both studies. No statistically significant differences in adverse events were observed between the hypothermia and normothermia groups in either trial, although the HACA study found a trend toward increased sepsis in the hypothermia group. Although well designed, these trials were limited by their use of strict enrollment criteria. Only 275 of the 3551 patients assessed for eligibility were enrolled in the HACA trial. Also, the lack of blinding in both trials allowed the potential for observer bias. The results of other randomized controlled trials and case series have supported the use of induced hypothermia.51-53

Systematic reviews of induced hypothermia after cardiac arrest suggest significant improvement in morbidity and mortality.<sup>54,55</sup>

# **AUTHORS' RECOMMENDATIONS**

- This chapter summarizes the evidence in changes in resuscitation skills and sequences recommended in the 2005 AHA guidelines for CPR and ECC.
- Several evidence-based changes were included in the 2005 CPR and ECC guidelines, including a C/V ratio of 30:2 and reduction of hands-off time, early defibrillation, administration of a one-shock versus a three-shock sequence, use of public access defibrillators, and a shift from primary rhythm-based therapies to a focus on neurologic outcomes.
- Vasopressors or antiarrhythmics should be administered during CPR, as soon as possible after a rhythm check.
- Moderate induced hypothermia is recommended in patients who have undergone in-hospital or out-of-hospital cardiac arrest with return of spontaneous circulation.
- Further research is required in nearly all aspects of CPR and ECC.

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# Should We Abandon the Pulmonary Artery Catheter in the Intensive Care Unit?

J. Steven Hata, Joss Thomas, Terence M. Cone

The pulmonary artery catheter (PAC) has been integral to the evolution of critical care medicine, perioperative anesthesia, and cardiology since its introduction in 1970.<sup>1</sup> Its technology has allowed the measurements of intracardiac pressures and cardiac output and has fostered treatment strategies augmenting systemic oxygen delivery. Early observational studies indicated that it offered greater accuracy in assessing hemodynamic function<sup>2</sup> and allowed for improvements in the prescription of fluid and drug therapies. To reduce ICU and perioperative risk,<sup>3</sup> anesthesiologists, intensivists, cardiologists, and surgeons widely adopted this device as part of their supportive armamentarium.<sup>3</sup> It has been estimated that more than 1.5 million patients per year received PACs with an incurred cost of an estimated \$2 billion.<sup>4</sup> The PAC has influenced both diagnostic risk categorization and treatment decisions for a variety of clinical disease states.<sup>5,6</sup> Increasingly, however, its use has been challenged.<sup>7</sup> During the past decade, comprehensive systematic reviews and randomized controlled trials have examined the effectiveness of the PAC in specific high-risk patient populations. This review will evaluate this evidence for the role of the PAC within critical care practice.

# PATHOPHYSIOLOGY AND MECHANISMS OF ACTION

The PAC has been proposed as an essential monitor to establish diagnoses and guide therapies in high-risk patient populations within critical care units and perioperative care.<sup>3,8</sup> The spectrum of disease states for which the PAC has been considered has been broad, each associated with potentially detrimental alterations of cardiac output and oxygen delivery. Importantly, early investigations suggested fundamental limitations in the bedside clinical assessments of left ventricular preload as well as cardiac output.<sup>9</sup> These observations supported a rationale for the use of the PAC to improve on physical examination and central venous pressure (CVP)-guided therapy.<sup>5</sup>

The PAC provides a continuous monitor of intracardiac pressures as well as repetitive measures of cardiac output and indices of systemic oxygen delivery and consumption. As a diagnostic monitor, it has guided clinical treatments of intravascular fluid support, diuretic therapy, and use of vasoactive drugs to effect the inotropic state of the heart.<sup>10,11</sup> PAC use in the critically ill has been associated with significant changes in clinical management (e.g., intravascular fluids, vasopressors, or diuretics).<sup>12</sup> Importantly, it has been a relevant tool to aid in our understanding of the pathophysiology of sepsis<sup>13</sup> and guided therapy designed to alter arterial vasomotor tone.<sup>14</sup> In the setting of chronic congestive heart failure, early studies supported the role of the PAC in administration of long-term vasodilator drug therapy.<sup>15</sup> To support perioperative care physicians have used the PAC to augment patient responses to high-risk surgery,<sup>16</sup> balancing the systemic challenges induced by blood loss, myocardial depression secondary to myocardial ischemia and volatile anesthetics, the systemic inflammatory response, and adverse changes in pulmonary function.

Based on the Frank-Starling relationship, the PAC has been used to optimize cardiac output.<sup>17</sup> This physiologic tenet postulates that myocardial muscle function of the left ventricle is related to the ventricular end-diastolic volume.<sup>18</sup> The PAC has provided estimates of optimal left ventricular preload with measurements of the pulmonary artery occlusion pressure (PAOP), thermodilution cardiac output, and mixed venous blood gas analysis. The validity of PAC-guided therapy requires understanding of potential distortions of the Frank-Starling relationship, including the confounding effects of juxtacardiac pressure (e.g., positive airway pressure during mechanical ventilation and positive end-expiratory pressure), alterations in left ventricular compliance, valvular heart disease, and other clinical factors.<sup>19</sup>

There are increasing concerns about the validity of the PAC to effectively guide supportive care. Although the use of the PAC appears to affect clinical decision making and modify clinical interventions, expert panels, based on available clinical trials, have questioned the impact of PAC-guided decisions on improving clinical outcomes.<sup>3</sup> Further, the degree to which the PAC influences overall treatment strategies is controversial. Of note, recent protocol-driven treatment strategies comparing the PAC with the central venous catheter (CVC) have shown similar prescriptions of fluid therapy, diuretic use, and vasoactive drug use in acute lung injury (ALI).<sup>20</sup>

Based on observational clinical trials, investigators have challenged the ability of measurements made with the PAC to predict fluid responsiveness in the critically ill.<sup>21–23</sup> The debate about this fundamental concern, that is, the predictive value of the PAC to estimate cardiac preload, is not new.<sup>24–26</sup> Echocardiography and nuclear medicine studies have supported that surrogates for left ventricular volume and cardiac function poorly correlate with PAC estimates in specific patient populations.<sup>26,27</sup> Importantly, recent studies support that the PAOP (as well as CVP) does not offer high predictive value in identifying fluid requirements.<sup>21,28,29</sup> These essential issues, combined with concerns of device-related complications as well as inconsistent understanding of device function,<sup>30,31</sup> provide plausible rationale for the failure of the PAC to improve clinical outcomes in randomized controlled trials.

# META-ANALYSES ADDRESSING THE EFFECT OF THE PULMONARY ARTERY CATHETER

Systematic reviews have assessed the value of the pulmonary artery catheter in guiding therapy and improving outcomes in (1) general intensive care unit (ICU) care and high-risk surgical patients, (2) ALI and sepsis, (3) advanced heart failure, and (4) ICU morbidity (Tables 43-1 through 43-4). These have coincided with a general decrease in the clinical use of the PAC in adult patients in the United States.<sup>32</sup> From 1993 through 2004, there was a significant reduction in the incidence of PAC use. This includes patients with myocardial infarction, sepsis, acute respiratory failure, pneumonia, and heart failure. Similarly, this trend appeared consistent with reduced PAC use in surgical patients, including noncardiac and cardiac surgery.<sup>32</sup>

# GENERAL INTENSIVE CARE AND HIGH-RISK SURGICAL PATIENTS

Several meta-analyses addressing intensive care and hospital survival after exposure to the PAC have been performed during the past decade (see Table 43-1). The overall weight of these reviews has supported that PACdirected care has not been associated with improvement of survival or confers efficiencies in medical practice. Recently, an important systematic review by Harvey and associates within the Cochrane Collaboration analyzed four randomized, controlled trials of the PAC after ICU admission. These included 1923 patients.<sup>33</sup> The PAC was not associated with significant differences in ICU or hospital mortality.<sup>33</sup> Similarly, a meta-analysis of 13 randomized controlled trials of 5051 patients showed no significant differences between PAC exposed and nonexposed ICU patients in terms of mortality.<sup>8</sup> PAC exposure, however, was associated with significant changes in supportive care with increased use of inotropic drug therapy (odds ratio [OR], 1.58; 95% confidence interval [CI], 1.29-12.12) and intravenous vasodilator administration (OR, 2.3; 95% CI, 1.75-3.15). Further, neither of these meta-analyses showed differences with respect to length of hospitalization (see Table 43-2).

Clinicians have prescribed the PAC in high-risk surgical patients as part of an overall strategy to limit perioperative complications. Early investigations supported the role of preoperative PAC placement and perioperative monitoring to achieve targeted hemodynamic profiles to improve overall outcomes.<sup>34,35</sup> Addressing this approach, Harvey and associates identified eight randomized controlled trials from 1989 to 2003 examining differences in mortality in high-risk adult surgical patients.<sup>33</sup> Evaluating a total of 2763 patients, these investigators found no significant mortality differences based on PAC exposure.

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Study	No. of Trials	No of Subjects (PAC/No PAC)	Intervention	Control	Outcomes	Odds Ratio (95% Confidence Interval)	
Shah et al, 2005 <sup>8</sup>	13	2536/2490	PAC (7 with HG; 5 with treatments)	No PAC	Mortality	1.04 (0.90, 1.20)	
Harvey et al, 2006 <sup>33</sup>	4	953/970 General ICU patients	PAC (4 without specific goals or treatments)	No PAC	Mortality	1.05 (0.87, 1.26)	
Harvey et al, 2006 <sup>33</sup>	5	1234/1161 High-risk surgical patients	PAC (5 with HG; 4 with treatments)	No PAC	Mortality	0.98 (0.72, 1.33)	
Barone et al, 2001 <sup>62</sup>	4	211/174 Vascular surgical patients	3 studies with PAOP and CI goals; 1 study with PAOP, Hgb, and Svo <sub>2</sub> goals; 3 preoperative	2 studies with CVP; 2 nonspecified	Mortality	No difference reported	

 Table 43-1
 Summary of Meta-Analyses on General Intensive Care Unit Patients and Perioperative

 Studies for All Mortality Outcomes

CI, cardiac index; CVP, central venous pressure; HG, hemodynamic goals; Hgb, hemoglobin; ICU, intensive care unit; PAC, pulmonary artery catheter; PAOP, pulmonary artery occlusion pressure; SvO<sub>2</sub>, mixed venous oxygen saturation.

# Table 43-2 Summary of Meta-Analysis on Intensive Care Unit and High-Risk Surgical Patients for Length-of-Stay Differences

Study	No. of Trials	No. of Subjects (PAC/No PAC)	Interventions	Control	Outcomes	Mean Difference (95% Confidence Interval)
Harvey et al, 2006 <sup>33</sup>	3	857/866 General ICU patients	PAC	No PAC	ICU length of stay	-0.21 (-1.46, 1.05)
Harvey et al, 2006 <sup>33</sup>	5	286/217 High-risk surgical patients	РАС	No PAC	ICU length of stay	1.57 (0.36, 2.79)
Shah et al, 2005 <sup>8</sup>	11	2451/2405	PAC (6 with HG; 4 with treatment prescriptions)	No PAC	Hospital days	0.11 (-0.51, 0.74)
Harvey et al, 2006 <sup>33</sup>	2	841/848 General ICU patients	РАС	No PAC	Hospital length of stay	-0.80 (-2.71, 1.12)
Harvey et al, 2006 <sup>33</sup>	5	286/217 High-risk surgical patients	РАС	No PAC	Hospital length of stay	0.35 (-0.005, 0.75)

HG, hemodynamic goals; ICU, intensive care unit; PAC, pulmonary artery catheter.

Table 43-3 Summary of Randomized Controlled Trials on ARDS or Sepsis							
Study	No. of Subjects (PAC/No PAC)	Study Design	Intervention	Control	Outcomes		
Wheeler et al, 2006 <sup>20</sup>	513/488	Randomized control	PAC using an explicit hemodynamic protocol	CVC	60-day mortality: difference 1.1% (95% CI, -4.4, 6.6)		
Richard et al, 2003 <sup>42</sup>	335/341	Randomized control	Early use of the PAC in shock, ARDS, or both	No PAC	28-day mortality: RR, 0.97 (95% CI, 0.86, 1.10)		
Harvey et al, 2006 <sup>33</sup>	519/522	Randomized control	PAC	No PAC	Hospital mortality: adjusted hazard ratio, 1.09 (95% CI, 0.94, 1.27)		
Rhodes et al, 2002 <sup>63</sup>	95/106	Randomized control	PAC	No PAC	28-day mortality: difference 0.3% (95% CI, -13, 14)		

CI, confidence interval; CVC, central venous catheter; PAC, pulmonary artery catheter; RR, relative risk.

# Table 43-4 Summary of Meta-Analysis of Maximizing Systemic Oxygen Delivery on Mortality

Study	No. of Trials	No. of Subjects (PAC/No PAC)	Interventions (No. of Studies)	Control	Outcomes	Summary Differences
Heyland et al, 1996 <sup>53</sup>	7	1291/1264	CI augmentation (4); Do <sub>2</sub> increase (5); Vo <sub>2</sub> increase (2)	Normal values	Mortality	Odds ratio, 0.86 (0.62-1.20)
Kern & Shoemaker, 2002 <sup>54</sup>	21	857/866	PAOP (18); Do <sub>2</sub> (14); CI (13); CVP (1); pHi (1)	Variable	Mortality	Mean difference, $-0.05 \pm 0.02$

CI, cardiac index; CVP, central venous pressure; Do<sub>2</sub>, systemic oxygen delivery; PAOP, pulmonary artery occlusion pressure; pHi, gastric mucosal pH; Vo<sub>2</sub>, systemic oxygen consumption.

This analysis included studies of both preoperative optimization and perioperative use (OR, 0.98; 95% CI, 0.73-1.33). Further, using five studies from 1988 to 1997, this meta-analysis identified no significant differences in ICU length of stay.

# PULMONARY ARTERY CATHETER IN SEPSIS AND ARDS

The incidence of sepsis is about 750,000 cases per year in the United States, with an estimated 40% of patients with severe sepsis developing ARDS, <sup>36,37</sup> the latter with reported mortal-ity rates of 40% to 60%.<sup>38</sup> Early retrospective and observational studies showed promising results supporting the role of the PAC to guide fluid management in sepsis and ARDS. A retrospective study of ARDS patients in 1987 reported that survivors managed with a PAC guidance received less fluid than nonsurvivors.<sup>39</sup> Subsequently, Humphrey and coworkers, in a retrospective study of ARDS patients, found that reduction of PAOP of at least 25% during acute management (i.e., the first 48 hours) was associated with significant improvement of survival.<sup>40</sup> Further, a retrospective analysis of patients with ARDS found that elevation of the PAOP to 18 mm Hg strongly correlated with mortality.<sup>41</sup> These retrospective and observational studies were limited by virtue of experimental design and methodology. In 2003, Richard and associates published a randomized controlled study evaluating the role of the PAC in the support of sepsis and ARDS<sup>42</sup> (see Table 43-3). In contrast to earlier studies, this investigation showed that PAC exposure did not confer a benefit for 28-day survival, differences in organ dysfunction, need for vasoactive agents, duration of mechanical ventilation, duration of ICU days, or duration of hospital stay. One important point of contention is that treatment decisions within this multicenter trial were prescribed by attending physicians as opposed to a monitorguided protocol. In addition, the study was underpowered for all variables other than mortality. The Fluid and Catheter Treatment Trial (FACTT), as part of the ARDS Clinical Trials Network, compared specific management guided by either the PAC or the CVC in patients with ALI.<sup>20</sup> This study showed no differences in clinical outcomes with respect to 60-day survival, ventilator-free days, renal function, hemodialysis, or vasopressor therapy. This investigation is relevant because of its explicit inclusion criteria and detailed management algorithms. This trial required specific devicerelated estimates of preload and diuretic use for goaldirected therapy. The trial was designed with a statistical power of 90% to detect a 10% discharge mortality difference. The results showed no differences in mean arterial pressure, net fluid balance, or proportion of vasopressor use between these medical devices. It was underpowered for a number of important treatment and management variables, and thus further study is warranted. Perhaps most important, patients with ARDS secondary to nonpulmonary causes were underrepresented. Again, further investigation of specific subgroups is warranted.

In conclusion, the consensus appears to be shifting away from the routine use of PAC in the management of sepsis and ALI/ARDS as evidenced by the Current International Guidelines for the Management of Septic Shock.<sup>43</sup>

# CARE OF HIGH-RISK CARDIAC PATIENTS

Since its introduction, the PAC has been used in the support of patients with acute myocardial infarction and congestive heart failure.<sup>1,5</sup> Supporting the use of the PAC, early investigations stressed the limitations of CVP measurement in the assessment of left heart function.<sup>5</sup> Recently, the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial, a multicenter, randomized controlled trial, compared the PAC and clinical assessment to clinical evaluation alone in 433 patients with advanced congestive heart failure.<sup>44</sup> Importantly, exposure to PAC-guided therapy failed to produce differences in terms of survival at 6 months, mortality, or hospital length of stay. Iatrogenic morbidity was significantly greater in the PAC group (21.9%) than in the control group (11.5%) at a level of significance of .04. The investigators concluded that the exposure to the PAC did not convey advantages in survival or reduced length of hospitalization in decompensated chronic congestive heart failure. With regard to perioperative care, there have been limited randomized controlled trials focusing on the role of the PAC in the support of coronary artery bypass or valvular heart surgery<sup>45</sup> and no published meta-analyses to date.

# COMPLICATIONS OF THE PULMONARY ARTERY CATHETER

The PAC has been associated with iatrogenic risks, including morbidity related to the process of central venous access and complications related to its indwelling, intrathoracic location.<sup>3</sup> Technical complications of placement have included arterial and venous hemorrhage, development of pneumothorax, atrial and ventricular arrhythmias, complete heart block, and air embolism.<sup>3</sup> The location of the PAC can predispose to iatrogenic injury, such as pulmonary artery rupture,<sup>46</sup> life-threatening hemoptysis, intravascular infection, venous thrombosis,<sup>47</sup> mural thrombus, endocarditis,<sup>48</sup> and pulmonary infarction among others.<sup>3</sup> Within the setting of a randomized controlled trial, catheter-related complications were rare, occurring at a rate of 0.08 ± 0.01 per catheter inserted.<sup>20</sup>

Contrasting these findings, a systematic review of studies from 1970 to 1996 evaluated the effect of the PAC in terms of development of organ failure,<sup>49</sup> a major cause of death in ICU care. This research supported statistically significant reduced relative risk for 0.78 (95% CI, 0.65-0.94) associated with the use of the PAC when focusing on markers of morbidity. These findings, however, have not been replicated in subsequent systematic reviews or confirmed in recent randomized controlled trials.<sup>42,50</sup>

Based on epidemiologic data, trauma patients with low severity of injury appeared to have increased risk with PAC exposure. In contrast, PAC use was associated with survival benefit in high-risk subgroups (e.g., high severity score, high base deficits, or advanced age).<sup>51</sup> Differences in severity of illness and clinical outcomes associated with device use were also apparent because patients with Acute Physiology and Chronic Health Evaluation (APACHE) II scores less than 25 were found to have increased mortality with PAC exposure. Scores of 25 to 31 were shown to have a slight benefit, whereas those with scores higher than 31 were shown to have significantly lower mortality when a PAC was used to guide therapy.<sup>52</sup> These findings have not been replicated to date in prospective randomized controlled studies in trauma patients.

# SUPRANORMAL HEMODYNAMIC SUPPORT

The PAC has been a fundamental tool in the "supranormal" hemodynamic support. Historically, hemodynamic augmentation to supranormal values of cardiac output has been controversial. The rationale for this treatment strategy has targeted a hypothesis that increased systemic delivery of oxygen would be associated with reduction in multiple-organ failure, a major cause of death within intensive care. The meta-analysis of Heyland and associates, evaluating studies from 1980 to 1994, reported no significant overall benefits from strategies of increased cardiac output and systemic oxygen delivery to standard care with a relative risk for 0.86 (95% CI, 0.62-1.20<sup>53</sup>; see Table 43-4). Within this analysis, however, a subgroup of high-risk perioperative patients showed a significant reduction in relative risk of 0.20 (95% CI, 0.07-0.55) with preoperative initiation of a supranormal, hemodynamic prescription. Similarly, a subsequent meta-analysis of supranormal physiologic indices as defined by a cardiac index higher than 4.5 L/min/m<sup>2</sup> systemic oxygen delivery greater than  $600 \text{ L/min/m}^2$ , and systemic oxygen consumption greater than 170 L/min/m<sup>2</sup> added to the controversy.<sup>54</sup> Within this investigation, the overall mortality rate reduction with supraphysiologic support was modest (i.e.,  $-0.05 \pm 0.02$ ). Subgroup analyses of this study, however, supported significant reduction in mortality if subjects were exposed to PAC-directed, supranormal goals *before* the development of organ failure.

The randomized controlled trial of Hayes and associates compared supranormal goal-directed therapy, using dobutamine, to a control group of critically ill patients.<sup>55</sup> In contrast to the referenced meta-analyses, this study showed a significant increase in mortality associated with goaldirected therapy to achieve supranormal physiologic indices. The results of this clinical trial continue to support caution in the use of this strategy within high-risk patient populations.

# OPTIONS TO REPLACE THE PULMONARY ARTERY CATHETER

Less invasive ICU monitors are available that appear to contribute to bedside clinical assessment, offering validated measures of cardiac output and fluid responsiveness. Echocardiography, with its noninvasive characteristics, may play an increasing role in ICU care to achieve rapid diagnoses in the hemodynamically unstable patient.<sup>56</sup> Two recent randomized controlled trials that evaluated esophageal Doppler for short-term ICU and operating room resuscitation have supported reduction in morbidity indices.<sup>57,58</sup> Similarly, technology has evolved using measurements from arterial catheters (e.g., arterial waveform analysis<sup>59</sup> and lithium-based cardiac output)<sup>60</sup> as part of goal-directed therapy. A recent randomized controlled trial of these methods compared with standard of care showed significant reduction of perioperative morbidity.<sup>61</sup> To date, however, further research is required to assess whether these methods can improve survival in the critically ill and be readily incorporated into the processes of critical care.

# SHOULD PULMONARY ARTERY CATHETERS BE ELIMINATED FROM THE INTENSIVE CARE UNIT?

Clinicians must carefully consider the benefit-to-risk ratio in the routine use of the PAC. Whatever the flaws in these studies may be, a series of randomized controlled trials have been unable to demonstrate relevant clinical benefits. To date, the large randomized controlled trials have focused on broad, albeit relevant, patient populations. As such, they have been underpowered to detect differences in outcomes for specific patient groups in which PACs have been incorporated into long standing treatment algorithms (e.g., right ventricular myocardial infarction, heart transplantation, high-risk coronary artery bypass surgery). It remains plausible that there exist patient groups in whom management strategies guided by the PAC might improve clinical outcomes. In addition, mortality may not be the ideal outcome variable. For example, the study by Richard indicated a trend (p =.06) away from increased creatinine in patients treated with the PAC.<sup>42</sup> Thus, studies addressing other outcomes (e.g., renal failure) may be of value. Finally, a limitation of all meta-analyses is the dependency on the specific diagnostic methods of device use and the specific catheterguided treatment strategies addressed.

The causal relationship of exposure to the PAC and a specific clinical outcome is highly complex. For individual ICUs, the effect of PAC exposure on patient clinical outcomes can be affected by (1) the clinical indication for PAC insertion; (2) the experience of the clinical team (e.g., intensivists, other physicians, critical care nursing); (3) the availability and analysis of the data acquired from the PAC; (4) the incidence of catheter-related complications; and (5) the overall management protocol. Each of these covariates, as well as the potential for interaction in primary and secondary outcomes, must be considered in the analysis of clinical studies as well as general critical care practice. The referenced investigations have focused largely on (and have been powered to detect differences in) survival. The value of the PAC in the assessment of other clinical outcomes is unknown.

Based on the results of the systematic reviews to date, the *routine use* of the PAC appears justifiably controversial. Further, the effects of the clinical trend toward reduced frequency of PAC use<sup>32</sup> on device-related risk are not known but are potentially relevant with decreased cumulative experience among clinicians and nurses.

# CONCLUSION

During the past 60 years, the PAC has contributed significantly to the understanding of many critical illnesses. That said, the balance of published peer-reviewed data does not demonstrate that the routine use of the PAC contributes to patient survival or improved clinical outcomes. Based on these findings, all clinicians must carefully reflect on the use of this biomedical device in the care of the critically ill.

# **AUTHORS' RECOMMENDATIONS**

- The PAC, with its ability to measure intracardiac pressures, cardiac output, and indices of oxygen delivery, has played an important role in the evolution of critical care.
- The weight of the systematic reviews associated with PAC exposure have not demonstrated improved survival compared with control groups. This lack of beneficial effect appears to be a consistent finding involving relevant patient populations, including preoperative optimization for high-risk surgery, supportive care for high-risk surgery, ALI, sepsis, and congestive heart failure. The PAC has not been associated with reduction in ICU or hospital length of stay in the studies cited within this review.
- It remains plausible that there are patient populations or relevant clinical outcomes (outside of mortality and length of stay) for which the diagnostic capabilities of the PAC to guide treatment may be valuable. Further research is required to support these hypotheses.

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# 44

# How Does One Diagnose and Manage Acute Myocardial Ischemia in the Intensive Care Unit?

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Intensivists face several challenges when critically ill patients present with myocardial ischemia or infarction. Patients may be admitted to the intensive care unit (ICU) with a primary diagnosis of cardiac injury. In other hospitalized patients, underlying atherosclerosis and noncardiac stresses such as hemorrhage, mechanical ventilation, and sepsis can precipitate a myocardial insult. A meta-analysis of patients in the ICU found elevated troponin levels in 12% to 85% of critically ill patients with a median frequency of 43%.<sup>1</sup> Although the incidence of myocardial injury, defined by elevations in troponin levels, is high, it is often unrecognized.<sup>1–3</sup> This chapter reviews the diagnosis, assessment, and management of critically ill patients with myocardial ischemia or infarction.

# **DIAGNOSIS: BIOMARKERS**

The diagnosis of myocardial infarction has been recently redefined to emphasize etiology and requires a troponin elevation above the 99th percentile of normal with at least one of the following criteria: ischemic ST- and T-wave changes, new left bundle branch block, new Q waves, percutaneous coronary intervention (PCI)-related marker elevation, or imaging suggestive of a new loss of viable myocardium.<sup>4</sup> In the setting of sudden death, myocardial infarction is diagnosed without an elevated troponin if ST-segment elevation, new left bundle branch block, evidence of fresh thrombus at angiography or autopsy, or new loss of viable myocardium occurs. Increases in biomarker levels of 3  $\times$  99th percentile for PCI and 5  $\times$  99th percentile for coronary artery bypass graft (CABG) also characterize myocardial infarction (Table 44-1).<sup>4,5</sup> The definition of myocardial infarction does not include myocyte necrosis from mechanical injury, which may occur in the setting of CABG or from myocardial cell death from etiologies such as sepsis, chest trauma, or cardioversion.<sup>4</sup>

Ischemia results when there is inadequate oxygen supply from coronary artery blood flow to satisfy the oxygen demands of the myocardium. Myocardial infarction can occur in the setting of coronary artery thrombus, inflammation, dissection, and plaque erosion or rupture.<sup>5</sup> Electrocardiogram (ECG) changes and historical symptoms such as angina, dyspnea, diaphoresis, nausea, syncope, and jaw, upper extremity, and epigastric discomfort may characterize myocardial ischemia. Ischemia often is accompanied by a failure in myocardial contractility that results from myocardial necrosis, stunning, or hibernation. A stunned myocardium occurs after coronary occlusion and produces regional wall motion abnormalities for hours or days despite reperfusion. Hibernation is an adaptive response to chronically reduced coronary blood flow and describes decreased myocardial contractility, a "self-preserving" mechanism to minimize ischemia or necrosis. After prolonged ischemia, myocardial infarction occurs, and an elevation in cardiac troponin will be seen.

When myocardial necrosis occurs, proteins such as cardiac troponins T and I, creatine phosphokinase (CPK), myoglobin, and lactate dehydrogenase (LDH) are released into the circulation. Because of their sensitivity and specificity, the rise and fall of troponin levels are the preferred biomarkers for the evaluation of myocardial injury. If troponin testing is not available, CK-MB measurements are the best alternative biomarker.<sup>4</sup> Troponin levels should be drawn at the onset of symptoms and 6 to 9 hours later to evaluate the enzyme's rise and fall. Occasionally, the patient may require a blood sample 12 to 24 hours later if the initial troponin evaluation was normal and the clinical suspicion for cardiac ischemia was high.<sup>4</sup> Troponin T and I are generally equivalent, except in patients with chronic kidney disease, in which troponins may stay elevated from impaired clearance. In patients with end-stage renal disease, an increase in troponin T without evidence of myocardial necrosis is more common than an increase in troponin I. Nevertheless, an increase in troponin T in the setting of renal failure is associated with an increased morbidity.

In critically ill patients with and without acute coronary syndromes, an elevated troponin level has been associated with increased mortality.<sup>1,6–9</sup> A rise in troponin values, however, does not indicate the mechanism of

# Table 44-1 Clinical Classification of Different Types of Myocardial Infarction

## TYPE 1

 Spontaneous myocardial infarction related to ischemia due to a primary coronary event such as plaque erosion and/ or rupture, fissuring, or dissection

# TYPE 2

 Myocardial infarction secondary to ischemia due to either increased oxygen demand or decreased supply, such as coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension

# TYPE 3

 Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, new left bundle branch block, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood

## **TYPE 4A**

• Myocardial infarction associated with percutaneous coronary intervention

## TYPE 4B

• Myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy

# TYPE 5

 Myocardial infarction associated with coronary artery bypass graft

From Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. J Am Coll Cardiol. 2007;50:2173-2195.

injury. Therefore, in the absence of ischemic features, elevations in troponin levels should prompt clinicians to search and examine their patients for nonischemic etiologies of myocardial injury. Many disease processes, such as sepsis, tachycardia, congestive heart failure, renal failure, pulmonary embolism, pulmonary hypertension, chemotherapy, burns, extreme exertion, and stroke are associated with an increase in troponin.<sup>4</sup> In sepsis, altered myocyte permeability may release troponin into the circulation and increase intracellular calcium. Direct myocardial injury from cytokine-mediated responses have been implicated in sepsis-induced myocardial depression.<sup>10–13</sup> Clinically, myocardial depression from sepsis is a reversible process that does not require revascularization.

An elevated troponin is often a result of myocardial injury, and its presence can provide the practitioner with insight into the severity of a patient's illness. Troponin levels have emerged as a marker of outcome in the ICU. In the ICU, however, it is critical to distinguish between elevated troponins as a marker of acute myocardial injury and as a reversible, treatable, and independent predictor of outcome.

Measurement of brain natriuretic peptide (BNP) in acute coronary syndrome (ACS) may have prognostic

value. An elevation in plasma BNP after ACS is associated with recurrent myocardial infarction, worsening heart failure, and death.<sup>14</sup>

# DIAGNOSIS: ELECTROCARDIOGRAPHY

Ordering an ECG is essential in patients with suspected cardiac ischemia or infarction. ECG findings such as the evolution of ST-segment abnormalities and Q waves can provide essential information regarding the duration, size, and location of injury. Characteristic features of myocardial ischemia and infarction are listed in Tables 44-2 and 44-3. When inferior myocardial infarction is suspected, a right-sided ECG should be recorded to evaluate right ventricular infarction.

ECGs should be interpreted in the context of troponin values because patients in the ICU may have conditions such as early repolarization, pericarditis, myocarditis, ventricular hypertrophy, hypokalemia, cholecystitis, tachycardia, and digitalis effect that may cause ECG changes without biomarker evidence of ischemia.<sup>4</sup>

Ordering an echocardiogram in the setting of myocardial ischemia provides diagnostic and prognostic information and detects complications. The diagnostic use of echocardiography is recommended in cases in which acute ischemia is not detected by standard means despite

# Table 44-2 Electrocardiographic Manifestationsof Acute Myocardial Ischemia in the Absenceof Left Ventricular Hypertrophy and LeftBundle Branch Block

## ST ELEVATION

• New ST elevation at the J-point in two contiguous leads with the cut-off points: ≥0.2 mV in men or ≥0.15 mV in women in leads V2 to V3 and/or ≥0.1 mV in other leads

## ST DEPRESSION AND T-WAVE CHANGES

• New horizontal or down-sloping ST depression ≥0.05 mV in two contiguous leads and/or T inversion ≥0.1 mV in two contiguous leads with prominent R wave or R/S ratio >1

From Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. J Am Coll Cardiol. 2007;50:2173-2195.

# Table 44-3 Electrocardiographic Changes Associated with Prior Myocardial Infarction

- Any Q-wave in leads V2 to V3  ${\geq}0.02$  sec or QS complex in leads V2 and V3
- Q-wave ≥0.03 sec and ≥0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4 to V6 in any two leads of a contiguous lead grouping (I, aVL,V6; V4 to V6; II, III, and aVF)\*
- R wave ≥0.04 sec in V1 to V2 and R/S ≥1 with a concordant positive T wave in the absence of a conduction defect

<sup>\*</sup>The same criteria are used for supplemental leads V7 to V9 and for the Cabrera frontal plane lead grouping.

From Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. J Am Coll Cardiol. 2007;50:2173-2195.

a high suspicion. The presence of left ventricular (LV) dysfunction or mitral regurgitation after myocardial infarction is an adverse prognostic finding. After myocardial infarction, echocardiography can detect complications such as residual ischemia, ventricular septal defects, papillary muscle rupture or dysfunction, free wall rupture, regurgitant lesions, LV thrombus, or tamponade.<sup>15</sup> Radionuclide ventriculography, myocardial perfusion scintography (MPS), and magnetic resonance imaging (MRI) are techniques that assess the viability of myocardial tissue and can characterize the extent of injury.<sup>4</sup>

Mechanically ventilated patients, particularly those who are chronically critically ill, often will undergo prolonged periods of ventilator weaning. A small prospective study found that myocardial ischemia detected by continuous ECG monitoring is common in patients requiring prolonged mechanical ventilation. Further, evidence of ischemia increased the risk for remaining ventilator dependent.<sup>16</sup> In mechanically ventilated patients with risk factors for coronary artery disease, myocardial ischemia detected by ST-segment analysis was noted in 24% of patients. In this patient population, the interruption of sedation was not associated with an increased occurrence of myocardial ischemia.<sup>17</sup> Therefore, ST-segment monitoring is encouraged during weaning from mechanical ventilation and a reduction in sedative infusions in patients with coronary artery disease is not contraindicated if needed to facilitate liberation from mechanical ventilation.

Diagnosing myocardial ischemia and infarction amenable to coronary intervention in the ICU can be difficult and challenging. Critically ill patients often are intubated and sedated and unable to communicate regarding ischemic symptoms. In addition, analgesia and sedation may mask symptoms of ischemia.<sup>18</sup> Because troponin levels may be elevated in ICU patients for a variety of reasons other than myocardial ischemia, biomarker evaluation is uncertain. In addition, imaging studies such as transthoracic echocardiography may be inadequate in the setting of positive-pressure ventilation, obesity, chronic obstructive pulmonary disease, chest tubes, and thoracic bandages. The use of contrast echocardiography, harmonic imaging and transesophageal echocardiography can improve the adequacy images obtained in critically ill patients.<sup>19</sup>

# MANAGEMENT: PATHOPHYSIOLOGIC BASES

The management of myocardial ischemia in critically ill patients is guided by the multifaceted nature of the problem and involves amelioration of inciting conditions such as hypoxemia, anemia, pain, fever, stress, and increased work of breathing. Supportive measures, hemodynamic control, and interventions to improve or restore myocardial perfusion are the mainstays of therapy. The clinician should search for reversible problems such as anemia and surgical or gastrointestinal bleeding, undertake corrective measures, and consider cardiology consultation for possible revascularization.

Maintenance of adequate oxygenation is essential. In patients with respiratory distress or hypoxemia, supplemental oxygen should be administered to maintain oxygen saturation at more than 90% (American College of Cardiology and American Heart Association [ACC/AHA] 2007 Non–ST-Elevation Myocardial Infarction [NSTEMI] guidelines, class I, level B recommendation).<sup>5</sup> Oxygen saturation above this level may reduce heart rate. Although there is no clear evidence that oxygen helps in the absence of respiratory compromise, it is a low-risk intervention that minimizes the potential for under recognized hypoxemia. Assisted ventilation may be required to improve gas exchange and to decrease work of breathing in patients with respiratory distress.

Anemia leads to diminished oxygen delivery and increases myocardial work and oxygen demand. It has been associated with the development of ischemia as well as with a higher incidence of adverse cardiac events or death in patients with unstable angina and myocardial infarction. In observational studies, the risk increases with the progressive decrease of hemoglobin below 10 to 12 g/dL.<sup>20</sup> Control of bleeding and prevention of anemia are two important aspects of the management of ischemia. Blood transfusion, however, has been linked to increased risk for death.<sup>21</sup> A large randomized controlled trial in critically ill patients has suggested that restrictive transfusion practices decrease cardiopulmonary complications and improve outcomes.<sup>22</sup> In the absence of good randomized controlled trials specifically addressing the relationship among the degree of anemia, transfusion threshold, and outcomes in patients with ischemia, the optimal transfusion targets remain unclear. Patients in the ICU without significant cardiac disease are likely to benefit from a restrictive transfusion threshold of 7 to 8 g/dL of hemoglobin. A higher target for hemoglobin may be considered in patients with preexisting cardiac disease. Given the problems associated with both anemia and transfusion, clinicians should try to limit blood loss (especially unnecessary blood draws) in ischemic and anemic patients.

# MANAGEMENT: PHARMACOLOGIC APPROACHES

Adequate analgesia plays an important role in the management of ischemia in the ICU. Narcotics have been used to control angina as well as pain from other sources that may precipitate ischemia. Morphine also decreases the heart rate, peripheral vascular resistance, and myocardial wall stress by reducing left ventricular preload and can be beneficial in the setting of pulmonary edema. Animal and human studies have suggested a role for morphine in ischemic preconditioning and reduction in infarct size. The effects of morphine on hemodynamics, however, are variable, and significant hypotension and bradycardia may worsen myocardial perfusion.<sup>23</sup> Additional compromise can be caused by respiratory depression. A large observational study in patients with acute coronary syndrome demonstrated increased unadjusted and adjusted rates of death and myocardial infarction with the use of intravenous morphine.<sup>24</sup> No randomized controlled trials are available to guide the use of morphine in ischemia, and the ACC/AHA guidelines support its use for STelevation myocardial infarction (STEMI)<sup>25</sup> but advise

caution in patients with unstable angina or NSTEMI (ACC/AHA 2007 NSTEMI guidelines, class IIa, level B recommendation).<sup>5</sup>

Nonsteroidal anti-inflammatory drugs (NSAIDs), with the exception of aspirin, and selective cyclooxygenase-2 inhibitors should not be used in patients with ischemia because of the increased risk for thrombotic events, reinfarction, and death<sup>26,27</sup> (ACC/AHA 2007 NSTEMI guidelines, class III, level C recommendation).<sup>5</sup>

Nitroglycerin decreases left ventricular preload and left ventricular wall stress. At higher doses, it also reduces afterload. Nitroglycerin dilates coronary arteries, both those with stenosis and the collateral vessels to the ischemic regions. Nitrates should not be administered during absolute or relative hypotension. If ischemia is not improved through sublingual or transdermal nitroglycerin, intravenous infusion can be started. Nitrate use in ischemia is based on observational data, but randomized trials demonstrate only a varying mortality benefit in myocardial infarction.<sup>28</sup> Meta-analysis of the trials supports some clinical utility.<sup>29</sup> Subsequent randomized controlled trials of therapies in ischemia have not reaffirmed the strength of the evidence for the use of nitrates. In the absence of a well-designed study of the effects of this class of medications, nitroglycerin continues to be a first line of therapy of ischemia (ACC/AHA 2007 NSTEMI guidelines, class I, levels B and C recommendation).<sup>5</sup>

β-Blockers decrease heart rate, contractility, and blood pressure, thus reducing cardiac work and oxygen consumption. The reduction in cardiac events and mortality with early administration of  $\beta$ -blockers during unstable angina and myocardial infarction has been supported by some randomized trials and meta-analyses and questioned by others.<sup>30–33</sup> Pooled analysis of several studies indicates that β-blockers reduced short-term mortality in patients with acute coronary syndromes who had PCI.<sup>34</sup> However, in patients with hemodynamic instability or with risk factors for heart failure such as low output state, low blood pressure, high heart rate, or older age, β-blockers may increase the risk for cardiogenic shock and should be used judiciously or avoided.<sup>35</sup> This class of medications should be used cautiously in patients with reactive airway disease and are best avoided in asthmatics<sup>36,37</sup> as well as in patients with significant atrioventricular (AV) block. Delayed administration of β-blockers as a secondary prevention measure in patients with LV dysfunction reduces mortality and reinfarction rate. A recent randomized controlled trial of carvedilol compared with placebo in addition to standard medical therapy in patients with LV dysfunction 3 to 21 days after myocardial infarction demonstrated reduced all-cause mortality and nonfatal myocardial infarction without significant increase in the incidence of shock.<sup>38</sup> During noncardiac surgery, β-blockers have the potential to reduce perioperative cardiac events as suggested in cohort studies, randomized controlled trials, and meta-analyses; however, recent trials and systematic reviews have challenged the presence and the magnitude of these effects.<sup>39-41</sup> The benefits appear significant mostly in high-risk patients. ACC/AHA 2007 NSTEMI guidelines classify use of oral β-blockers as class I, level B recommendation and intravenous use as class IIa, level B recommendation.<sup>5</sup>

Calcium channel blockers include agents with varying hemodynamic effects. The evidence from trials and meta-analyses supports the use of drugs with negative chronotropy such as verapamil and diltiazem.<sup>42,43</sup> In the setting of ischemia, they reduce myocardial oxygen demand by decreasing heart rate, contractility, and afterload along with arterial dilation resulting in improvement of coronary blood flow. Calcium channel blockers control tachyarrhythmias and are helpful when β-blockade is contraindicated. However, they should be avoided in patients with LV dysfunction and used cautiously in patients with decreased AV conduction. Short-acting dihydropyridines (e.g., nifedipine), on the other hand, have been associated with increased adverse events, especially when used without concomitant β-blockade.44 ACC/AHA 2007 NSTEMI guidelines classify use of nondihydropyridine calcium channel blockers as a class I, level B recommendation in lieu of  $\beta$ -blocker and as a class IIa, level C recommendation along with β-blocker.<sup>5</sup>

Angiotensin-converting enzyme (ACE) inhibitors improve blood pressure control and ventricular remodeling and reduce the death rate in high-risk patients with ischemia and myocardial infarction. The benefit is particularly evident in patients with LV dysfunction and heart failure after myocardial infarction.<sup>45</sup> ACE inhibitors should be used orally in the acute setting and avoided in the presence of hypotension. Similar effects are noted with angiotensin-receptor blockers (ARBs), which can be used when ACE inhibitors are contraindicated. ACC/AHA 2007 NSTEMI guidelines classify use of ACE inhibitors and ARBs as a class I, level A recommendation in the setting of LV dysfunction.<sup>5</sup>

Antiplatelet agents such as aspirin, alone or with anticoagulation therapy, reduce the risk for death or myocardial infarction in patients with ischemia and should be administered unless significant bleeding risk from gastrointestinal, intracranial, or other source exists.46-48 Withdrawal of aspirin therapy, used for primary or secondary prevention in patients with coronary artery disease, has increased the incidence of cardiovascular adverse events. Interruption of drug therapy should be avoided, and it should be restarted as soon as bleeding risk has been reduced, particularly in the perioperative period.<sup>49</sup> The use of aspirin according to the ACC/AHA 2007 NSTEMI guidelines is a class I, level A recommendation.<sup>5</sup> Other antiplatelet agents are the adenosine diphosphate (ADP)-receptor antagonists, the thienopyridines ticlopidine and clopidogrel. They are useful alone or in conjunction with aspirin for the treatment of unstable angina and myocardial infarction and result in decreased cardiovascular death and myocardial infarction<sup>50-52</sup> (ACC/AHA 2007 NSTEMI guidelines, class I, level A recommendation).<sup>5</sup> Clopidogrel has a more favorable side-effect profile than ticlopidine. These agents increase the risk for minor and major bleeding. Inconsistency in the platelet inhibition with clopidogrel and clopidogrel resistance have been observed in some patient subgroups. A new platelet inhibitor, prasugrel, has been approved by the FDA and it has higher and more consistent level of platelet inhibition, faster onset and less metabolic variability, along with higher risk of bleeding complications.<sup>53</sup> The benefits of prasugrel have been noted in diabetic patients in particularly; whereas in patients

older than 75 years or wit weight less than 60 kilograms the benefits are not evident and the bleeding risk is higher.<sup>53</sup> The focused update of the ACC/AHA guidelines on STEMI and PCI recommends the use of the prasugrel as alternative to clopidogrel in the setting of acute coronary syndrome and PCI.<sup>54</sup> In critically ill patients, the potential benefits should be weighed against the associated risk, especially in the perioperative setting. Double antiplatelet therapy (DAT) with aspirin and thienopyridine after PCI reduces the incidence of major cardiovascular events. Patients with preexisting coronary stents warrant special consideration. The presence of bare-metal stents requires 1 month of uninterrupted DAT while drug-eluting stents require at least 12 months of such therapy. The 2009 ACC/AHA guideline update suggests a consideration for continuation of DAT past 15 months for drug – eluding stents (class IIb, level C recommendation).<sup>54</sup> Premature discontinuation of therapy has led to a higher rate of stent thrombosis and fatal myocardial infarction. Therefore, therapy should be discontinued only in the case of significant bleeding risk.<sup>55,56</sup> An intravenous glycoprotein IIb/IIIa inhibitor added to a thienopyridine may be beneficial if an invasive coronary intervention is planned (ACC/AHA 2007 NSTEMI guidelines, class I, level A recommendation).<sup>5</sup> Additional issue in patients on DAT is the evidence of attenuation of the antiplatelet activity of clopidogrel and, to lesser degree prasugrel, by proton-pump inhibitors (PPI), in particularly omeprazole, since critically ill patients often are administered these mediations for prophylaxis and treatment of gastric ulcer disease.<sup>57</sup> There are no indications for such attenuation by other classes of mediations suppressing the gastric acid secretion such as histamine 2 blockers; therefore, in critically ill patients on thienopyridine therapy when gastric acid suppression is indicated, alternatives to PPI may need to be considered and the benefits of antisecretory drugs should be weighed against the risk of coronary events.

Anticoagulation is an essential aspect of the therapy for ischemia and myocardial infarction. The available agents range from unfractionated heparin (UFH) and factor Xa inhibitors such as low-molecular-weight heparin (LMWH) and fondaparinux to the direct thrombin inhibitors (DTIs) argatroban and bivalirudin. The initiation of anticoagulation should be strongly considered in critically ill patients with unstable angina and myocardial infarction. However, the benefits should be weighed against the risk for bleeding, particularly in the perioperative setting. No particular anticoagulation regimen has been proved superior, and the choice should be guided by the bleeding hazard related to the drug pharmacokinetics, pharmacodynamics, and reversal ability as well as the risk for heparin-induced thrombocytopenia (HIT).<sup>58–60</sup> DTI are generally reserved for use in patients with HIT or prior use of UFH, but bivalirudin can be considered as acceptable alternative to UFH for primary PCI intervention according to the 2009 ACC/ AHA guideline update (class I and IIa).<sup>54</sup> ACC/AHA 2007 NSTEMI and STEMI guidelines classify anticoagulation agents as a class I, level A recommendation.<sup>5,24</sup>

Statins decrease myocardial infarction, stroke, and cardiovascular mortality. In patients with acute coronary syndromes, early aggressive statin therapy may reduce unstable angina and reinfarction. Therefore, these medications should be considered when PCI is indicated.<sup>61–63</sup> Patients in the ICU may already be taking statins. Prolonged withdrawal should be avoided because adverse effects have been shown in surgical ICU patients.<sup>64,65</sup> Other studies have suggested that statins may or may not be protective against renal, pulmonary, and multiorgan failure.

Other investigational drugs may prove useful in the future. Atrial natriuretic peptide in a randomized controlled trial decreased infarct size and improved long-term ejection fraction in patients with acute myocardial infarction who had revascularization. However, this drug was associated with a higher incidence of severe hypotension. A trial of the adenosine triphosphate (ATP)-sensitive potassium channel opener nicorandil demonstrated improved long-term ejection fraction but did not affect infarct size.<sup>66</sup> The calcium sensitizer levosimendan had positive inotropic effects and arterial and venous vasodilatory properties. It improved preload, contractility, and afterload without increasing oxygen consumption. In a small randomized controlled trial of patients with or without cardiogenic shock after acute myocardial infarction and revascularization, levosimendan significantly improved hemodynamics and coronary flow reserve compared with placebo or dobutamine.67,68

Severe hyperglycemia worsens outcomes in critically ill patients. In diabetic and nondiabetic patients with acute coronary syndrome, hyperglycemia was associated with cardiovascular complications and increased incidence of mortality, effects consistently seen in the setting of PCI.69-71 Tight glycemic control with insulin infusions has become a prevalent intervention in the contemporary ICU and has important benefits in the management of ischemia. The target glucose range at which the maximal benefits are realized while avoiding the risk for hypoglycemia remains to be determined. In a trial of intensive insulin therapy, a protocol used 80 to 110 mg/dL as a target range,<sup>72</sup> whereas others have aimed to keep blood glucose less than 200 mg/dL. Recent multicenter trials have failed to demonstrate the benefits of tight glucose goal of 80 to 110 mg/dL, while finding increased risk for hypoglycemia with this goal.73-74 In the 2009 focused update on the ACC/AHA STEMI guidelines, the previous recommendations for insulin infusion to normalize blood glucose in STEMI have been replaced with recommendations for use of insulin-based regimen to maintain blood glucose under 180 mg/dL while avoiding hypoglycemia (class IIa, level B).<sup>54</sup>

Therapy interventions according to the level of efficacy in the 2007 ACC/AHA NSTEMI<sup>5</sup> and STEMI<sup>25</sup> guidelines are summarized in Table 44-4.

# MECHANICAL SUPPORT AND CORONARY REVASCULARIZATION

In patients with acute ischemia with hemodynamic instability, intra-aortic balloon pump counterpulsation can be used for circulatory support during revascularization<sup>75</sup>

American College of Cardiology Non–ST Elevation a	nd ST Elevation Myocardial Infarction Guidelines
Class I (benefit significantly outweighs risk; intervention is indicated and should be done)	Oxygen in hypoxia Nitroglycerin sublingual or intravenous β-Blocker orally Long-acting nondihydropyridine calcium channel blocker as β-blocker alternative ACE inhibitor or ARB orally with LV dysfunction Discontinue NSAID Aspirin Antiplatelet agents: thienopyridine (±glycoprotein IIb/IIIa inhibitor) Anticoagulation Maintenance of blood glucose <180 mg/dL with insulin-based regimen, avoidance of hypoglycemia
Class IIa (benefit outweighs risk; additional focused studies are needed; intervention is reasonable and can be beneficial)	<ul> <li>Oxygen in all ischemia</li> <li>Morphine</li> <li>β-Blocker IV</li> <li>Long-acting nondihydropyridine calcium channel blocker in addition to β-blocker alternative</li> <li>ACE inhibitor or ARB orally without LV dysfunction</li> <li>IABP</li> <li>Glycoprotein IIb/IIIa inhibitor</li> <li>Anticoagulation</li> </ul>
Class IIb (benefit may outweigh risk; further studies are needed and may be considered; effectiveness is uncertain)	Extended-release nondihydropyridine calcium channel blocker Immediate-release dihydropyridine calcium antagonists with adequate β-blockade
Class III (risk outweighs benefit; not recommended and may be harmful)	Nitrates in hypotension, tachycardia or bradycardia, or along with phosphodiesterase inhibitor for erectile dysfunction Immediate-release dihydropyridine calcium antagonists without adequate β-blockade ACE inhibitor IV NSAID

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; IABP, intra-aortic balloon pump; LV, left ventricular; NSAID, nonsteroidal antiinflammatory drug.

(ACC/AHA 2007 NSTEMI and STEMI guidelines, class IIa, level C recommendation).<sup>5,2</sup>

The decision to proceed with invasive interventions aimed at revascularization in addition to medical management is best done with the assistance of a cardiology consult. In the cardiology setting, patients with unstable angina and NSTEMI who have refractory angina despite optimal medical therapy or patients with hemodynamic instability benefit from early invasive strategy. Survival and quality of life improved with early invasive therapy compared with conservative management in stabilized patients as well.<sup>76,77</sup> ACC/AHA 2007 NSTEMI<sup>5</sup> and STEMI<sup>25</sup> guidelines classify early invasive therapy as class I, levels A and B recommendation. Invasive intervention should be avoided in patients with significant comorbidities in whom the risks for performing such intervention outweigh the potential benefits. Many patients in the ICU are in a state of acute decompensation and therefore may not be suitable candidates for invasive intervention. In the perioperative setting, the bleeding risk often precludes the institution of aggressive anticoagulation needed for revascularization.

# AUTHORS' RECOMMENDATIONS

- · Troponin elevations are common in ICU patients. Although not always due to myocardial ischemia or infarction, such elevations are associated with poor outcome.
- Electrocardiography and imaging studies may further define pathophysiology and assist in prognosis.
- Pharmacologic therapy of myocardial ischemia and infarction includes  $\beta$ -blockade, statin therapy, and aspirin.
- · Although acute coronary revascularization may occasionally be performed, in most ICU patients, comorbidities, contraindications, and instability usually preclude acute CABG or PCI.

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# Table 44-4 Recommendation for Interventions According to the 2007 American Heart Association

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# How Is Cardiogenic Shock Diagnosed and Managed in the Intensive Care Unit?

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Cardiogenic shock (CS) is defined as an inability of the heart to provide adequate blood flow to maintain the metabolic demands of tissue despite adequate intravascular volume. This definition, and similar variants, has been used for decades in numerous textbooks despite its inherent vagaries. For practical purposes, most would agree that CS exists when patients exhibit sustained hypotension with evidence of impaired cardiac function. With few exceptions, CS is an emergency that requires prompt diagnosis and appropriate therapy. This chapter reviews how to best diagnose and manage CS in the intensive care unit (ICU).

# EPIDEMIOLOGY AND ETIOLOGY

Although there are a plethora of theoretical causes of CS in the ICU (Table 45-1), the most frequent cause of CS in the ICU is acute coronary syndrome (ACS) resulting in left ventricular dysfunction.<sup>1,2</sup> Autopsy studies have shown that more than 40% of left ventricular myocardium must be sacrificed for CS to ensue.<sup>3,4</sup> Other relatively common causes, usually as a result of acute myocardial infarction (AMI), include acute mitral regurgitation, cardiac tamponade (from ventricular free wall rupture), and ventricular septal rupture.<sup>5</sup> CS occurs in 8.6% of patients sustaining ST-elevation myocardial infarction (STEMI) and in roughly 2.5% of patients with sustained non-ST-elevation myocardial infarction (NSTEMI).<sup>6,7</sup> Rarely, drugs have been shown to incite CS. In the Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT), the incidence of CS was 5% in patients receiving early metoprolol (roughly 30% greater than those who did not receive metoprolol).<sup>8</sup> Finally, all of the above scenarios incite an acute inflammatory response that augments the initial insult and results in a vicious cycle that, if left untreated, culminates in death (Fig. 45-1).<sup>9</sup> A large, recently published trial gives insight into the mortality rate of patients having sustained STEMI.<sup>10</sup> Overall mortality rates for all patients were 7.8% at 7 days and 9.9% over 30 days. However, for those patients who sustained STEMI with CS (6.5% of the population), the mortality rate was 68% over 30 days. Although this trial took place outside of the United States, it certainly emphasizes the profound effect that CS has on mortality. Studies within the United States have confirmed such an effect.<sup>11–13</sup> Recent evaluation of mortality trends within the United States, however, reveals that a changing management scheme has decreased the mortality of this disease significantly (60.3% in 1995 versus 47.9% in 2004).<sup>6</sup> Although this change in mortality is undoubtedly multifactorial, few would argue that an increased rate of cardiac catheterization (51.5% in 1995 versus 74.4% in 2004) and of percutaneous cardiac intervention (27.4% in 1995 versus 54.4% in 2004) had a major impact. Of note, during this registry period (that included more than 250,000 patients in more than 750 U.S. hospitals), there was no change in the use of intra-aortic balloon pumps (IABPs, 39%) or in immediate coronary artery bypass graft (CABG) surgery (3%).

# DIAGNOSIS

What is evident from almost all studies is that rapid diagnosis of CS is imperative if one wants to treat promptly and decrease mortality. Hemodynamic criteria consistent with a diagnosis of CS include sustained ( $\geq$ 30 minutes) hypotension with systolic blood pressure less than 90 mm Hg, depressed cardiac index (<2.2 L/min/m<sup>2</sup>), and elevated pulmonary artery occlusion pressure (PAOP, >15 mm Hg).<sup>14</sup> From the aforementioned indices, it would appear that one should be able to rapidly identify this entity if cardiac index (CI) is known. However, many patients with CS develop a distributive shock, lowering their systemic vascular resistance (SVR) and normalizing their CI.<sup>15</sup> Thus, it is necessary that the clinician have a systematic method of diagnosing CS.

In the absence of more objective data, a critically ill patient in shock usually has hypovolemia, sepsis, pulmonary embolism, or myocardial ischemia. As with most ailments, diagnosis begins with the physical examination. Often, the diagnosis can be made simply by placing one's hands on the patient's extremities. Frequently, CS manifests with cold and clammy extremities as the body attempts to maintain adequate perfusion to vital organs by peripheral vasoconstriction. With impaired myocardial contraction, auscultation of the lungs frequently reveals crackles due to an elevated left ventricular end-diastolic pressure (LVEDP) with exudate filling the pulmonary

## Table 45-1 Causes of Cardiogenic Shock

## ACUTE MYOCARDIAL INFARCTION

- Pump failure
  - Large infarction
  - Smaller infarction with preexisting left ventricular dysfunction
  - Infarction extension
- Severe recurrent ischemia
- Mechanical complications
  - Acute mitral regurgitation caused by papillary muscle rupture
  - Ventricular septal defect
  - Free-wall rupture
  - Pericardial tamponade
- Right ventricular infarction

## OTHER CONDITIONS

- · End-stage cardiomyopathy
- Myocarditis
- Myocardial contusion (blunt cardiac injury)
- Prolonged cardiopulmonary bypass
- Septic shock with myocardial depression
- Aortic stenosis
- Left ventricular outflow tract obstruction
- Obstruction to left ventricular filling (e.g., mitral stenosis)
- Acute aortic insufficiency
- Pulmonary embolism
- Pheochromocytoma

interstitium. Obviously, however, most physical examination findings, although supportive of a diagnosis, are nonspecific. Therefore, additional information is frequently needed. A chest radiograph should be ordered in any patient presenting with symptoms of shock. Signs of interstitial edema (often in the absence of physical examination findings) are suggestive of CS. An electrocardiogram should be ordered and examined for signs of myocardial ischemia. If CS remains a consideration, cardiac enzymes should be sent.

Echocardiography is the test of choice to diagnose CS and should be ordered promptly. The sensitivity of this modality approaches 100%, whereas the specificity is roughly 95%.<sup>16,17</sup> If transesophageal imaging is unavailable, contraindicated, or too cumbersome, transthoracic echocardiography should be ordered. A quick examination should allow rapid assessment of any left or right ventricular dysfunction, new valvular regurgitation, pericardial effusion, and ventricular septal rupture.<sup>16</sup> Rapid availability of this imaging modality may preclude the need for further invasive monitors because pulmonary artery systolic pressure and PAOP can be estimated by Doppler echocardiography.<sup>18</sup> Precise physiologic parameters are frequently necessary both to diagnose and to manage patients with CS. Invasive monitoring is probably warranted if there are persistent signs of hypoperfusion despite adequate volume therapy. The American College of Cardiology and American Heart Association (ACC/ AHA) gives a class IIa (weight of evidence and opinion is in favor of usefulness and efficacy) recommendation for placement of a pulmonary artery catheter (PAC) in patients with CS.<sup>19</sup> PACs can aid in diagnosis and can be helpful with subsequent management, although data showing a mortality benefit are equivocal.<sup>20-22</sup> There are data to suggest that certain calculated indices, such as cardiac power and stroke work index, may have short-term prognostic value.<sup>23</sup> Interpretation of PAC data requires a detailed knowledge of pathophysiology. A quick look at the numbers will rarely yield the diagnosis. Most causes of cardiogenic shock result in elevated central venous and pulmonary arterial pressures (the exception being isolated right ventricular ischemia). To differentiate the various causes, a detailed understanding of the various waveforms is necessary.



Figure 45-1. Vicious cycle of cardiogenic shock. iNOS, inhaled nitric oxide synthase; LVEDP, left ventricular end-diastolic pressure; NO, nitric oxide; SVR, systemic vascular resistance. (From Antman EM, Braunwald E. Acute myocardial infarction. In: Braunwald ED, Fauci E, Kasper D, eds. Harrison's Principles of Internal Medicine, 15th ed. New York: McGraw-Hill; 2001:1395.)

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**Figure 45-2.** Components of the central venous pressure (CVP) waveform. ECG, electrocardiogram.

The central venous pressure (CVP) is probably the most underused physiologic parameter. A plethora of information can be obtained with proper analysis. To interpret the various waves, the scale must be set so that all portions of the wave can be seen (usually a scale with 20 to 30 mm Hg maximum is optimal). The various components of the CVP can be seen in Figure 45-2. By breaking the waveform into various cardiac events, it becomes apparent that not all elevated venous pressures are equal. Cardiac tamponade will cause a monophasic CVP with a very small *x*-descent, whereas right ventricular ischemia with tricuspid regurgitation will yield a very large, fused c-v wave. The c-v wave is a fused 'c' and 'v' wave resulting from severe tricuspid regurgitation. Because of the regurgitant flow, there is an inability to differentiate the slight increased atrial pressure generated from closure of the tricuspid valve and atrial filling during atrial diastole. A complete analysis of CVP waveform is beyond the scope of this chapter, and the reader is referred to other texts.<sup>24,25</sup>

The equivalent CVP for the left side of the heart is the PAOP. Similarly, by correctly identifying the waves and translating this into a portion of the cardiac cycle, various pathologies become unmasked.<sup>26–28</sup> Acute mitral regurgitation is associated with very large V waves on PAOP. Acute cardiac ischemia often first manifests as left ventricular diastolic dysfunction. This, in turn, leads to a higher left ventricular end-diastolic volume (LVEDV) that causes an elevated LVEDP. Although this culminates in an elevated PAOP, by evaluating the waveform, an exaggerated A wave is consistent with diastolic dysfunction.

# MANAGEMENT: AN EVIDENCE-BASED APPROACH

Management of CS should focus on augmentation of oxygen delivery and blood pressure to maximize tissue perfusion. A delay in diagnosis or therapy will have a direct impact on mortality. Management of CS can be pharmacologic therapy, mechanical therapy, or revascularization.

# Pharmacologic Therapy

It should be stated at the outset that there have been no large controlled trials evaluating the efficacy of different vasopressor or inotrope therapies in CS.

Initial treatment for patients with CS should focus on restoration of normal hemodynamics, oxygenation, and avoidance of arrhythmia. In patients without significant pulmonary edema, it is reasonable to administer a fluid challenge before vasopressor therapy. If pulmonary edema is present or there is no response to a fluid challenge, pharmacologic therapy should be initiated. Pharmacologic therapy for CS initially should focus on those compounds that have both inotropic as well as vasopressor activity.<sup>29,30</sup> Drugs to consider as first-line treatment include norepinephrine, dopamine, dobutamine, epinephrine, and phenylephrine. There is some evidence, however, that dopamine administration for CS may in fact increase mortality<sup>31</sup>; however, this has not been validated in randomized controlled studies. Additionally, in patients with heart failure, a 2002 meta-analysis showed a trend (not statistically significant) with increased mortality in patients given adrenergic inotropic agents.<sup>32</sup> Part of the reason for these observations may be that the improved hemodynamics seen with these agents come at a cost of increased myocardial oxygen consumption. More recently, vasopressin was used in place of norepinephrine and showed similar hemodynamic effects.<sup>33</sup> Although phosphodiesterase inhibitors (e.g., milrinone) may be considered (particularly with right ventricular dysfunction), the resultant decrease in SVR is often not well tolerated by the hemodynamically unstable patient. Finally, levosimendan, an investigational calcium sensitizer that also promotes coronary vasodilation, continues to show promise as a novel treatment for CS.<sup>34–36</sup> These studies highlight the need for randomized controlled trials to confirm the efficacy of one therapy over another. In general, maintenance of normal physiologic parameters (e.g., mean arterial pressure, cardiac index) should be the goal. Although high-dose vasopressors have been associated with poorer survival, this finding may be an epiphenomenon representing only those patients who present with greater hemodynamic instability.37

# Mechanical Therapy

In patients who are unresponsive to conventional pharmacologic therapy, mechanical augmentation of flow may be of benefit. The ACC/AHA guidelines give placement of an intra-aortic balloon pump (IABP) a class I recommendation.<sup>19</sup> The only randomized trial to evaluate the efficacy of IABP (with or without thrombolysis) in patients with CS was able to show a dramatic decrease in 6-month mortality rate (39% versus 80%; P < .05) in patients with severe shock who received an IABP.<sup>38</sup> Nonrandomized trials also have shown decreased mortality. However, the use of this device is frequently associated with more aggressive therapies such as revascularization.<sup>39</sup> One of the inherent benefits of IABP counterpulsation devices is that they can be placed at the bedside to augment diastolic pressure as well as reduce left ventricular afterload (without increasing myocardial oxygen demand). The incidence of major complications (e.g., arterial injury and perforation, limb ischemia, visceral ischemia) with IABP insertion is 2.5% to 3.0%.<sup>39,40</sup> If an IABP is contraindicated (e.g., severe aortic insufficiency, severe peripheral vascular disease, aortic aneurysm and dissection) or unavailable, or the patient is unresponsive to its effects, ventricular assist device (VAD) placement may be considered.<sup>41,42</sup> A variety of other devices, including institution of extracorporeal membrane oxygenation (ECMO) and placement of the CardioWest total artificial heart, also have been tried with varying success.<sup>43–45</sup> Newer percutaneous VADs are making this option more feasible in smaller centers.<sup>46</sup> A 2005 investigation randomized patients with CS to IABP or TandemHeart (a percutaneous left ventricular assist device [LVAD]).<sup>47</sup> Although there were no significant differences in 30-day mortality between the two groups, patients in the LVAD subgroup had a significant improvement in hemodynamics, renal function, and clearance of serum lactate compared with the IABP cohort. A more recent multicenter randomized trial comparing TandemHeart with IABP in 42 patients with CS revealed similar improvements in hemodynamics with the LVAD without a statistically significant difference in 30-day mortality.<sup>48</sup> Although many of these newer devices appear promising, there will clearly be a limited number of centers that will have access to such technology. Experience with device placement and hemodynamic management is necessary for optimal benefit. In the National Registry of Myocardial Infarction, IABP use was independently associated with survival in those centers with experience in their use.<sup>49</sup> Finally, many of these devices are placed as a bridge to cardiac transplantation, and resources must be available to continue this, often lengthy, workup.

# Revascularization Therapy

Although management of AMI is beyond the scope of this chapter, a brief synopsis is provided here. Because AMI is frequently the inciting event culminating in CS, reestablishing blood flow to the affected myocardial territory is of utmost importance.<sup>50</sup> It has become evident that prompt revascularization reduces the mortality of this disease. One method of reestablishing coronary arterial flow is by the administration of thrombolytic agents. In a randomized trial involving more than 40,000 patients with AMI, the GUSTO-I trial demonstrated a survival advantage with the use of tissue plasminogen activator (tPA) over streptokinase.<sup>51</sup> Since those results have been published, a number of other thrombolytics have been developed; however, randomized trials have been unable to show a difference with respect to CS progression between tPA and these newer agents.<sup>52</sup> The preferred modality of revascularization remains either percutaneous coronary intervention (PCI) or CABG<sup>13,53–55<sup>1</sup></sup> and thrombolytic therapy for CS after STEMI is a class I indication only in patients in whom more definitive therapy is contraindicated or unavailable.<sup>29,56</sup> Although a facilitated PCI strategy (i.e., planned immediate PCI after fibrinolytic administration) has not been shown to be effective,<sup>57,58</sup> fibrinolytics may still be considered in those situations in which PCI is not attainable for more than 90 minutes, the patient is within 3 hours of his or her infarction, and there are no contraindications.<sup>59</sup> The recently published Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) trial emphasized this aspect, showing that early revascularization reduced mortality by 22% in those patients who presented with CS and by 16% in those who developed CS subsequent to admission.<sup>60</sup> The question of how and when it is best to achieve reperfusion has been evaluated. The SHOCK trial prospectively randomized 302 patients presenting with CS due to AMI to either emergency revascularization (either CABG or PCI) or medical stabilization.<sup>53</sup> Although 30-day mortality was similar for both groups, there was a significant survival advantage in the early revascularization group at 6 months, 1 year, and 6 years. This trial did not demonstrate an advantage of one revascularization therapy over another. Given these results and others, early revascularization (either with PCI or CABG surgery) therapy is a class I recommendation by the ACC/AHA for patients younger than 75 years with CS complicated by ACS.<sup>6</sup> Although there are very few data to support revascularization in the non-ST-segment elevation CS population, the SHOCK registry did find a nonsignificant decrease in mortality among those patients who underwent early revascularization.<sup>1</sup>

# **AUTHORS' RECOMMENDATIONS**

Cardiogenic shock requires rapid diagnosis and appropriate therapy to significantly affect mortality. ICU patients often have multiple-organ failure, and differentiating CS from other forms of shock can often be difficult. In patients in whom a diagnosis of CS is being entertained, we recommend the following:

- Maximize oxygen delivery, immediately obtain an electrocardiogram, place invasive monitoring (at least arterial and central venous monitoring), and undertake laboratory (including cardiac enzymes) evaluation.
- Rapid echocardiography may not only confirm the diagnosis but may aid in management.
- If echocardiography is not immediately available and there are no signs of pulmonary edema, we recommend giving an initial intravenous fluid challenge with 500 mL of crystalloid. Repeat fluid challenge may be necessary if there is no increase in blood pressure or right atrial pressure.
- If the patient remains in CS despite adequate intravascular volume, we recommend dobutamine or norepinephrine as first-line vasopressor therapy to maintain mean arterial pressure higher than 60 mm Hg. Vasopressin can be added if there is not rapid improvement in mean arterial pressure.
- If there is not a dramatic improvement in perfusion within 1 hour, placement of an IABP should be considered.
- In patients with electrocardiographic changes suggestive of myocardial ischemia, an immediate search for a culprit vessel should be sought, and early revascularization should be considered.
- It is important to recognize that the treatment of CS often crosses multiple disciplines. Communication among the intensivist, invasive cardiologist, and cardiac surgeon is often necessary to ensure optimal care with optimal timing. As bedside echocardiography becomes more commonplace in ICUs, there is no doubt that intensivists will be diagnosing this entity more frequently and in a more timely manner.

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# When Is Hypertension a True Crisis and How Should It Be Managed in the Intensive Care Unit?

John G.T. Augoustides

Systemic hypertension is a global priority because it is common and serious.<sup>1,2</sup> Hypertension affects about 1 billion people worldwide. About 7 million die each year from hypertension.<sup>1,2</sup> Based on systolic or diastolic pressure elevations, the seventh report of the Joint National Committee has categorized hypertension as either stage 1 or stage 2 (Table 46-1).<sup>1</sup> A hypertensive crisis is typically defined as acute severe hypertension defined by a diastolic blood pressure of 110 mm Hg or higher or a systolic blood pressure 180 mm Hg or higher.<sup>2–4</sup>

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Before the advent of effective antihypertensive therapy, the prevalence of hypertensive crises was 7% of all hypertensive patients. In the contemporary era, this has decreased to 1% of all hypertensive patients owing to the efficacy of current vasodilator therapy.<sup>1–4</sup> Although the incidence of hypertensive crises in the intensive care unit (ICU) has not been clearly defined, it is common not only in the medical setting but also in the perioperative setting.<sup>5–7</sup>

From the above considerations, it follows that a hypertensive crisis is an ICU complication that may often be encountered. This chapter describes a clinical approach to the diagnosis and management of this hemodynamic emergency in the ICU.

# CLINICAL CLASSIFICATION OF AN ACUTE HYPERTENSIVE CRISIS: EMERGENCY VERSUS URGENCY

It is essential that the systemic blood pressure be measured frequently and correctly. If the noninvasive blood pressure cuff is being used, the patient's arm should be level with the heart, and the cuff should be the correct size (it should encircle about 80% of the arm).<sup>3</sup> When using an arterial line, accurate measurement of the blood pressure requires a patent arterial catheter in the arterial lumen and an adequately dampened system that is zeroed level with the heart.<sup>8</sup> Although heparinized flush is commonly used to maintain radial artery patency, a recent randomized trial found that it offered no

advantage over placebo.<sup>9</sup> Importantly, radial artery pressure may underestimate central arterial pressure in settings that include hypothermia and after cardiopulmonary bypass.<sup>8,10</sup>

*Hypertensive crises* are defined as hypertensive emergencies or hypertensive urgencies. A *hypertensive emergency* is defined as severe hypertension with acute endorgan damage (actual or threatened). The main clinical examples of hypertensive emergencies are summarized in Table 46-2. Hypertensive emergencies, by definition, are life-threatening and mandate immediate intravenous vasodilator therapy with titratable short-acting agents in an ICU setting (Table 46-3). In contrast, a hypertensive urgency is defined as severe hypertension without apparent or threatened end-organ damage. Nonetheless, treatment is indicated. An approach to the management of hypertensive urgencies is outlined in Table 46-4.

The remainder of this review will be devoted to the diagnosis and management of true hypertensive emergencies, that is, those clinical scenarios in which there is severe hypertension with actual or threatened acute endorgan damage.

# CLINICAL FEATURES IN THE MANAGEMENT OF SELECTED HYPERTENSIVE EMERGENCIES

# **Neurologic Hypertensive Emergencies**

Patients with severe hypertension and neurologic abnormalities (including altered mental status) require a thorough physical examination. This should include visualization of the optic fundi by direct ophthalmoscopy. Hypertensive patients with papilledema, new retinal hemorrhage, and new retinal exudates not only suffer from a hypertensive emergency but often simultaneously exhibit a degree of hypertensive encephalopathy. A complete neurologic examination will detect neurologic deficit due to a stroke or overaggressive vasodilator therapy ("hypotensive overshoot").

Table 46-1 Classification and Suggested Management of Blood Pressure in Adults					
Blood Pressure Classification	Systolic Blood Pressure		Diastolic Blood Pressure	Lifestyle Modification	Drug Therapy
Normal	<120 mm Hg	and	<80 mm Hg	Encourage	None
Prehypertension	120-139 mm Hg	or	80-89 mm Hg	Yes	None
Stage 1 hypertension	140-159 mm Hg	or	90-99 mm Hg	Yes	Yes
Stage 2 hypertension	≥160 mm Hg	or	≥100 mm Hg	Yes	Yes

Adapted from Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure. JAMA. 2003;289:2560-2572.

# Table 46-2Clinical Scenarios in Which SevereHypertension Is an Emergency

## NEUROLOGIC

- Hypertensive encephalopathy
- Subarachnoid hemorrhage
- Intracranial hemorrhage
- · Thrombotic stroke with severe hypertension
- Head trauma

# CARDIOVASCULAR

- Left ventricular failure
- Unstable angina
- Myocardial infarction
- Aortic dissection
- After cardiac or vascular surgery (threatened suture lines)

### RENAL

- · Gross hematuria
- · Acute renal dysfunction or failure

## SEVERE CATECHOLAMINE EXCESS

- Pheochromocytoma
- Drug withdrawal, e.g.,  $\beta$ -blockers, clonidine
- Interactions with monoamine oxidase inhibitors

Neurologic hypertensive emergencies often have overlapping features (Table 46-5). Hypertensive encephalopathy is often the most difficult to diagnose.<sup>11</sup> The pathophysiology involves disruption of the blood-brain barrier and loss of cerebral autoregulation. This results in diffuse cerebral edema and neurologic dysfunction. Based on a small case series, hypertensive encephalopathy may be associated with posterior leukoencephalopathy. This process involves white matter edema concentrated in the parietal and occipital regions of the brain.<sup>12</sup>

Hypertensive encephalopathy is frequently a diagnosis of exclusion: stroke, intracranial hemorrhage, seizures, and mass lesions must have been ruled out.<sup>13,14</sup> Although there are no definitive data, expert opinion indicates that the therapy of choice for hypertensive encephalopathy is a vasodilator titrated in an ICU setting. This pharmacologic relief is often associated with significant neurologic improvement. Similarly, expert consensus suggests that changes in the neurologic examination may reflect a new process—a new stroke or hypotensive overshoot—that requires immediate intervention.

The remaining neurologic hypertensive emergencies are diagnosed more readily. Strokes, whether thrombotic or hemorrhagic, are typically present with focal neurologic deficits and are confirmed through brain imaging (computed axial tomographic scanning or magnetic resonance imaging).<sup>15,16</sup> Subarachnoid hemorrhage has characteristic clinical features with diagnostic confirmation by either lumbar puncture or brain imaging. In subarachnoid hemorrhage, oral nimodipine is used to prevent delayed neurologic deficits secondary to vasospasm. Although it may have a vasodilator effect, nimodipine is not effective for acute management of severe hypertension.<sup>14,15</sup> Severe hypertension associated with head trauma is problematic because the blood pressure goal is uncertain.<sup>17</sup> Recommendations for first-line vasodilator drugs and blood pressure goals for the neurologic hypertensive emergencies are sum-marized in Table 46-6.<sup>14–18</sup>

Elevations in blood pressure after craniotomy also are hypertensive emergencies.<sup>19</sup> In a retrospective single-center case-controlled study of 11,214 adult patients who underwent craniotomy (1976 to 1992), intracranial hemorrhage often was preceded by either intraoperative or postoperative hypertension (defined as a systolic blood pressure > 159 mm Hg or a diastolic blood pressure > 89 mm Hg).<sup>19</sup> Patients with intracranial hemorrhage had an 11.4-fold increase in mortality (18.2% versus 1.6%; P < .05) and a 2.2-fold increase in median hospital stay (24.5 days versus 11.0 days; P < .05). Because control of blood pressure is easily accomplished and intracranial hemorrhage is devastating, vasodilator therapy is indicated in this patient population when blood pressure is higher than 160/90 mm Hg.

# **Cardiovascular Hypertensive Emergencies**

## Hypertension with an Acute Coronary Syndrome

Hypertension may contribute to coronary ischemia from processes such as coronary atherosclerosis, left ventricular hypertrophy, an activation of coagulation and platelets.<sup>20–22</sup> The goal of therapy in hypertensive patients with an acute coronary syndrome is to minimize ischemia. In patients with a history of mild or no hypertension, vasodilator therapy can be titrated for symptom

Table 46-3 Drugs for Management of a Hypertensive Crisis							
Antihypertensive Agent	Dosage Range	Onset of Action	Duration of Action	Adverse Effects	Special Indications		
Nitroglycerin	25-200 μg/min as intravenous infusion	2-5 min	5-10 min	Headache, vomiting, tolerance, methemoglobinemia	Myocardial ischemia Cocaine intoxication		
Sodium nitroprusside	1-10 μg/kg/min as intravenous infusion	Immediate	1-2 min	Vomiting, thiocyanate, and cyanide poisoning	Caution with raised intracranial pressure, azotemia, or spinal ischemia		
Nicardipine	5-15 mg/hr as intravenous infusion	5-10 min	15-30 min, but may last past 4 hr	Headache, vomiting, tachycardia	Caution in acute heart failure		
Diltiazem	0.2-0.5 μg/kg intravenous bolus, then 5-15 mg/hr as intravenous infusion	5-10 min	2-4 hr, but may last past 6 hr	Hypotension, heart failure, bradycardia, heart block	Caution in bradycardia, heart block, and heart failure		
Esmolol	250-500 μg/kg/min intravenous bolus, then 50-100 μg/kg/min as infusion	1-2 min	10-30 min	Bronchospasm, heart block, heart failure	Aortic dissection Avoid in cocaine intoxication		
Labetalol	20-80 mg bolus, followed by 1-5 mg/min as infusion	5-10 min	3-6 hr	Bronchospasm, heart block, heart failure	Caution in acute heart failure Avoid in cocaine intoxication		
Enalapril	1.25-5.00 mg every 6-8 hr IV	15-30 min	6-12 hr	Hypotension in high- renin states	Acute ventricular failure Caution in azotemia and renal artery stenosis		
Fenoldopam (dopamine-1 agonist)	0.1-0.3 μg/kg/min as IV infusion	2-5 min	30 min	Headache, vomiting, tachycardia	Caution with glaucoma		
Hydralazine	10-20 mg IV	10-20 min	1-4 hr	Headache, vomiting, tachycardia	Eclampsia		
Phentolamine	5-15 mg as IV bolus	1-2 min	10-30 min	Headache, vomiting, tachycardia	Catecholamine excess states		

# Table 46-4 Suggested Clinical Approach to a Hypertensive Urgency

- 1. Confirm that the blood pressure is truly severe ( $\geq 180/$ 110 mm Hg)
- 2. Confirm that there are no symptoms and/or signs compatible with threatened or actual end-organ damage
- 3. Detect and manage triggering factors, such as:
  - Pain: administer analgesia
  - Discontinuation of preoperative and intraoperative drugs: replace as indicated
  - Urinary retention: drain bladder
  - Disturbances in the metabolic milieu
    - Hypoxia: treat cause; administer oxygen
    - Hypercapnia: treat cause; support ventilation
  - Hypoglycemia: treat cause; administer glucose
- 4. If still hypertensive after the above measures, consider antihypertensive therapy to lower blood pressure gradually

\*Severe hypertension with no real or threatened end-organ damage.

relief. The optimal blood pressure will depend on the particular clinical presentation, but in general it can be normalized as long as that level of blood pressure is clinically tolerated. In patients with a history of hypertension or with a blood pressure higher than 160/ 100 mm Hg, the recommendation based on expert consensus from the American College of Cardiology (ACC) and American Heart Association (AHA) is reduction to a level that is 20% to 30% below the initial mean arterial pressure.<sup>23</sup>

The treatment of hypertension in this setting often requires multiple agents. The ACC/AHA guidelines recommend nitroglycerin and β-blockers for the acute management of hypertension in an acute coronary syndrome. Nitroglycerin is a coronary vasodilator and thus may also improve myocardial oxygen supply. β-Blockers decrease myocardial work and thus oxygen demand to alleviate ischemia. In addition, β-blockers dampen the activation of coagulation.<sup>24</sup>

			5	
Clinical Feature	Hypertensive Encephalopathy	Subarachnoid Hemorrhage	Intraparenchymal Hemorrhage	Acute Infarction
History of hypertension	Universal	Common	Common	Common
Duration of symptoms	Usually subacute	Acute	Acute	Acute
Headache	Severe	Severe	Variable	Variable
Focal neurologic deficit	Unusual; varies with hypertension severity	Variable	Depends on location of hemorrhage	Depends on location of infarction
Retinopathy	Universal; typically severe grades	Variable (mild to severe)	Variable (mild to severe)	Variable (mild to severe)
Brain imaging	Usually normal	May show hemorrhage	Often delineates site and extent of hemorrhage	Frequently delineates site and extent of infarction
Lumbar puncture (if performed)	Typically normal, opening pressure may be elevated	Frank blood initially; xanthochromic later	Frank blood initially; xanthochromic later	Typically normal, opening pressure may be elevated
Acute treatment	Intensive care unit (ICU) Intravenous vasodilators	Neurosurgical ICU Intravenous vasodilators (nimodipine)	ICU Vasodilator therapy may be indicated to intermediate range (e.g., 160/100 mm Hg)	ICU No vasodilator therapy

# Table 46-5 Similarities and Differences in Selected Neurologic Hypertensive Emergencies

# Table 46-6 Neurologic Hypertensive Emergencies with Recommended Drug Therapy and Blood Pressure Targets

Hypertensive Emergency	Recommended Intravenous Vasodilator Therapy Options	Blood Pressure Target
Hypertensive encephalopathy	Labetalol, nicardipine, nitroprusside	25% reduction in MAP over 4-8 hr
Acute cerebral infarction	Labetalol, nitroglycerin, nicardipine, nitroprusside	If patient is eligible for lytic therapy, initiate treatment if SBP > 180 mm Hg or DBP > 110 mm Hg If patient is ineligible for lytic therapy, initiate treatment if SBP > 220 mm Hg or DBP > 120 mm Hg
Parenchymal hemorrhage (raised ICP)	Esmolol, labetalol, nicardipine, nitroprusside	Maintain MAP < 130 mm Hg or SBP < 180 mm Hg for first 24 hr
Parenchymal hemorrhage (normal ICP)	Esmolol, labetalol, nicardipine, nitroprusside	Maintain MAP < 110 mm Hg or SBP < 160 mm Hg for first 24 hr
Subarachnoid hemorrhage	Esmolol, labetalol, nicardipine, nitroprusside	Maintain SBP 130-160 mm Hg
Acute head trauma	Esmolol, labetalol, nicardipine, nitroprusside	Routine vasodilator therapy not recommended Consider in selected cases 0%-25% reduction in first 4 hr (controversial) If there is monitoring of intracranial pressure, maintain cerebral perfusion pressure 50-70 mm Hg
Hypertension after craniotomy	Short-acting parenteral agent preferable Esmolol, labetalol, nicardipine, nitroprusside	Initiate the rapy if SBP $\geq 160~\text{mm}$ Hg or DBP $\geq 90~\text{mm}$ Hg

DPB, diastolic blood pressure; ICP, intracranial pressure; MAP, mean arterial pressure; SBP, systolic blood pressure.

Adapted from Panicelli AM. Hypertension management in neurologic emergencies. *Ann Emerg Med.* 2008;51:S24-S27; and Adams Jr HP, del Zoppo G, Alberts MJ, et al. Guidelines for the early management of adults with ischemic stroke: A guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups. The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. *Stroke*. 2007;38:1655-1711.
The presence of severe hypertension may profoundly influence clinical decision making in an acute coronary syndrome. Based on expert consensus, thrombolytic therapy for ST-elevation myocardial infarction is contraindicated in patients with a blood pressure higher than 185/ 100 mm Hg.<sup>20</sup> Furthermore, expert consensus suggests that antithrombin agents should be used cautiously in patients with severe hypertension and altered mental status until the neurologic evaluation is completed because these agents would be contraindicated in the presence of cerebral hemorrhage.<sup>20</sup> Therefore, the prompt control of severe hypertension in this setting is mandatory to facilitate optimal patient management.

#### Hypertension with Left Heart Failure

Patients with acute heart failure often present with hypertension. This occurs whether they have systolic or diastolic heart failure.<sup>25</sup> The presenting systolic blood pressure is an independent predictor of mortality in this patient group.<sup>25</sup> Current expert consensus suggests that patients with acute heart failure, pulmonary edema, and a systolic blood pressure higher than 90 mm Hg should receive vasodilator therapy.<sup>20</sup> Nitroglycerine, administered either sublingually or intravenously, is the preferred vasodilator in this setting. However, the required dose of nitroglycerin may be substantially greater than that routinely used for an acute coronary syndrome. Indeed, the typical dose often exceeds 120 µg per minute. As per expert consensus from the practice guideline from the Heart Failure Society of America (HFSA), second-line vasodilator agents include nitroprusside and intravenous angiotensin-converting enzyme inhibitors.<sup>26</sup> Because spontaneous resolution of hypertension often occurs quickly, the HFSA guideline recommends dosage reductions of administered vasodilators after 24 hours.

Current research is investigating the role of new candidate vasodilators in acute heart failure. These include vasopressin and endothelin antagonists. The results of these randomized trials will define the role of these newer agents.<sup>27</sup>

#### Hypertension with Aortic Dissection

Acute aortic dissection was classified by the JNC-7 report as a hypertensive emergency.<sup>1</sup> Because dissection of the ascending aorta or aortic arch also is a surgical emergency, the management of hypertension in this setting is perioperative.<sup>28</sup> Based on expert consensus, the guidelines from the European Society of Cardiology (ESC) Task Force on Aortic Dissection recommend initial analgesia with titrated morphine sulfate followed by titration of  $\beta$ -blockade with propranolol, metoprolol, esmolol, or labetalol. The goal is a systemic systolic blood pressure of 100 to 200 mm Hg.<sup>29</sup> If needed, expert consensus from the ESC recommends sodium nitroprusside for further systemic vasodilation. This approach is consistent with a recent expert review. These practitioners proposed a goal systolic blood pressure of 110 mm Hg and a regimen of titrated narcotic analgesics, intravenous β-blockers, and vasodilators such as sodium nitroprusside.<sup>28</sup> Both the ESC task force guidelines and the expert review suggest verapamil or diltiazem as alternatives in patients with contraindications to  $\beta$ -blockade.<sup>28,29</sup>

In contrast, the recent ACC/AHA guidelines for valvular heart disease caution that  $\beta$ -blockade should not be first-line therapy for control of hypertension associated with aortic dissection with severe acute aortic regurgitation.<sup>30</sup> In this clinical setting,  $\beta$ -blockers decrease compensatory tachycardia and aggravate aortic regurgitation, increasing the risk for acute heart failure and death.<sup>30</sup> Emergency management of hypertension in aortic dissection should consist of analgesia with narcotic analgesics and intravenous vasodilator therapy (sodium nitroprusside or nicardipine).  $\beta$ -Blockade may be used when severe ventricular dysfunction and severe aortic regurgitation have been ruled out by echocardiography.

#### Hypertension after Carotid Revascularization

Carotid endarterectomy or stenting may be associated with postprocedural hypertension that can adversely affect clinical outcome. Specifically, hypertension following carotid endarterectomy has been associated with death and stroke (P = .04) and with a trend toward cardiac complications (P = .07).<sup>31</sup> Although hemodynamic instability is common after carotid stenting, hypotension and bradycardia are more common than hypertension. In a recent series of 132 patients, the incidence of postprocedural hypertension was only 6.8%, compared with 32.6% for hypotension and 15.9% for bradycardia.<sup>32</sup> In another recent stent series of 500 patients, hemodynamic depression was persistent in 17% of cases, especially in patients with calcified lesions (odds ratio [OR], 1.89; 95% confidence interval [CI], 1.25 to 2.84; P < .002) or abnormalities that involved the carotid bulb (OR, 2.18; 95% CI, 1.46 to 3.26; P < .0001).<sup>33</sup> Patients with persistent hemodynamic depression were at significant risk for adverse clinical events, including stroke.

Severe vascular complications after carotid intervention include the cerebral hyperperfusion syndrome (CHS) and intracranial hemorrhage (ICH). Two recent large series of 4494 and 450 patients, respectively, reported a 1.1% to 1.4% incidence of CHS and a 0.6% to 0.7% incidence of ICH.<sup>34,35</sup> Although these complications are rare, they are associated with significant periprocedural mortality and morbidity. The onset of CHS usually occurs within 12 hours of stenting and within 6 days of endarterectomy. Both CHS and ICH after carotid intervention are associated with hypertension in the postprocedural period. Further risk factors for CHS include treated stenosis of more than 80% or a contralateral stenosis of more than 80%.

Aggressive management of blood pressure after carotid intervention is recommended to reduce the incidence of CHS and ICH. The systolic blood pressure should be maintained lower than 140 mm Hg for the first 48 hours (EMCREG-2008).<sup>36,37</sup> In patients at risk for or with CHS or ICH, systolic blood pressure should be maintained lower than 120 mm Hg.<sup>36,37</sup> In a recent series of 836 patents undergoing carotid stenting, use of these blood pressure management criteria was associated with significant reductions in CHS (29.4% to 4.2%; *P* = .006) and ICH (17.6% to 0%; *P* = .006).<sup>36</sup>

#### Hypertension in the Perioperative Period

Uncontrolled hypertension in the perioperative period may become life-threatening. Concerns extend beyond the potential for development of hemorrhagic shock. Bleeding after carotid endarterectomy or neck surgery may result in airway obstruction.<sup>38</sup> As discussed earlier, hypertension after craniotomy may lead to serious intracranial hemorrhage and adverse outcomes.<sup>19</sup> Conversely, impaired blood flow to key organs has been implicated in the pathogenesis of the postoperative organ dysfunction syndrome. Therefore, the medical management of perioperative hypertension must balance the risks for surgical hemorrhage with the risks for end-organ hypoperfusion.

An important exception to control of perioperative hypertension is the neurologic emergency of paraplegia after descending thoracic aortic repair. Although data derived from randomized controlled trials are lacking, some experts believe that spinal cord ischemia may be relieved by improving spinal perfusion with systemic hypertension (mean arterial pressure, 80 to 100 mm Hg) and titrated drainage of cerebrospinal fluid.<sup>39,40</sup> In this scenario, many practitioners believe that relative systemic hypertension is essential to prevent spinal cord ischemia. This takes priority over the threat of bleeding from aortic suture lines.<sup>39</sup> Frequently, in this scenario of an ischemic sympathectomy from acute spinal shock, an elevated mean arterial pressure requires administration of titrated vasoconstrictors such as phenylephrine, norepinephrine, or vasopressin.<sup>41</sup>

The onset of perioperative hypertension often is acute. This complication merits immediate pharmacologic intervention despite the fact that it may be transient. As a result, use of potent and rapidly acting agents with a short half-life ("fast-on and fast-off" agents such as sodium nitroprusside, nicardipine, nitroglycerin, and labetalol) is recommended.  $\beta$ -Blockade is particularly useful for hypertensive patients who had been receiving  $\beta$ -blockers preoperatively or who are at high risk for perioperative cardiovascular complications.<sup>42,43</sup>

#### **Renal Hypertensive Emergencies**

Patients presenting with true hypertensive emergencies often have microscopic hematuria or acute renal dysfunction. Gross hematuria is less common and therefore merits urology consultation once the blood pressure has been controlled. Renal replacement therapy may be required when the systemic blood pressure has been managed. However, there is potential for long-term renal recovery if hypertension is tightly managed.<sup>44</sup>

Although data to support the practice are limited, pharmacologic therapy for a hypertensive crisis with renal insufficiency and failure traditionally has involved titrated sodium nitroprusside.<sup>16</sup> However, the dopamine-1 agonist fenoldopam has several advantages in this setting. It avoids the risk for cyanide and thiocyanate toxicity with prolonged infusion. It also has beneficial acute renal effects such as natriuresis, diuresis, and reductions in serum creatinine.<sup>45</sup> Nonetheless, data to support the use of this agent are lacking.

# Severe Catecholamine Excess Resulting in Hypertensive Emergencies

True hypertensive emergencies due to catecholamine excess are rare. Actual causes are listed in Table 46-7. Current

## Table 46-7 Recommendations for Cardiovascular Hypertensive Emergencies

#### ACUTE CORONARY SYNDROME

- Blood pressure (BP) > 160/100 mm Hg merits treatment
- Goal BP is 20%-30% lower than baseline
- Preferred agents are nitroglycerin and β-blockers
- Avoid thrombolytics if BP > 185/110 mm

#### ACUTE LEFT HEART FAILURE

- Systolic BP > 90 mm Hg merits treatment
- · Preferred agents are nitroglycerin and angiotensin blockers
- Reduce doses of vasodilators after 24 hr of therapy

#### ACUTE AORTIC DISSECTION

- Maintain systolic BP < 110 mm Hg
- Initial therapy is analgesia with titrated morphine
- Preferred agents are β-blockers, sodium nitroprusside, and nicardipine
- Avoid β-blockade with contraindications such as asthma, acute heart failure, bradycardia, and aortic regurgitation
- Calcium channel blockers such as verapamil and diltiazem are recommended alternatives to β-blockade

#### HYPERTENSION IN THE PERIOPERATIVE PERIOD

- Maintain blood pressure within 20% of baseline except when there is potential for serious bleeding, e.g., postcraniotomy; aortic suture lines
- In situations with potential for serious bleeding, maintain the systolic blood pressure < 140 mm Hg, as long as clinically tolerated
- Preferred agents include sodium nitroprusside, nitroglycerin, esmolol, nicardipine, and labetalol
- Perioperative β-blockade is recommended for vascular surgical patients, patients at high risk for perioperative cardiac complications, and patients on chronic preoperative β-blocker therapy

#### HYPERTENSION AFTER CAROTID PROCEDURES

- Maintain systolic blood pressure < 140 mm Hg for the first 48 hr
- Preferred agents include sodium nitroprusside, nitroglycerin, and nicardipine
- Neurologic deficits require prompt neuroimaging to guide BP management
  - Cerebral edema and/or parenchymal hemorrhage due to the reperfusion syndrome may merit maintenance of systolic blood pressure < 120 mm Hg</li>
  - Ischemic stroke, on the other hand, may require augmentation of blood pressure to improve cerebral perfusion

recommendations for all these hypertensive emergencies characterized by catecholamine excess are summarized in Table 46-8.

#### Pheochromocytoma

The progressive reduction in perioperative mortality associated with excision of pheochromocytoma (from 3.9% to 0%) has been attributed to advances in perioperative management of the associated hypertension.<sup>46,47</sup> Nonetheless, the patient with pheochromocytoma may present in hypertensive crisis, requiring aggressive management in the ICU for control of systemic vascular resistance Table 46-8 Recommendations for HypertensiveEmergencies Due to Catecholamine Excess

#### PHEOCHROMOCYTOMA

- Control hypertensive crisis with phentolamine, sodium nitroprusside, and nicardipine
- Prepare for surgery with α-blockade as first-line treatment
- Consider β-blockade only after initial α-blockade
- Consider metyrosine for suppression of tumor catecholamine synthesis
- Vasopressor administration may be required postoperatively in the intensive care unit

#### MONAMINE OXIDASE INHIBITORS

- Control hypertensive crisis with phentolamine, sodium nitroprusside, and nicardipine
- Avoid trigger agents
- Consider serotonin blockade with cyproheptadine in the serotonin syndrome

#### DRUG WITHDRAWAL

- Control hypertensive crisis with β-blockade, sodium nitroprusside, and/or nicardipine
- Titrate replacement therapy to effect, e.g., β-blocker, clonidine

and cardiovascular stabilization.<sup>48,49</sup> Elective surgical resection is indicated after medical stabilization has been achieved.

#### Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors (MAOIs), such as phenelzine, tranylcypromine, isocarboxazid, and selegiline, have been used for management of depression since the 1950s.<sup>50</sup> Their popularity has diminished due to the acute hypertensive crisis precipitated by tyramine-containing foods such as aged cheeses, bananas, soy condiments, and red wine.

Monamine oxidases inactivate neurotransmitters such as dopamine, epinephrine, norepinephrine, serotonin, and tyramine (a precursor of dopamine). These enzymes are present in the nervous system, the liver, the gastrointestinal tract, and the mitochondria. Ingested tyramine is catabolized in the digestive tract. In the presence of an MAOI, tyramine enters the bloodstream and causes a significant release of norepinephrine from peripheral adrenergic neurons. This is responsible for the acute hypertensive crisis. In addition, MAOIs interact with indirectly acting sympathomimetics such as ephedrine, pseudoephedrine, and phenylpropanolamine. These agents, which often are used in over-the-counter nasal decongestants, also can precipitate a hypertensive crisis.<sup>51</sup> In severe cases, hypertensive control has required intensive care unit (ICU) admission for titration of intravenous vasodilators such as nitroprusside or nicardipine.

MAOIs also adversely interact with meperidine. This drug combination may precipitate the serotonin syndrome, characterized by mental status changes, autonomic hyper-reactivity, and neuromuscular abnormalities.<sup>52</sup> The serotonin syndrome can be fatal.<sup>53,54</sup> The management of the serotonin syndrome includes avoidance of pharmacologic triggers, supportive care, and administration of serotonin

receptor blockers such as cyproheptadine.<sup>54</sup> The hypertensive aspect of this syndrome has been effectively managed with short-acting intravenous agents such as nitroprusside and esmolol. In severe cases, hyperthermia due to excessive muscular activity may require sedation, neuromuscular blockade with vecuronium, and mechanical ventilation.<sup>54</sup>

# Drug Withdrawal

Perioperative  $\beta$ -blockade has been extensively reviewed in recent ACC/AHA guidelines.42,43 These guidelines recommend that hypertensive patients on β-blockers continue to receive their medication despite the absence of randomized controlled trials. This recommendation reflects a concern for the development of β-blocker withdrawal. This syndrome, which involves sweating, tachycardia, hypertension, and in severe cases, cardiac arrhythmias and myocardial ischemia, was originally described on discontinuation of propranolol, the first widely available  $\beta$ -blocker.<sup>55</sup> In a case series, perioperative withdrawal of propranolol was associated with significant myocardial ischemia.<sup>55</sup> A recent prospective observational cohort study of 2588 adult outpatients found that the risk for myocardial infarction was further significantly increased by withdrawal of cardioselective β-blockade.<sup>56</sup> Management involves reinstitution of β-blockade and may require ICU admission.

Clonidine is a centrally acting  $\alpha$ -agonist available in oral, transdermal, and parenteral formulations. In hypertensive patients chronically managed with  $\alpha_2$ -agonists, discontinuation is dangerous. Experts recommend that withdrawal be avoided because it is associated with severe delirium, hypertension, and myocardial ischemia that may require ICU admission.<sup>56–59</sup>Again, reinstitution of the drug will permit control and resolution of these features.

#### RECENT ADVANCES

The U.S. Food and Drug Administration has recently approved clevidipine butyrate for intravenous control of hypertension.<sup>60</sup> Clevidipine is a dihydropyridine calcium channel blocker that is a selective arterial vasodilator that decreases systemic vascular tone. Because it is insoluble in water, it is formulated as an oil-in-water emulsion. As a result, the drug formulation also contains soybean oil, glycerin, and egg yolk derivatives. Intravenous administration causes vasodilation within 5 minutes. This effect is completely reversed within 5 to 15 minutes with discontinuation.<sup>60</sup>

Clevidipine was evaluated for management of perioperative hypertension associated with cardiac surgery (ESCAPE-1 trial: N = 105; ESCAPE-2 trial: N = 110)<sup>61,62</sup> and for management of severe hypertension (VELOCITY trial: N = 126; 102 of 126 had demonstrable end-organ injury on presentation).<sup>63</sup> Contraindications include allergy to soy or eggs, defective lipid metabolism, and aortic stenosis.

This novel agent has proven efficacy in the management of a hypertensive emergency. Its precise niche in the management of hypertensive emergencies remains to be determined.

# **AUTHORS' RECOMMENDATIONS**

All my recommendations are summarized in the accompanying tables. These reflect current multidisciplinary guidelines, including those from the American Heart Association, American College of Cardiology, American Stroke Association, American College of Physicians, Heart Failure Society of America, European Society of Cardiology, and the Emergency Medicine Cardiac Research Education Group. This participation of experts from a variety of medical specialties underlines the prevalence and importance of severe hypertension in multiple disease states.

- The prompt and effective management of hypertension in the ICU depends on differentiating a hypertensive urgency from a true hypertensive emergency.
- The management of a true hypertensive emergency should be based on a working knowledge of current guidelines, as tabulated in this chapter.
- The management of severe hypertension in a clinical emergency should be based on selection of recommended intravenous vasodilators at therapeutic doses, titrated to recommended goals.
- The correction of severe hypertension in a clinical emergency should be integrated with the management of the associated disease state.

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# How Does One Manage and Treat Atrial Fibrillation in Postoperative Critically III Patients?

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Supraventricular arrhythmias are the most common rhythm disturbance encountered in postsurgical patients.<sup>1</sup> The incidence of postoperative atrial fibrillation may be as high as 50% after cardiac surgery,<sup>2</sup> 40% after pneumonectomy,<sup>3</sup> and 20% after lung resection.<sup>4</sup> In addition, other postsurgical patients have an incidence of new-onset supraventricular arrhythmias approaching 10%.<sup>5</sup>

Patients who develop supraventricular arrhythmias after major noncardiac surgery are at increased risk for stroke and have significantly higher early and late mortality.<sup>5</sup> After cardiac surgery, atrial fibrillation may herald a prolonged ICU course,<sup>2</sup> increased risk for stroke, and increased risk for early and late mortality.<sup>6</sup> Cost of care in a patient who develops postoperative atrial fibrillation is increased by an average of \$10,000.<sup>7</sup> Thus, the human and economic toll of this disease entity in the postsurgical patient population is quite large.

### **RISK FACTORS**

Multiple risk factors that predispose patients to atrial fibrillation have been identified (Table 47-1).<sup>8–10</sup> Recognition of these risk factors preoperatively can lead to alterations in perioperative medical management and modification of surgical techniques. Of importance, every 10-year increase in age beyond 30 years is associated with a 75% increase in risk of new-onset atrial fibrillation after cardiac surgery.<sup>8</sup> The risk for developing atrial fibrillation in octogenarians may be greater than 50% in coronary artery bypass graft (CABG) patients.<sup>9</sup> In addition, obesity and increased body mass index have also been shown to be predictors of postoperative atrial fibrillation.<sup>10</sup>

# PATHOGENESIS

The pathogenesis of atrial fibrillation in the postoperative period is complex and multifactorial. Disease processes and conditions such as advanced age, pulmonary disease, and valvular heart disease predispose to atrial enlargement and fibrosis, which provide the substrate for conduction abnormalities.<sup>11</sup> The inflammatory response induced by surgery is associated with increased levels of circulating catecholamines related to pain, anemia, fluid shifts, and inotrope administration. These factors trigger supraventricular arrhythmias by altering atrial refractoriness and conductivity thereby predisposing to automaticity and reentrant rhythms.<sup>12</sup>

The type of surgery performed has a marked impact on the incidence of perioperative atrial fibrillation. In patients undergoing intrathoracic procedures, direct surgical manipulation or compression of the atria contributes to the pathogenesis of atrial fibrillation.<sup>13</sup> During cardiac surgery, myocardial ischemia and ventricular dysfunction can lead to atrial dilation and elevation of atrial pressures that further contribute to atrial irritability.<sup>13</sup> Although the data in general surgery patients are not as robust as in cardiac surgical patients, minimally invasive laparoscopic techniques may decrease the risk for postoperative atrial fibrillation when compared with open approaches.<sup>13,14</sup> This finding has been interpreted to imply that attenuation of the inflammatory response after surgery may decrease the risk for developing postoperative supraventricular arrhythmias.

# WHAT STRATEGIES ARE EFFECTIVE FOR PROPHYLAXIS OF ATRIAL FIBRILLATION?

Although atrial fibrillation in postsurgical patients is a well-recognized phenomenon, the implementation of prophylactic therapies to prevent new or recurrent arrhythmias remains controversial. As knowledge of causative factors and the resulting pathophysiology continues to advance, the pool of potentially beneficial interventions has broadened. Conceptually, prophylactic strategies against atrial fibrillation fall into one of four categories: electrolyte (magnesium) administration, atrial pacing, antiarrhythmic agents, or anti-inflammatory agents (Table 47-2). In general, the utility of prophylactic strategies has been most thoroughly evaluated in post–cardiac

# Table 47-1 Comparison of the Risk Factors for Permanent Atrial Fibrillation and **Postoperative Atrial Fibrillation**

Risk Factor	Permanent	Cardiac	Noncardiac
Epidemiologic			
Advanced age	Х	Х	Х
Male gender	Х	Х	Х
Height*	Х		
Medical conditions			
CAD <sup>†</sup>	Х		
HTN <sup>‡</sup>	Х	Х	
LAE/LVH <sup>§</sup>	Х		
CHF	Х	Х	Х
Cardiomyopathy	Х		
Valvular disease	Х	Х	Х
Prior AF <sup>¶</sup>	N/A	Х	Х
Myocarditis	Х		
CHD	Х		
OLD	Х	Х	Х
OSA	Х		
PVD**	Х	Х	х
Obesity	Х	Х	
DM <sup>§</sup>	Х		
Hyperthyroidism <sup>††</sup>	Х		
Alcohol <sup>‡‡</sup>	Х		

\*Permanent AF.<sup>30</sup>

<sup>†</sup>Permanent AF.<sup>26,28–30</sup> <sup>‡</sup>Permanent AF<sup>29,30</sup> cardiac.<sup>5</sup>

<sup>§</sup>Cardiac,<sup>9</sup> noncardiac.<sup>2</sup>

<sup>¶</sup>Permanent AF.<sup>2</sup>

<sup>11</sup>Permanent AF.<sup>34</sup>

\*\*Cardiac,<sup>9</sup> noncardiac.<sup>2</sup>

<sup>‡‡</sup>Not supported as a risk factor in all studies (Psaty et al. found protective).<sup>30</sup> X - risk factor present; permanent - permanent atrial fibrillation; cardiac -POAF after cardiac surgery; noncardiac - POAF after noncardiac surgery; height - tall stature; CAD - coronary artery disease; HTN - hypertension; LAF/LVH - left atrial enlargement/left ventricular hypertrophy; prior AF history of prior atrial fibrillation; CHD - congenital heart disease; OLD obstrutive lung disease; OSA - obstructive sleep apnea; PVD - peripheral vascular disease; DM - diabetes mellitus; alcohol - significant alcohol use.

From Mayson SE, Greenspon AJ, Adams S, et al. The changing face of postoperative atrial fibrillation prevention: A review of current medical therapy. Cardiol Rev. 2007;15:232.

surgery patients. Therefore, considerations pertaining to risk and pathophysiology in this population must be considered before extrapolating data to the general surgical population.

#### Magnesium

Electrolyte derangements and membrane instability are postulated to play important roles in the pathogenesis of atrial fibrillation, particularly in the postoperative setting.

The importance of the magnesium depletion that typically occurs during cardiopulmonary bypass and after diuretic administration has been studied in post-cardiac surgery patients. In a meta-analysis, 16 trials including 2029 patients evaluating the use of prophylactic magnesium were identified. Supraventricular arrhythmias occurred significantly less often in patients treated with magnesium compared with controls (23% versus 31%).<sup>15</sup> It remains unclear whether avoidance of hypomagnesemia or achievement of supranormal magnesium levels was responsible for the observed benefit. In a different review of 14 trials encompassing 1853 patients, only 1 study demonstrated a statistically significant magnesiumassociated decrease in arrhythmias. Nonetheless, current guidelines of the American College of Chest Physicians (ACCP) recommend maintenance of serum magnesium levels in the normal range after cardiac surgery and suggest that empirical supplementation be considered in this high-risk population.<sup>13</sup>

#### **Atrial Pacing**

Atrial pacing has been proposed as a strategy to decrease the incidence of atrial fibrillation after cardiac surgery. It is theorized that overdrive suppression of supraventricular foci may retard the development of atrial fibrillation in the immediate postsurgical period. Heterogeneity within the literature examining pacing for atrial fibrillation prophylaxis makes interpretation of the data challenging. Nonetheless, several meta-analyses have been published. In a review of 13 prospective randomized controlled trials in which right atrial pacing, left atrial pacing, or biatrial pacing was employed, Archbold and Schilling found the most significant reduction in postoperative atrial fibrillation occurred in patients receiving biatrial pacing (relative risk [RR], 0.46; 95% confidence interval [CI], 0.30 to 0.71).<sup>16</sup> Pacing protocols varied but usually were set 10 to 20 beats above the intrinsic rate for a period ranging from 1 to 5 days. In a similar meta-analysis comparing different prophylactic atrial pacing strategies, Daoud and associates found that biatrial pacing using either a fixed high-rate or variable rate overdrive and right atrial pacing with variable rate overdrive significantly reduced the incidence of post-cardiac surgery atrial fibrillation.<sup>17</sup> More recently, a meta-analysis of 12 trials encompassing 1708 patients (regardless of site or algorithm employed) found a significant decrease in the incidence of postoperative atrial fibrillation (RR, 0.67; 95% CI, 0.54 to 0.84) after cardiac surgery.<sup>18</sup> In summary, biatrial pacing after cardiac surgery appears to be more efficacious in preserving sinus rhythm than right or left atrial pacing, but a definitive conclusion is limited by the lack of large, well-controlled studies.

Current guidelines of the ACCP recommend consideration of biatrial pacing for prophylaxis in high-risk cardiac surgical patients.<sup>19</sup> In contrast, the American College of Cardiology and American Heart Association (ACC/ AHA) offer no such recommendations.<sup>20</sup> Although potentially advantageous, this strategy has not been explored in the non-cardiac surgery population. Pacing is limited to patients with implanted pacemakers or temporary epicardial pacing wires placed after cardiac surgery.

<sup>&</sup>lt;sup>††</sup>Permanent AF.<sup>3</sup>

Drugs	Trials, <sup>†</sup> No.	Patients Analyzed, No.	Does Therapy Reduce Postoperative AF vs Control?	Strength of Recommendation	Quality of Evidence Grade	Net Benefit
Beta-blockers (class II)	29	2,901	Yes	А	Fair	Substantial
Sotalol	8	1,279	Yes	В	Good	Intermediate
Amiodarone	10	1,699	Yes	В	Good	Intermediate
verapamil	4	541	Inconclusive	D	Low	None
Diltiazem	1	60	Inconclusive	D	Low	None
Magnesium	14	1,853	Inconclusive	D	Low	None
Digoxin	10	1,401	Inconclusive	Ι	Low	None
Digoxin + Propranolol	2	292	Yes	С	Low	Small/weak
Dexamethasone	1	216	Yes	Ι	Low	Conflicting
GIK	3	102	Inconclusive	D	Low	None
Insulin	1	501	Inconclusive	D	Low	None
Triiodothyronine	2	301	Inconclusive	D	Low	None
Procainamide	2	146	Inconclusive	D	Low	None
Alinidine	1	32	Inconclusive	D	Low	None
Quinidine	1	100	Inconclusive	D	Low	None

Table 47-2 Clinical Recommendations for Prophylactic Drug Therapies

\*GIK = glucose-insulin-potassium.

Current clinical recommendations for prophylactic therapy to prevent post-operative atrial fibrillation, with strength of recommendation, quality of evidence, and net benefit of therapy.

From Bradley D et al. Pharmacologic prophylaxis: American College of Chest Physicians guidelines for the prevention and management of postoperative atrial fibrillation after cardiac surgery. Chest. 2005;128:39s.

# **β-Blockers**

Considering the role of increased sympathetic tone in the pathogenesis of atrial fibrillation, it is not surprising that  $\beta$ -blockers have long been the cornerstone of outpatient therapy for tachyarrhythmias. Many studies have confirmed the utility of  $\beta$ -blockers for the postoperative prophylaxis of atrial fibrillation. For example, in a metaanalysis of 27 randomized trials in 2002, Crystal and associates found that  $\beta$ -blockers reduced the risk for developing atrial fibrillation following cardiac surgery by more than 60% (RR, 0.39; 95% CI, 0.28 to 0.52).<sup>21</sup> These findings were confirmed in a 2004 meta-analysis of 58 trials by the same author.<sup>22</sup> The antiarrhythmic benefit was observed when  $\beta$ -antagonists were started before or immediately after surgery and was independent of the agent or dose used. In the post-general thoracic (noncardiac) surgery patient population, a meta-analysis of two studies totaling 129 subjects demonstrated that perioperative β-blockade significantly reduced the incidence of postoperative atrial tachyarrhythmias (RR, 0.40; 95% CI, 0.17 to 0.95) but also increased the risk for hypotension and pulmonary edema.<sup>23</sup> The calculated protective effect of β-blockers in some of these trials (and by extension in meta-analysis) may have been overestimated by failure to adequately account for  $\beta$ -blocker withdrawal in the control groups. Of greater concern, more recent data have uncovered potential adverse outcomes associated with perioperative β-blockade. In 2004, the Beta Blocker Length

of Stay (BLOS) trial demonstrated that  $\beta$ -blocker–naïve post-cardiac surgery patients who received metoprolol in the perioperative period had a significantly increased length of stay in both the intensive care unit and hospital compared with placebo.<sup>24</sup> The Perioperative Ischemia Evaluation (POISE) trial, a large randomized controlled study (8351 patients) in a non-cardiac surgical population, found that perioperative β-blockers decreased the incidence of cardiac arrest (3.6% versus 5.1%) and myocardial infarction (4.2% versus 5.7%), but there was an increased risk for perioperative hypotension, bradycardia, stroke (1.0% versus 0.5%) and all-course mortality.<sup>25</sup> A post hoc analysis suggested that the increased incidence of clinically significant hypotension, bradycardia, and stroke may contribute to the increased risk for death observed in the treatment group. Additionally, a recent metaanalysis of 33 randomized controlled trials totaling 12,306 patients confirmed these findings, particularly the increased risk of bradycardia, hypotension, and nonfatal stroke observed in the experimental group.<sup>26</sup>

Both the 2006 ACC/AHA/ESC guidelines on atrial fibrillation<sup>11</sup> and the ACCP 2005 guidelines on pharmacologic prophylaxis for cardiac surgery<sup>12</sup> recommend preoperative or early postoperative  $\beta$ -blocker administration as standard therapy unless contraindicated. However, these recommendations must be reevaluated in light of the new evidence. The acute administration of highdose  $\beta$ -blocker therapy for the prevention of postoperative atrial fibrillation in a low-risk population may be associated with more risk than benefit. However,  $\beta$ -blockers should be continued in patients currently taking them and in patients with significant coronary artery disease or at high risk for a perioperative cardiac event.

# Sotalol

Sotalol is a class III antiarrhythmic agent that has both  $\beta$ and potassium channel-blocking activity. A meta-analysis of eight randomized, controlled trials totaling 1294 patients showed a significant reduction in post-cardiac surgical atrial fibrillation (odds ratio [OR], 0.35; 95% CI, 0.26 to  $(0.49)^{21}$  that was not superior to standard  $\beta$ -blockers.<sup>22</sup> Despite these findings, methodologic concerns (e.g., small populations, open-label design, selection bias) and potentially dangerous side effects (QT prolongation, torsades de pointes, hypotension, and bradycardia) have limited the use of sotalol in the post-cardiac surgical population. The current ACC/AHA guidelines ascribe a class IIb recommendation (efficacy less well established) for prophylaxis after cardiac surgery in patients who are not candidates for  $\beta$ -blockers.<sup>12</sup> The applicability of this guideline to noncardiac surgical patients is yet to be determined.

#### Amiodarone

Amiodarone, one of the most commonly used antiarrhythmic agents in the intensive care unit (ICU) setting, is frequently the antiarrhythmic of choice in patients with obstructive lung disease or cardiomyopathy. The prophylactic use of amiodarone to prevent post operative atrial fibrillation has been studied extensively. A meta-analysis of 19 randomized controlled trials involving 3295 cardiac surgical patients found that use of amiodarone was associated with significant reductions in the incidence of postoperative atrial fibrillation (OR, 0.50; 95% CI, 0.43 to 0.59), ventricular tachyarrhythmias (OR, 0.39; 95% CI, 0.26 to 0.58), and neurologic events (OR, 0.53; 95% CI, 0.30 to 0.92).<sup>27</sup>

The possibility of toxic side effects with this drug, however, is of great concern. Long-term use of amiodarone has been associated with hepatic, pulmonary, and endocrine toxicity. In addition, amiodarone administration can cause significant bradycardia, heart block, and hypotension. A meta-analysis of 18 trials (3408 patients) performed to assess the safety of amiodarone to prevent atrial fibrillation after cardiac surgery found an increased risk for bradycardia and hypotension in the amiodaronetreated group but no other statistically significant differences in other measured end points (heart block, myocardial infarction, stroke, and death).<sup>28</sup> These findings were most apparent in patients treated with high doses (>1 g per day), with intravenous formulations, and when initiated in the postoperative period.

The most recent ACC/AHA guidelines ascribe a class IIA recommendation for post–cardiac surgery atrial fibrillation prophylaxis with amiodarone,<sup>11</sup> whereas ACCP guidelines recommend consideration of amiodarone prophylaxis for patients in whom  $\beta$ -blockers are contraindicated.<sup>12</sup> There are insufficient data available to recommend amiodarone prophylaxis for patients undergoing noncardiac surgery.

#### **Calcium Channel Blockers and Digoxin**

Few data support the use of other antiarrhythmic drugs for atrial fibrillation prophylaxis. Although an earlier meta-analysis found little value in the use of nondihydropyridine calcium channel antagonists in preventing postoperative atrial fibrillation,<sup>29</sup> a recent meta-analysis suggests that calcium channel blockers do indeed decrease the incidence of postoperative atrial fibrillation after cardiac surgery.<sup>30</sup> In addition, a recent meta-analysis of four studies in patients undergoing general thoracic surgery found that calcium channel blockers were effective in preventing postoperative atrial fibrillation.<sup>23</sup> Currently, neither the ACCP nor the ACC/AHA guidelines recommend calcium channel blockers for the prevention of atrial fibrillation following cardiac surgery.

Digoxin had been advocated as effective prophylaxis against postoperative atrial fibrillation. The literature, however, does not support this. A meta-analysis found that the incidence of postoperative atrial fibrillation after cardiac surgery was not significantly decreased by digoxin use.<sup>29</sup> In fact, one study noted an increased risk for postoperative atrial fibrillation after thoracic surgery in patients who received digoxin.<sup>23</sup> No consensus guide-lines recommend the use of digoxin for postoperative atrial fibrillation prophylaxis.

#### Modulation of the Inflammatory Response

Recently, there has been growing interest in the suppression and modulation of the inflammatory response to prevent postoperative atrial fibrillation. A recent metaanalysis of 14 studies (1412 patients) found a modest reduction in new-onset atrial fibrillation after cardiac surgery in patients randomized to steroid therapy (RR, 0.71; 95% CI, 0.59 to 0.87).<sup>31</sup> Although steroids have many effects and stimulate different responses in different tissues, at least part of this effect may reflect suppression of inflammation. Similarly, the anti-inflammatory effects of statins are believed to contribute to the observed reduction in new-onset atrial fibrillation in patients receiving statin therapy. A meta-analysis of 3 randomized controlled trials and 16 observational studies comprising 31,725 patients found that the incidence of postoperative atrial fibrillation after cardiac surgery was significantly reduced by statins (OR, 0.67; 95% CI, 0.51 to 0.88).32 Although these results are intriguing, larger prospective studies of both statins and steroids need to be performed to confirm these findings and elucidate the mechanisms of their postulated prophylactic response.

# WHAT IS APPROPRIATE THERAPY FOR NEW-ONSET POSTOPERATIVE ATRIAL FIBRILLATION IN PATIENTS WITH HEMODYNAMIC INSTABILITY?

When approaching postoperative atrial fibrillation, it is important to distinguish arrhythmias that result in hemodynamic instability from those that do not. In the former case, Advanced Cardiac Life Support guidelines call for immediate synchronized cardioversion to sinus rhythm.

Data from prospective randomized trials suggest that biphasic shocks are more effective than monophasic shocks in converting atrial fibrillation to sinus rhythm.<sup>33</sup> Although historically, low-energy (50 to 100 J) shocks were used to convert atrial arrhythmias to sinus rhythm, a recent retrospective review of 2522 attempted electrical cardioversions found that initial shocks of less than 200 J increased the risk for subsequent development of ventricular arrhythmias and the conversion of atrial fibrillation to atrial flutter.<sup>34</sup> There was no detected increase in postcardioversion bradycardia or heart block in patients who received initial high-energy shocks. It would therefore seem prudent to use biphasic shocks with initial energy of 200 J for electrical cardioversion of patients with postoperative atrial fibrillation and hemodynamic instability.

# WHAT IS APPROPRIATE THERAPY FOR POSTOPERATIVE ATRIAL FIBRILLATION IN A HEMODYNAMICALLY STABLE PATIENT: RATE CONTROL OR RHYTHM CONTROL?

The initial approach to the development of postoperative atrial fibrillation in the patient who is not hemodynamically compromised is to control the ventricular response rate. After this has been accomplished, electrical or pharmacologic cardioversion can be attempted. Early restoration of sinus rhythm theoretically avoids the need for anticoagulation, improves quality of life, decreases the risk for thromboembolic events, improves hemodynamics, and decreases the incidence of future episodes of atrial fibrillation. Well-powered studies examining the superiority of rhythm control over rate control in postoperative atrial fibrillation are lacking. Interestingly, the data supporting the advantages of chronic rhythm control over rate control in the outpatient population have failed to demonstrate the superiority of rhythm control. No studies have shown definitively that rhythm control is superior to rate control or vice versa for the primary outcome measure of mortality in outpatients. These conclusions are based on a number of large randomized controlled trials. The Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) trial was the largest of these studies, enrolling 4060 patients. The mean follow-up in the study was 3.5 years, and no significant mortality difference between the rate control and rhythm control groups was found. However, there was a slightly higher incidence of noncardiovascular death, stroke (7.3% versus 5.7%), and hospitalization (80% versus 73%) in the rhythm control group. The increased rate of stroke was attributed to absent or subtherapeutic anticoagulation, and the increased rate in noncardiac mortality in the rhythm group was attributed to deleterious effects of antiarrhythmic agents. Subgroup analysis suggested better outcomes for patients in the rhythm control group who were younger than 65 years and in patients with left ventricular dysfunction. Other smaller studies, Rate Control versus Electrical Cardioversion (RACE), Pharmacological Intervention in Atrial Fibrillation (PIAF), Strategies of Treatment of Atrial Fibrillation (STAF), and How to Treat Chronic Atrial Fibrillation (Hot Café) were initially

interpreted to exhibit similar findings. The strategy of rhythm control offered no overall mortality benefit and may have contributed to an increased incidence of noncardiac death.

The definition of successful rhythm control may be too restrictive. Total and continuous cessation of dysrhythmias may be an unrealistic goal. Perhaps a more attainable end point would be long-term commitment to sinus rhythm with a marked reduction in overall number and frequency of episodes of atrial fibrillation. Reevaluation of the data from the rate versus rhythm trials suggests that remaining in sinus rhythm may confer several advantages. These include improved hemodynamics, reduction of thromboembolic events, lower mortality, improved quality of life, and improved exercise tolerance.35-38 A good discussion supporting the early restoration and maintenance of sinus rhythm was presented by van Gelder and Hemels.<sup>39</sup> A post hoc analysis of the AFFIRM trial, Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy (CHF-STA) trial, and Danish Investigators of Arrhythmia and Mortality on Dofetilide (DIAMOND) trial concluded that restoration of sinus rhythm is a marker for improved survival.<sup>40–42</sup> The largest multicenter randomized study of 4060 patients found sinus rhythm to be a predictor of survival, with a 47% reduction in mortality. The premise that maintenance of sinus rhythm improves outcome remains controversial and awaits further clarification.

The current literature confirms that both rate control and rhythm control are acceptable approaches to addressing atrial fibrillation. Choice may depend on the specific circumstances. Postoperative atrial fibrillation should be considered an entity distinct from chronic atrial fibrillation. More than 90% of patients who develop post-CABG atrial fibrillation revert to sinus rhythm within 6 to 8 weeks, a fact that underscores this distinction.<sup>43</sup> Advances in our understanding of the pathophysiology and development of new drugs and therapeutic interventions may confound the application of these earlier rate versus rhythm studies when developing strategies for treating atrial fibrillation in the future. The potential beneficial impact of emerging interventions such as atrial ablation are only now being investigated and awaits large multicenter studies. In addition, a multimodal approach with wider application of angiotensin-receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors, and statins may potentially affect success in restoring and maintaining sinus rhythm.

#### **Rate Control**

Most of the data concerning rate control for postoperative atrial fibrillation comes from the cardiac surgical literature. As such, it may not be appropriate to extrapolate these data to the general postoperative patient population.

β-Blockers, with their ability to modulate the hyperadrenergic tone encountered in the postoperative patient, are considered first-line agents for rate control in both the ACC/AHA guidelines section on postoperative atrial fibrillation<sup>11</sup> and the ACCP guidelines on the management of postoperative atrial fibrillation after cardiac surgery (Table 47-3).<sup>44</sup> The nondihydropyridine calcium Table 47-3 Clinical Recommendations, Evidence Grade, and Benefit of Pharmacologic Agents for Control of Ventricular Rate in Patients with Postoperative Atrial Fibrillation

Drug	Strength of Recommendation	Evidence Grade	Net Benefit
Beta- blockers	В	Low	Intermediate
Calcium channel blockers	В	Low	Intermediate
Amiodarone	Ι	Low	Small/weak
Digoxin	Ι	Low	None
Propafenone	D	Low	Negative
Dofetilide	D	Low	Negative

From Martinez EA, Epstein AE, Bass EB. Pharmacologic control of ventricular rate. Chest. 2005;128:56S-60S.

channel blockers are recommended as second-line agents. Amiodarone is recommended for patients having significant cardiac or pulmonary dysfunction in whom the alternatives may be contraindicated.

#### **Rhythm Control**

Because of the self-limited nature of most cases of postoperative atrial fibrillation, the ACC/AHA guidelines only recommend pharmacologic or electrical cardioversion when the patient is symptomatic or when the rate cannot be effectively controlled.<sup>11</sup> Both the ACC/AHA and ACCP guidelines recommend the use of amiodarone, particularly for patients with depressed left ventricular function. For patients with normal left ventricular function, sotalol, class 1A antiarrhythmics (procainamide), and ibutilide are acceptable choices as well. Antiarrhythmic use for postoperative atrial fibrillation should be continued for 4 to 6 weeks after surgery.<sup>45</sup>

# ANTICOAGULATION STRATEGY BEFORE RESTORATION OF SINUS RHYTHM: ATRIAL FIBRILLATION FOR LESS THAN 48 HOURS

It is common practice for patients with new onset of atrial fibrillation of less than 48 hours' duration to proceed to cardioversion without transesophageal echocardiography (TEE) or anticoagulation. There are no randomized controlled studies that examine the need for early anticoagulation before cardioversion for these patients. Although cardioversion of new-onset atrial fibrillation without anticoagulation would appear safe, the risk for embolization may persist. In a study describing early restoration of sinus rhythm, the incidence of thromboembolic events was 0.8%.<sup>46</sup> Further complicating this issue is the fact that the inflammatory response to surgery induces a hypercoagulable state that may increase the risk for a thromboembolic event. Currently, the ACCP guidelines on antithrombotic

therapy in atrial fibrillation recommend unfractionated or low-molecular-weight heparin for patients presenting with new-onset atrial fibrillation before cardioversion.<sup>40</sup> In the postoperative setting, the risk for anticoagulation for cardioversion must be weighed against the risk for bleeding. Therefore, it may be prudent to selectively anticoagulate before cardioversion of high-risk patients having atrial fibrillation of less than 48 hours' duration.

# ANTICOAGULATION STRATEGY BEFORE RESTORATION OF SINUS RHYTHM: ATRIAL FIBRILLATION FOR MORE THAN 48 HOURS

At times, patients present to the ICU having been in atrial fibrillation for more than 48 hours. In these individuals, anticoagulation before cardioversion is the accepted standard. ACC/AHA and ACCP guidelines recommend 3 weeks of anticoagulation (target international normalized ratio [INR] of 2.5) before cardioversion of patients with chronic atrial fibrillation (Fig. 47-1).<sup>12,40</sup> Vitamin K antagonism by warfarin administration is the most commonly accepted practice. Data from a European observational study found that a greater INR produced a better outcome. The incidence of thromboembolic events was 0.8% (4 of 530 patients) when the INR was 2.0 to 2.4 compared with no events when the INR was 2.5 or greater.<sup>47</sup> Maintenance of patients within a tight therapeutic INR range can be difficult. In a large retrospective study from a community-based health care plan database, about one third of the group was within the therapeutic INR range (2.0 to 3.0) less than 20% of the time and only 19% of patients were maintained within the therapeutic range most or all of the time.<sup>48</sup> As expected, INR levels lower than 2.0 were associated with an unadjusted risk of 2.39 for stroke and 5.68 for thromboembolism. INR levels higher than 3.0, however, were associated with an unadjusted relative risk of 2.11 for intracranial hemorrhage. Because tight therapeutic control may be difficult to achieve, the choice of a target INR must balance the risk for bleeding complications against the risk for being subtherapeutic and increasing the risk for stroke.



**Figure 47-1.** Adjusted odds ratio for ischemic stroke and intracranial bleeding in relation to intensity of anticoagulation. (*Reproduced* with permission from ACC/AHA/ESC 2006 Guidelines for Management of Patients with Atrial Fibrillation. Circulation 2006;114;e257.)

# DO ALL PATIENTS REQUIRE A LONG COURSE OF ANTICOAGULATION BEFORE ELECTIVE CARDIOVERSION?

An alternative approach to 3 to 4 weeks of anticoagulation before elective cardioversion in patients with atrial fibrillation for longer than 48 hours is to perform echocardiography. TEE has a higher sensitivity for detection of thrombus formation in the left atrium and atrial appendage than the transthoracic approach. In a large randomized study of 1222 patients requiring elective cardioversion, the Assessment of Cardioversion Using Transesophageal Echocardiography (ACUTE) trial demonstrated that TEEguided screening for atrial thrombus was as effective in reducing thromboembolic events as anticoagulation.<sup>49</sup> Additionally, the ACUTE trial showed that early restoration of sinus rhythm after TEE significantly reduced bleeding complications compared with the control group (29% versus 5.5%).<sup>50</sup> Both the ACCP and ACC/AHA guidelines recommend precardioversion TEE as an alternative strategy to anticoagulation before pharmacologic or electrical cardioversion. The TEE-guided approach to expedite restoration of sinus rhythm is of particular interest for postoperative patients who may be at increased risk for hemorrhagic events related to anticoagulation.

# SHOULD ANTICOAGULATION BE INSTITUTED OR CONTINUED AFTER ELECTRICAL CARDIOVERSION TO SINUS RHYTHM?

The period following conversion to sinus rhythm is associated with an increased risk for thrombus formation and subsequent embolization. Several explanations have been proposed for this increased risk. The recurrence of asymptomatic atrial fibrillation ranges from 40% to 60%,<sup>51,52</sup> and other predisposing factors such as atheromatous disease and poor ventricular function also may increase the risk for thromboembolism.<sup>53</sup> Perhaps the most significant factor is the transient decrease in atrial mechanical function that occurs after cardioversion to sinus rhythm. A number of echocardiographic studies have noted decreased mechanical function of the left atrium and atrial appendage.<sup>54</sup> This transient atrial contractile dysfunction may be related to the duration of atrial fibrillation. Mechanical dysfunction after cardioversion appears to last 24 hours in patients having atrial fibrillation of less than 2 weeks' duration, 1 week in patients with atrial fibrillation of 2 to 6 weeks' duration, and 1 month for more prolonged precardioversion atrial fibrillation.<sup>55</sup> To date, there is no pharmacologic intervention to hasten the return of atrial mechanical activity. Impaired postcardioversion left atrial contractility may place patients at increased risk for thromboembolic stroke after restoration of sinus rhythm.

Support for continued anticoagulation can be gleaned from the AFFIRM<sup>56</sup> and RACE<sup>57</sup> trials. Anticoagulation during these studies was often discontinued after restoration of sinus rhythm. Ischemic events occurred at equal frequency in both arms of the trials (rate control and rhythm control). Review of the data showed that such complications occurred most often after anticoagulation was terminated (rhythm control group) or when the INR was subtherapeutic (rate control group). Although the patients in these studies had chronic (not postoperative) atrial fibrillation, restoration of sinus rhythm in subtherapeutic or non-anticoagulated patients was associated with the increased incidence of thromboembolic events. Further, the literature that provides the basis for these recommendations in general does not distinguish between patients who required electric cardioversion and those who spontaneously or pharmacologically converted to sinus rhythm. It seems prudent that guidelines for both electrical and pharmacologic cardioversion be followed in a similar manner.

Restoration of sinus rhythm in critically ill patients can often be accomplished after a short period of atrial fibrillation. Current guidelines of the ACCP recommend 4 weeks of anticoagulation to an INR of 2.5 for patients who are cardioverted after an episode of atrial fibrillation lasting more than 48 hours. For episodes less than 48 hours in duration, the ACCP guidelines do not recommend postcardioversion anticoagulation.<sup>58</sup> The ACC/AHA guidelines add that the decision to initiate postcardioversion anticoagulation for patients with atrial fibrillation of less than 48 hours' duration should be based on the patient's risk for development of thromboembolism.<sup>11</sup> Although neither the ACCP nor ACC/AHA guidelines specifically address postcardioversion anticoagulation for postoperative atrial fibrillation, it seems prudent to follow these recommendations in this setting, provided that the risk for bleeding does not outweigh the risk for a thromboembolic event.

# **AUTHORS' RECOMMENDATIONS**

- The pathogenesis of atrial fibrillation in the postoperative period is complex and multifactorial. The inflammatory response and increased levels of circulating catecholamines induced by surgery trigger supraventricular arrhythmias by altering atrial refractoriness and conductivity predisposing to automaticity and reentrant rhythms.
- The type of surgery performed has a significant impact on the incidence of perioperative atrial fibrillation. Direct surgical manipulation or compression of the atria or pulmonary veins is associated with postoperative atrial fibrillation.
- Prophylactic strategies against atrial fibrillation include maintenance of electrolytes (magnesium), atrial pacing, and administration of antiarrhythmic agents. Other strategies that include a role for anti-inflammatory agents have been proposed and are under active investigation.
- β-Adrenergic antagonists and alternative agents (sotalol and amiodarone) are recommended for prophylaxis against atrial fibrillation by the ACC/AHA guidelines. Patients taking β-blockers on an outpatient basis should continue receiving them during the perioperative period. However, the prophylactic use of such agents in patients with low cardiac risk is controversial.
- Postoperative atrial fibrillation associated with hemodynamic instability should be treated with biphasic cardioversion at 200 J.
- Postoperative atrial fibrillation is often an acute event with a high conversion rate to sinus rhythm. The premise that maintenance of sinus rhythm improves outcome remains

controversial. Both rate and rhythm control are acceptable approaches to treating chronic atrial fibrillation.

- Patients with new onset of atrial fibrillation of longer than 48 hours' duration are at increased risk for thromboembolic events and should receive anticoagulant therapy. Anticoagulation should be temporarily continued after restoration of sinus rhythm because of a transient decrease in atrial mechanical function that increases the risk for thromboembolic events. Potential benefits of anticoagulation must be weighed against the risks for postoperative bleeding.
- Examination of the left atrium and appendage by TEE for thrombus formation is recommended before elective cardioversion in order to reduce the risk for an embolic event.

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# Is Right Ventricular Failure Common in the Intensive Care Unit? How Should It Be Managed?

Isaac Halickman, Steven M. Hollenberg

# BACKGROUND

In 1616, William Harvey described the relationship of the right ventricle (RV) to the pulmonary circulation.<sup>1</sup> For many years after that, this cardiac chamber has been underappreciated at the bench and at the bedside. In 1943, after demonstrating that ablation of the RV free wall in dogs had little effect on central venous pressure (CVP), Starr concluded that the RV was merely a passive conduit.<sup>2</sup> It was not until 1974 that Cohn and colleagues first noted the importance of the RV. These investigators recognized that RV infarction was common and difficult to manage. RV involvement in inferior myocardial infarction has been found to increase mortality eightfold,<sup>3</sup> and RV dysfunction in acute pulmonary embolism (PE) is a predictor of mortality.<sup>4</sup>

RV failure is defined as the inability of the RV to provide adequate blood flow through the pulmonary circulation at a normal CVP. RV failure is common and coexists with a broad range of critical illnesses. These include respiratory failure, sepsis, PE, and RV myocardial infarction. Despite this, the RV remains poorly studied when compared with the left ventricle (LV). Cardiologists focus on the LV, and pulmonologists tend to concentrate on the causes and treatment of pulmonary hypertension. In fact, the RV is barely mentioned in the American College of Cardiology and American Heart Association (ACC/AHA) practice guidelines, and no recommendations are provided for management of RV dysfunction.<sup>5</sup>

The heterogeneity of illnesses and varying degrees of disease severity make randomized controlled trials difficult to conduct in critically ill patients with RV dysfunction. Most intensive care unit (ICU) therapies are instituted based on clinical reasoning from pathophysiologic considerations and extrapolation from trials in other settings. Because of this, this review will begin with brief consideration of normal and abnormal RV function.

# PHYSIOLOGY

The physiology of the RV differs dramatically from that of the LV. The RV is not simply a weak LV. The RV wall is 3 to 4 times thinner than that of a normal LV. RV contraction moves from the apex to the outflow tract with peristalsis-like motion. The normal RV generates one sixth the work of the LV while moving the same volume of blood. The easily distensible RV pumps blood into the low-pressure pulmonary circuit. This allows the RV to accommodate dramatic variations in venous return while maintaining constant cardiac output. Global function of the RV depends on contributions from the interventricular septum and the RV free wall.<sup>6</sup>

#### PATHOPHYSIOLOGY

The RV responds to increased afterload first by increasing contractility and later by dilating according to the Frank-Starling mechanism. Guyton<sup>7</sup> showed that with progressive constriction of the pulmonary artery, generated RV pressure rises until the RV can no longer compensate. At that point, systemic pressure and cardiac output fall (Fig. 48-1). As RV systolic pressure increases, RV ischemia may ensue.

When RV failure occurs due to either excessive contractile demand or impaired contractile function, CVP rises. Ultimately, RV dilation occurs. This eventually becomes maladaptive through increased wall stress, impairing contraction and impinging on the LV through the interventricular septum<sup>8</sup> (Fig. 48-2).

#### DIAGNOSIS

No one sign, symptom, or laboratory test perfectly identifies RV failure. However, RV failure is not present if the jugular venous pressure (JVP) is normal. A parasternal



**Figure 48-1.** The limits of right ventricular (RV) contractile function in the setting of increasing pulmonary artery outflow obstruction, with the resulting abrupt and catastrophic collapse in systemic hemodynamics once RV compensatory mechanisms are exhausted. PA, pulmonary artery; RA, right atrial. (*Modified from Guyton AC, Lindsey AW, Gilluly JJ. The limits of right ventricular compensation following acute increase in pulmonary circulatory resistance.* Circ Res. 1954;2:326-332.)



**Figure 48-2.** Ventricular interdependence. Right ventricle (RV) failure and dilation leading to encroachment of interventricular septum on the left ventricle (LV), causing increased left ventricular enddiastolic pressure.

heave, right third heart sound, loud P2, TR murmur, hepatomegaly, ascites, and peripheral edema may be present in RV failure. Electrocardiogram (ECG) findings are nonspecific, but right-axis deviation, R/S > 1 in V1, and P pulmonale may be seen. Absence of pulmonary congestion with elevated CVP is often considered most specific for RV failure. However, severe RV failure can lead to shift of the interventricular septum and increased left ventricular end-diastolic pressure (LVEDP), and this may cause pulmonary congestion (see Fig. 48-2). Serum brain natriuretic peptide (BNP) level may be increased with RV failure, although the sensitivity is lower than in LV failure.

The assessment of RV function can be challenging. Cardiac magnetic resonance imaging (MRI) is now an accepted standard because of its spatial resolution and ability to show the RV's complex geometry. However, MRI use in the ICU is limited by its lack of availability and the difficulty of continuously monitoring critically ill patients in the scanner. Radionuclide scanning is limited by poor spatial resolution, the need for background radiation correction, and lack of portability. Contrast ventriculography is invasive and provides limited incremental information when compared to echocardiography.<sup>9</sup>

Echocardiography is a noninvasive, portable modality that can be used to assess the size and function of the RV. Right and left heart hemodynamics can be estimated using Doppler techniques. With transthoracic echocardiography (TTE), the normal-sized RV should be less than two thirds the size of the LV. When it is larger than this, the RV is considered dilated. RV size can be measured from the apical four-chamber view using planimetry.<sup>10</sup>

RV function can be estimated visually by examining the contractility of the RV free wall and interventricular septum. One quantitative approach involves determination of the volumes at end systole and end diastole. However, this method is limited by the false assumption that the RV is a cylindrical structure. In the four-chamber view, the systolic excursion of the tricuspid annular plane (TAPSE; normal =  $2.46 \pm 0.5$  cm) can be measured by positioning the M-mode cursor on the lateral portion of the tricuspid annulus. This movement reflects the baseto-apex shortening of the right ventricle in systole and has been shown to correlate well with RV function.<sup>11</sup>

RV hypokinesia that spares the RV apex (McConnell sign) once was thought to be specific for acute pulmonary embolus.<sup>12</sup> RV volume overload causes dilation of RV and is characterized by septal flattening and shift toward the LV during diastole. Pressure overload causes RVH (right ventricular hypertrophy), flattening of the septum, and septal displacement toward the LV throughout the cardiac cycle.<sup>10</sup>

The main pitfall of TTE in ventilated critically ill patients is that echo images are often suboptimal and technically limited. Transesophageal echocardiography can be used when TTE images are uninterpretable.

# CAUSES OF RIGHT VENTRICULAR DYSFUNCTION

The causes of RV failure can be divided into RV pressure overload, RV volume overload, decreased RV contractility, or a combination of these (Fig. 48-3). Sepsis is a disease process that may involve two different mechanisms of RV dysfunction: myocardial depression and increased pulmonary vascular resistance.<sup>13</sup>

# MANAGEMENT OF RIGHT VENTRICULAR FAILURE

Definitive therapy for an acutely decompensated RV requires primary treatment of the underlying condition in addition to hemodynamic support. The RV is very resilient and can recover substantially if the underlying condition is successfully addressed.<sup>14</sup> Examples include percutaneous coronary intervention for RV infarction and thrombolysis or open surgical embolectomy for massive PE.



# RIGHT VENTRICULAR MYOCARDIAL INFARCTION

RV myocardial infarction is a distinct clinical entity, and there is a reasonable evidence base regarding its management. For this reason, RV myocardial infarction will be examined separately.

One third of inferior wall myocardial infarctions are accompanied by RV infarction. This typically occurs when there is acute thrombotic occlusion of the right coronary artery (RCA) proximal to the RV marginal branches.<sup>15</sup> In acute RV injury, chamber enlargement, depressed contractility, and impaired ventricular emptying lead to elevated right-sided volume and pressure. The RV also experiences decreased compliance, further raising pressures. This leads to a conformational change in the RV that may affect the LV through ventricular interdependence.

The classic clinical features of RV myocardial infarction are hypotension, systemic venous congestion, and clear lungs. ECG findings of ST elevation of more than 1 mm in right-sided lead V4 in the presence of inferior wall injury are reliable and predictive of RV myocardial infarction (88% sensitive, 78% specific).<sup>16</sup> Other ECG findings include atrioventricular nodal block and right bundle branch block. Hemodynamic findings include elevated right atrial pressure in relation to left-sided filling pressures. Equalization of diastolic filling pressures between the right atrium, RV, and pulmonary capillary wedge pressure may be seen. The steep y descent of the right atrial pressure tracing and the characteristic dip and plateau of the RV pressure tracing make this entity more hemodynamically similar to constrictive pericarditis and serve to differentiate RV myocardial infarction from cardiac tamponade. Two-dimensional echocardiography is useful in identifying RV chamber enlargement and wall

motion abnormalities of the free wall. Paradoxical septal motion can be seen in the presence of RV pressure-volume overload.

RV myocardial infarction may be complicated by cardiogenic shock and high-grade atrioventricular block, both of which affect mortality.<sup>17,18</sup> Right atrial dilation can lead to atrial fibrillation that may further affect hemodynamics.

Treatment of RV myocardial infarction includes close monitoring in a specialized cardiac unit. Unlike LV infarction, the initial treatment is volume expansion. However, excess fluid administration can cause overdilation of the right ventricle, compromising LV filling and cardiac output.<sup>19</sup> Berisha and associates<sup>20</sup> determined that the RV achieves its maximal stroke work with right atrial pressure from 0 to 14 mm Hg. The optimal pulmonary capillary wedge pressure was 17 mm Hg in this study. In the setting of low cardiac index and optimized LV filling, inotropic support with dobutamine can be used. In general, nitrates, morphine, diuretics, and other vasodilators should be avoided. Central hemodynamic monitoring may be helpful for diagnostic purposes and for guiding therapy.<sup>19,21</sup> Maintenance of sinus rhythm and atrioventricular synchrony is crucial in maximizing RV preload and function.<sup>22,23</sup> Intra-aortic balloon pump counterpulsation may be considered when there is ongoing ischemia or refractory hemodynamic instability.<sup>18</sup>

For various reasons, fibrinolytic therapy has demonstrated limited benefit in acute inferior myocardial infarction with RV involvement. First, reocclusion has been shown to be more common when the RCA is the infarctrelated artery. Second, mortality from acute inferior myocardial infarction is considerably less than for anterior myocardial infarction. Finally, RV function has been shown to improve spontaneously over time even in the

absence of reperfusion therapy.<sup>18</sup> A retrospective analysis of 1110 patients enrolled in phase II of the Thrombolysis in Myocardial Infarction trial showed that fibrinolysis reduced the frequency of RV dysfunction in patients with inferior infarction as demonstrated by radionuclide ventriculography. In a prospective trial, Giannitsis administered tissue plasminogen activator (tPA) along with antithrombotic and antiplatelet therapy within 4 hours of symptom onset to 90 patients presenting with inferior myocardial infarction with or without RV involvement.<sup>24</sup> Coronary angiography performed later in the hospital course found that normal coronary flow was more likely in those without RV myocardial infarction. In RV myocardial infarction, complications were higher, and late vessel patency was only 29% 12 days after tPA administration.<sup>2</sup>

The advantages of percutaneous transluminal coronary angioplasty (PTCA) over fibrinolysis include better infarct-related artery (IRA) patency rates, lower incidence of intracranial hemorrhage, and decreased recurrent ischemia. Bowers and colleagues studied 53 patients who presented with inferior and RV myocardial infarction with contractile dysfunction who were taken for emergent PTCA.<sup>25</sup> Restoration of flow to the major RV branches was achieved in 77% of patients, and those who had successful reperfusion had early recovery of RV function, as early as 1 hour as assessed by echo. Those who had unsuccessful reperfusion had protracted hemodynamic compromise requiring inotropic support with a mortality rate of 58%, compared with 2% in the reperfused group. Emergency revascularization efforts in these patients is now a class I recommendation in the ACC/AHA guidelines for the treatment of acute myocardial infarction.<sup>26</sup>

#### **BASIC MANAGEMENT PRINCIPLES**

Patients with RV failure often are preload dependent. However, volume loading has the potential to overdistend the ventricles. This may cause increased wall tension, decreased contractility, increased ventricular interdependence, impaired LV filling, and reduced systemic cardiac output.<sup>14</sup> The utility of volume loading appears to depend on various factors. These include the baseline cardiovascular function of the patient, the degree of RV afterload, and the volume status. An initial trial of volume may be appropriate for patients with decompensated RV failure, provided there is no evidence of pulmonary edema or increased right-sided preload conditions.<sup>14</sup> If signs of RV volume overload, including a CVP greater than 15 mm Hg, or septal shift, are noted on echocardiography, the initiation of pressors and inotropes without additional volume administration may be prudent. Pulmonary artery catheterization may be helpful in determining the ideal volume-loading conditions.<sup>14</sup>

Mechanical ventilatory support for patients with acute RV failure should aim to improve oxygenation and ventilation without worsening RV impedance, venous return, or diastolic function. Hypoxemia and acidosis can contribute to increased pulmonary vascular resistance.<sup>27,28</sup> A low respiratory rate and low tidal volume should be used to limit gas trapping, which may increase pulmonary vascular resistance. Lower positive end-expiratory pressure settings may also limit the effect of mechanical ventilation on pulmonary vascular resistance.<sup>14</sup>

Hemodynamic support of the patient with decompensated RV failure often requires combinations of vasopressors and inotropes. The normotensive patient with evidence of decreased cardiac output should be started on inotropic therapy, with vasopressors added if a hypotensive response develops.<sup>14</sup> The hypotensive patient with decreased cardiac output should receive vasopressors, preferably norepinephrine first, and then inotropes if cardiac output remains low.<sup>14</sup> Dobutamine has been shown to have beneficial effects on RV contractile function in pulmonary hypertension without affecting pulmonary vascular resistance.<sup>29</sup> During RV infarction, dobutamine has been shown to exert overall favorable hemodynamic effects and is considered the inotrope of choice.<sup>19,30</sup>

One study examined the effects of inhaled nitric oxide (NO) in 13 patients with RV infarction and cardiogenic shock.<sup>31</sup> Acute hemodynamic improvement was seen, with a 24% increase in cardiac output along with a 12% decrease in right atrial pressure, a 13% decrease in pulmonary artery pressure, and a 36% decrease in pulmonary vascular resistance. Systemic blood pressure and pulmonary capillary wedge pressure were unchanged.<sup>31</sup> The presumed mechanism was selective pulmonary vasodilation.

Intra-aortic balloon pumps in RV failure may augment right coronary artery perfusion, reduce ischemia, and allow for the weaning of vasopressors that adversely affect pulmonary vascular resistance.<sup>32</sup> RV assist devices may improve hemodynamics and act as bridges to cardiac transplantation in patients with RV failure secondary to disease intrinsic to the ventricle.<sup>14</sup>

# VASODILATOR THERAPY

The goal of vasodilator use in RV failure is to improve right-sided cardiac output by reducing afterload. There is substantial evidence concerning vasodilator therapy in pulmonary arterial hypertension and also some data in secondary pulmonary hypertension (Table 48-1). Available therapies include prostaglandins, endothelin antagonists, and phosphodiesterase inhibitors.

Prostacyclin has both vasodilatory and antiplatelet properties.<sup>33,34</sup> Use of intravenous epoprostenol (a formulation of prostacyclin) was a watershed in therapy for severe pulmonary hypertension. A randomized openlabel 12-week clinical trial demonstrated improved hemodynamics, exercise tolerance, and mortality with epoprostenol compared with placebo in patients with pulmonary arterial hypertension (PAH).<sup>34</sup> Long-term follow-up studies have demonstrated 1-, 2-, and 3-year survival rates of 85% to 88%, 70% to 76%, and 63%, respectively. These rates are substantially higher than would have been predicted.<sup>35,36</sup> Similar long-term hemodynamic and survival benefits have been observed in patients with scleroderma and pulmonary hypertension with epoprostenol treatment.<sup>33</sup> Intravenous administration of epoprostenol causes systemic hypotension. Further, intravenous use of this drug is complicated by its very short half-life, requiring administration through continuous infusion, its

Table 40-1 Prospective Studies of Vasoullator Therapy in Chronic Pullionary Type tension					
Study	No. of Patients	Drug	Descriptor	NYHA Class Etiology	Results
Barst et al, 1996 <sup>34</sup>	81	Epoprostenol IV	Multicenter open comparison of conventional therapy alone vs. conventional therapy along with an intravenous infusion of epoprostenol	Classes III and IV PPH	At 12 weeks: Improvement on a 6-min walk test Improvement of hemodynamics Eight patients in the conventional-therapy group died during the study, whereas no deaths occurred in the epoprostenol group (P = .003)
Badesch et al, 2000 <sup>33</sup>	111	Epoprostenol IV	Multicenter open comparison of conventional therapy alone vs. conventional therapy along with an intravenous infusion of epoprostenol	Classes II-IV Scleroderma and mod. PHTN	At 12 weeks: Improvement on a 6-min walk test Improvement of hemodynamics No mortality benefit
Simonneau et al, 2003 <sup>53</sup>	470	Treprostinil subcutaneous	Double-blind placebo vs. treprostinil	Classes II-IV PPH, connective tissue disease, congenital left-to-right shunt	At 12 weeks: Modest but significant median increase of 16 m on the 6-minute walk test Treprostinil appeared to improve indices of dyspnea, signs and symptoms of pulmonary hypertension, and hemodynamic measures significantly
Galie et al, 2002 <sup>54</sup>	130	Beraprost PO	Double-blind, placebo-controlled	Classes II and III Multiple etiologies	At 12 weeks: Minimal improvement in 6-min walk test No change in hemodynamics Frequent side effects
Barst et al, 2003 <sup>55</sup>	116	Beraprost PO	Double-blind placebo-controlled	Classes II and III	Improved 6-min walk scores at 3 and 6 mo Effect not sustained at 9 and 12 mo
Olschewski et al, 2006 <sup>56</sup>	207	Iloprost INH	Multicenter placebo-controlled They used a combined end point of a 10% increase in patients' scores on a 6-min walk test and improvement in NYHA functional class	Classes III and IV PPH, CTD, chronic thromboembolic	<ul> <li>At 12 weeks:</li> <li>17% of treated patients reached this end point, compared with 4% of the placebo group (<i>P</i> = .007)</li> <li>Hemodynamics values measured after inhalation were better in the iloprost group</li> <li>Short half-life requires multiple doses (6-12) due to short duration of action</li> </ul>

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Table 48-1 Prospective Studies of Vasodilator Therapy in Chronic Pulmonary Hypertension—Cont'd					
Study	No. of Patients	Drug	Descriptor	NYHA Class Etiology	Results
Channick et al, 2001 <sup>41</sup>	33	Bosentan PO	Double-blind placebo	Class III PPH	Patients receiving bosentan had a mean gain of 76 m in the 6-minute walk test ( $P = .02$ ) and significant improvements in pulmonary artery pressure, cardiac output, and pulmonary vascular resistance
Rubin et al, 2002 <sup>57</sup>	213	Bosentan PO	Double-blind placebo	Classes III and IV PPH	<ul> <li>On 6-min walk test, a gain of 44 m among patients in the overall study population (<i>P</i> &lt; .001)</li> <li>Patients receiving bosentan also had improvement in the time to clinical worsening</li> <li>High incidence of serum aminotransferase increases</li> </ul>
Galie et al, 2005 <sup>58</sup>	64	Ambrisentan PO	Double-blind placebo	Classes II and III idiopathic PAH or PAH associated with collagen vascular disease, anorexigen use, or human immunodeficiency virus infection	At 12 weeks: Ambrisentan increased 6-min walk test Improvements were also observed in Borg dyspnea index, WHO functional class, subject global assessment, mean pulmonary arterial pressure
Barst et al, 2004 <sup>59</sup>	178	Sitaxsentan PO	Multicenter placebo, vs. sitaxsentan, 100 mg and 300 mg	Classes II-IV idiopathic, associated with connective tissue disease and PAH associated with congenital heart defects	At 12 weeks: 7% increase in peak oxygen consumption per unit time (Vo <sub>2</sub> ) in 300 mg group only Both 100 mg and 300 mg had 9% increase on 6-min walk test 9.5% of 300-mg group had liver abnormalities
Galie et al, 2005 <sup>39</sup>	278	Sildenafil	Double-blind placebo-controlled sildenafil (20, 40, 80 mg)	Classes II-IV PPH, CTD, and repaired congenital disease	At 12 weeks: Improvement of 45-60 m on 6-min walk test Improved hemodynamics No dose-response relationship

CTD, connective tissue disease; PAH, pulmonary arterial hypertension; AH, portal hypertension; PPH, primary pulmonary hypertension.

concentration, mandating infusion through a central venous catheter, and its instability at room temperature so that ice packs must be used to keep it cold before and during infusion. Inhaled epoprostenol has an effect on hemodynamics and oxygenation similar to that of NO in patients with acute respiratory distress syndrome (ARDS).<sup>37</sup> Epoprostenol has a longer half-life (3 to 6 minutes) than NO. Therefore, recirculation leads to greater pulmonary and systemic hypotensive effects with less improvement in oxygenation.<sup>37</sup> Inhaled NO and nebulized prostacyclin have been observed to have additive effects, for example, after lung transplantation.<sup>38</sup>

NO mediates its effects by increasing cyclic guanosine monophosphate (GMP) in vascular smooth muscle cells and inhibiting phosphodiesterases that inactivate cyclic GMP. Sildenafil is an inhibitor of phosphodiesterase type 5, the isoform most abundant in the lung. Sildenafil alone improves hemodynamics and exercise tolerance in patients with pulmonary hypertension. It also augments and prolongs the effects of inhaled NO and has been shown to improve hemodynamics in open-label and small crossover trials.<sup>39</sup> Sildenafil can act synergistically with inhaled iloprost without significant adverse hemodynamic effects.<sup>39</sup>

Endothelin-1 is a potent vasoconstrictor that might increase vascular tone in pulmonary hypertension. There are two distinct endothelin receptors: ETA, found on smooth muscle cells, mediates vasoconstriction and hypertrophy, whereas ET<sub>B</sub> on endothelial cells mediates the release of NO and prostacyclin. Bosentan is a dual  $ET_A/ET_B$  endothelin receptor antagonist that can be given orally. Randomized trials of bosentan in patients with pulmonary hypertension demonstrate improved hemodynamics, symptoms, right heart function, and functional class.<sup>40,41</sup> Selective ET<sub>A</sub> receptor blockade would appear to be a promising strategy because ET<sub>B</sub>-mediated release of NO and prostacyclin would be expected to be beneficial. Sitaxsentan, a selective ET blocker, has been shown to improve hemodynamics and exercise tolerance in patients with pulmonary hypertension.<sup>40,42</sup>

In acute RV failure, however, data are sparse. Most concern pulmonary vasodilation with inhaled nitric oxide (iNO).<sup>37</sup> iNO is rapidly inactivated and thus has minimal effects on systemic blood pressure. Its effects are limited to ventilated areas of the lung. This, in theory, may improve ventilation-perfusion matching. Inhaled NO is usually well tolerated. However, it may precipitate acute pulmonary edema in patients with LV dysfunction. Other risks include platelet dysfunction and the formation of toxic compounds such as peroxynitrites.<sup>37</sup> Use is limited by its high cost and significant rebound effects on discontinuation.

The physiologic benefits demonstrated in ARDS patients have led to the use of inhaled NO as a supportive treatment for acute RV dysfunction in other settings. A nonrandomized study<sup>43</sup> evaluated inhaled NO in critically ill patients with pulmonary hypertension and echocardiographically diagnosed acute RV failure. The etiologies of RV failure included ARDS, pulmonary hypertension, chronic obstructive pulmonary disease, PE, and obstructive sleep apnea. In responders, inhaled NO significantly reduced the pulmonary artery pressures and pulmonary vascular resistance and consequently increased cardiac output, stroke volume, and mixed venous oxygen saturation. No mortality benefit was demonstrated. Other studies have demonstrated hemodynamic improvement in patients with RV dysfunction after cardiac surgery<sup>44</sup> and with acute massive PE.<sup>45</sup>

Atrial septostomy has been used in severe pulmonary hypertension with concomitant RV failure. The creation of a shunt at the atrial level decompresses the right heart. This leads to a reduction in RV end-diastolic pressure, decreased wall tension, and improved contractility. Although the right-to-left shunt leads to oxygen desaturation, increased left-sided filling augments cardiac output and appears to improve oxygen delivery.<sup>46</sup> The use of RV assist devices can be considered if significant organ dysfunction has not yet occurred.<sup>47,48</sup>

Heart and heart-lung transplantation may be considered in patients with RV failure, although they are often unsuitable candidates. Severe RV failure itself is a risk factor for unsuccessful bridging to transplantation.<sup>14</sup> RV failure secondary to recurrent PE causing chronic thromboembolic pulmonary hypertension may be treated with surgical pulmonary thromboendarterectomy.

#### MISCELLANEOUS THERAPIES

Diuretics should be used judiciously when appropriate to decrease volume load on the distended RV. The use of digoxin in patients with RV dysfunction is controversial. In a study of the short-term effects of digoxin in 17 patients with severe primary pulmonary hypertension,<sup>49</sup> cardiac index improved mildly, and catecholamine levels decreased. However, pulmonary vascular resistance did not change, and mean pulmonary artery pressures increased. Because there are more effective drugs to treat RV dysfunction and supraventricular arrhythmias, digoxin is not commonly used in the ICU in this setting. Calcium channel blockers have not been studied in critically ill patients with PAH. The negative inotropic effects of these agents may precipitate fatal worsening of RV failure.<sup>48</sup> Aside from treatment of acute and chronic thromboembolic diseases, only one retrospective study suggests benefit from anticoagulation in patients with pulmonary hypertension.50

#### PROGNOSIS

RV failure may be a marker of the severity of the underlying disease process and often is a poor prognostic sign. In patients with heart failure, RV function is an important predictor of exercise tolerance and survival.<sup>51</sup> Cardiogenic shock due to RV failure is associated with a high mortality rate, similar to shock from LV failure.<sup>52</sup>

The presence of RV infarction affects the prognosis in inferior myocardial infarction.<sup>16,17</sup> The underlying disorder and its degree of reversibility also influence the prognosis among patients with RV failure.

### **AUTHORS' RECOMMENDATIONS**

- Evidence-based data concerning treatment of RV failure in the ICU are relatively sparse. Few randomized controlled trials focus on the treatment of this clinical entity.
- Many of the disease processes encountered in the ICU, including sepsis and respiratory failure, may be associated with RV failure.
- Many of the therapies used commonly for critically ill patients with RV dysfunction (e.g., volume resuscitation, mechanical ventilation) can worsen their clinical state.
- The dearth of studies on RV failure in the ICU reflects (1) heterogeneity of etiologies, (2) heterogeneity of disease severity, (3) lack of a portable gold standard imaging modality, and (4) underestimation of the importance of the RV.
- Most current ICU therapies for RV dysfunction are based on pathophysiologic considerations and extrapolation from trials in other settings.

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# Pulmonary Hypertension in ARDS: Is It Important and Should We Treat It?

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In this chapter, we systematically examine the evidence linking acute respiratory distress syndrome (ARDS) with pulmonary hypertension, the implications of pulmonary hypertension and consequent right ventricular failure for patient outcomes, and the data related to pulmonary vasodilator therapies in this patient group.

#### PULMONARY HYPERTENSION IN ARDS

Pulmonary hypertension in ARDS was described in the late 1970s and was soon accepted as a key cause of death.<sup>1</sup> A consistent observation in reports at the time was that nonsurvivors of ARDS demonstrated pulmonary artery pressures that continued to rise throughout the early phase of the illness. Later, systematic studies, such as the European Collaborative ARDS study,<sup>2</sup> confirmed the prognostic significance of pulmonary artery pressures for these patients. In that report, a logistic regression analysis that included multiple hemodynamic measures and other factors identified day 2 systolic pulmonary artery pressure (24.1  $\pm$  6.7 mm Hg for eventual survivors versus 28.4  $\pm$  8.5 mm Hg for eventual nonsurvivors) as a potent independent predictor of mortality.

How common is pulmonary hypertension in ARDS? There are surprisingly few data to accurately answer this question. Zapol and Snider<sup>3</sup> found that all of the 30 ARDS patients in their series had elevated pulmonary artery pressures, even after correction of hypoxemia. Clinical trials in ARDS have consistently reported baseline mean pulmonary pressures of 29 to 30 mm Hg.<sup>4,5</sup> More recently, using a cut-off value for the mean pulmonary artery pressure of 25 mm Hg, 92.2% of ARDS patients had pulmonary hypertension, although it was severe (defined by a mean pulmonary artery pressure of greater than 45 mm Hg) in only 7.4%.<sup>6</sup>

A combination of factors may contribute to the development of pulmonary hypertension in patients with ARDS. Correlations between lung edema and pulmonary artery pressures have been demonstrated.<sup>7</sup> Intravascular thrombosis causing microvascular occlusion was an important factor in a pig model,<sup>8</sup> and postmortem studies have demonstrated widespread pulmonary thromboembolism in 95% of cases of ARDS.<sup>9</sup> Although marked hypoxic pulmonary vasoconstriction was present in nonventilated areas of the lung in patients with ARDS,<sup>10</sup> the impact of this phenomenon on overall pulmonary hemodynamic measures is uncertain. Sibbald and colleagues,<sup>1</sup> for example, reported that the severity of pulmonary hypertension in ARDS correlated poorly with the degree of hypoxia. Hypoxic pulmonary vasoconstriction may be a weak contributor because it is partially or wholly inhibited by factors such as locally released nitric oxide or prostaglandin. Further, pulmonary hypertension in ARDS may persist even after the resolution of hypoxemia. One possible explanation is that pulmonary vascular smooth muscle cells proliferate over time. This results in a diminution in wall compliance.

Inflammatory mediators released in sepsis may increase vascular tone in the pulmonary circulation while decreasing it in the systemic circulation. Cytokines such as tumor necrosis factor- $\alpha$  have been implicated, but their exact role is unclear. Endothelin-1 (ET-1) is a potent pulmonary vasconstrictor and activator of vascular smooth muscle proliferation. ET-1 expression is upregulated in patients with ARDS, although currently there is no evidence directly implicating ET-1 in ARDS-related pulmonary hypertension.

# PULMONARY HYPERTENSION, RIGHT HEART FAILURE, AND DEATH

The thin-walled right ventricle is accustomed to pumping into a low-pressure circuit and therefore responds poorly to increases in afterload. In the critically ill patient, multiple factors, such as fluid overload, negative inotropy associated with sepsis, and elevated mean airway pressures may impair right ventricular function. This is supported by data indicating that right ventricular failure both predicts and appears to cause the death of 30% of patients with ARDS.<sup>6,11</sup> In an echocardiography-based study that evaluated the right heart in 23 patients with ARDS,<sup>12</sup> 9 patients were found to have normal right ventricular function, whereas 9 other patients had a slightly enlarged right ventricle with normal systolic function. The remaining 5 patients had a severely enlarged right ventricular size. These findings suggest detrimental ventricular interdependence. Notably, all the patients in that study had normal left ventricular systolic function by two-dimensional echocardiography. Severe right heart failure was strongly associated with death.

Vieillard-Baron and associates<sup>13</sup> used echocardiography to evaluate the right heart in ARDS. Right ventricular dysfunction was present in 19 of 75 (25%) patients on day 2. Many of these patients also had evidence of left ventricular diastolic dysfunction. Although mortality was the same as that for patients without right ventricular dysfunction, the duration of respiratory support was longer. Of particular interest in this study, elevated Paco<sub>2</sub> was identified as the sole independent predictor of acute right ventricular failure. This may reflect increased dead space associated with high levels of positive end-expiratory pressure (PEEP) and worse outcomes with ARDS. For example, Poelaert and coworkers<sup>14</sup> found that incremental PEEP induced cyclic augmentation of right ventricular outflow impedance. Jardin and Vieillard-Baron<sup>15</sup> illustrated that higher plateau pressures were associated with marked increases in acute right heart failure and death.

# PULMONARY VASODILATOR THERAPIES IN ARDS

#### Inhaled Nitric Oxide

Nitric oxide (NO) is a free radical gas that was identified in 1987 as the elusive endothelium-derived relaxing factor.<sup>16</sup> After native generation in the endothelium, NO enters local vascular smooth cells where it activates soluble guanylate cyclase (sGC). This enzyme stimulates the conversion of guanosine 5'-triphosphate (GTP) to cyclic guanosine monophosphate (cGMP) with consequent cellular hyperpolarization and attenuation of calcium entry to the muscle cytoplasm. The net result is vasodilation. Deficiencies in NO production<sup>17</sup> and attenuated responsiveness to NO<sup>18</sup> in the pulmonary circulation have been identified and are now accepted as important factors in the pathogenesis of both primary and secondary pulmonary hypertension.

Within a year of the discovery of NO, inhaled NO was confirmed as an effective pulmonary vasodilator in patients with primary pulmonary hypertension.<sup>19</sup> Shortly thereafter, several small case series describing the use of NO therapy for patients with acute lung injury and pul-monary hypertension appeared in the literature.<sup>20–22</sup> These studies reported not only decreases in pulmonary vascular resistance and pulmonary artery pressures but also significant improvements in oxygenation. For example, in 1993, Rossaint and colleagues<sup>22</sup> gave 18 ppm inhaled NO to 10 patients with ARDS. Pulmonary artery pressures decreased by an average of 6 mm Hg whereas pulmonary vascular resistance decreased by an average of 71 dyn • sec •  $cm^{-5}$  from baseline. There were no significant changes in systemic blood pressure or cardiac output. Most compelling to clinicians at the time, however, was an average increase in the Pao<sub>2</sub>/Fio<sub>2</sub> ratio of 51 mm Hg. Inhaled NO was adopted for the treatment of severe ARDS in short order. Indeed, a survey of intensive care physicians' practices across Europe showed that, by 1998, 98.5% of respondents considered ARDS an indication for inhaled NO, whereas 71% considered that  $Pao_2/Fio_2$  ratios were sufficient criteria for initiating treatment.<sup>23</sup>

In these early studies, three observations were made that would later become contentious. The first of these was that the response to NO, whether based on decreased pulmonary artery pressures or on improved oxygenation, was largely predictable and almost universal. It was later established that, at most, 40% to 60% of ARDS patients responded to inhaled NO with an improvement in one or both of these parameters.<sup>5</sup> Prediction of likely responders was difficult.<sup>24</sup> The second observation was that the response to inhaled NO was sustained over a prolonged period of treatment. Later data, in contrast, demonstrated the development of tachyphylaxis within 2 to 3 days.<sup>5</sup> The final observation was that, although daily interruptions of inhaled NO were noted to cause increases in pulmonary artery pressures,<sup>22</sup> these changes were not believed to be problematic. Rebound pulmonary hypertension after withdrawal was later appreciated as a phenomenon of real consequence, albeit one that could be overcome.

Early enthusiasm for inhaled NO was curtailed by negative phase 2<sup>25,26</sup> and phase 3<sup>5,27</sup> trials showing that NO did not improve overall survival in ARDS. This was supported by meta-analyses of trials of NO therapy in ARDS.<sup>28,29</sup> Additionally, NO may have an adverse effect on renal function.<sup>28</sup> In the United States, concerns about clinical efficacy of NO have been reinforced by the high costs associated with the delivery system. The results of a Canadian survey were likely representative of worldwide practice: by 2004, less than 40% of critical care physicians were using NO as therapy in ARDS, and then only selectively.<sup>30</sup>

#### Prostaglandins

Prostaglandins are vasodilators that act through intracellular adenylate cyclase leading to a decrease in intracellular calcium. Various prostaglandins and their analogs have been shown to improve exercise capacity and quality of life in chronic primary pulmonary hypertension<sup>31</sup> but have little impact on mortality.

During the late 1980s, a number of reports described the use of intravenous prostaglandin E1 (PGE1) for ARDS. PGE1 appeared to exert its effects both as an anti-inflammatory and a pulmonary vasodilator. The finding that pulmonary artery pressures were indeed decreased—by about 15% when given in the typical dose range<sup>32</sup>—prompted two randomized controlled trials. The first, and smaller of the two, was limited to ARDS in surgical patients and suggested a survival advantage.<sup>33</sup> The subsequent larger and more inclusive trial failed to confirm this. Indeed, the authors reported systemic hypotension and increases in intrapulmonary shunting.<sup>34</sup> As these results were emerging, reported successes with inhaled NO fueled attempts to find an inhaled prostaglandin. Iloprost, a synthetic analog of prostacyclin, emerged as a drug stable in aerosolization and suitable for inhalation. In 1993, Walmrath and

coworkers<sup>35</sup> first reported the use of aerosolized iloprost in three patients with ARDS. Pulmonary vascular resistance and intrapulmonary shunt decreased, and oxygenation improved, all by 30% to 40%. These findings were confirmed 3 years later by two reports involving rather small numbers of patients.<sup>4,36</sup>

Iloprost compares well with inhaled NO for the treatment of pulmonary hypertension in ARDS. Prostacyclin and its analogs have a longer half-life (2 to 3 minutes) than NO (seconds). Although this could increase the risk for systemic vasodilation and hypotension, in practice, this does not appear to be a significant problem.<sup>37,38</sup> Indeed, 50 ng/kg per minute, the upper end of the dose range for iloprost, caused no systemic hemodynamic effects in children with acute lung injury.<sup>38</sup> Prostacyclin also is a potent inhibitor of platelet aggregation. In the absence of increased bleeding, this may be of benefit.

Nonetheless, comparisons of iloprost and NO are complicated by the limited published data. There are several small studies. Van Heerden and colleagues<sup>4</sup> showed drug equivalency for iloprost, 50 ng/kg per minute, and NO, 10 ppm, in five hypoxemic ARDS patients. Zwissler and associates<sup>36</sup> compared 1, 10, and 25 ng/kg/min iloprost with NO 1, 4, and 8 ppm and found that both drugs produced roughly comparable effects. This also established limited dose-response curves for ARDS patients. Similarly, in 16 ARDS patients, Walmrath and coworkers<sup>39</sup> found that iloprost (average dose, 7.5 ± 2.5 ng/kg per minute) and inhaled NO (average dose, 18 ppm) were equally effective. Finally, similar comparative studies in primary pulmonary hypertension point to roughly comparable clinical effects of the two agents.<sup>40</sup>

NO is degraded to nitrogen dioxide, a potential toxin. NO also requires an expensive delivery and monitoring system. Iloprost does not have this problem because it can be delivered by simple nebulizer systems. As with inhaled NO, however, rebound hypertension on drug withdrawal has been reported.<sup>41</sup> What remains to be conclusively demonstrated is whether prostaglandins may succeed in NO-unresponsive patients and vice versa. Because NO and prostaglandins exert their effects by entirely different mechanisms, the hypothesis is an attractive one, but which patients will respond to either remains difficult to predict. Data from Domenighetti and colleagues suggest that patients with ARDS of pulmonary origin are less likely to respond than those with ARDS of extrapulmonary origin,<sup>42</sup> but a direct comparison with NO was not performed. Brett and associates, notably, found no predictors of response to inhaled NO.<sup>24</sup> Finally, as with NO, there are no data suggesting that inhaled prostacyclin alters outcome in ARDS.

#### **Phosphodiesterase Inhibitors**

Enoximone, amrinone, and milrinone are inhibitors of phosphodiesterase type 3 (PDE-3), the enzyme that catalyzes the breakdown of cyclic adenosine monophosphate (cAMP) in myocardium and vascular smooth muscle. Inhibition of this enzyme increases myocardial contractility and causes widespread vasodilation. Although longterm survival rates are not improved for patients with chronic cardiac failure taking oral milrinone, this class of drugs is widely used in the setting of acute cardiac failure in cardiac surgical patients.<sup>43,44</sup> Decreases in output impedance should particularly favor the failing right ventricle. In a retrospective comparison of milrinone and dobutamine in 329 patients with acutely decompensated cardiac failure, milrinone produced greater decreases in pulmonary vascular resistance with greater improvements in cardiac output.<sup>45</sup> Similarly, in patients with severe pulmonary hypertension undergoing transplantation preassessment, milrinone<sup>46</sup> or enoximone<sup>47</sup> potently decreased pulmonary vascular resistance and increased cardiac index.

Sildenafil is an orally administered, highly selective inhibitor of PDE-5. This subtype of PDE is present in abundance in the smooth muscle cells of pulmonary vasculature. Inhibition of PDE-5 prevents the breakdown of cGMP, thereby augmenting the vasodilating effects of native and inhaled NO.

There are several reports of sildenafil treatment for patients with new-onset, life-threatening pulmonary hypertension related to acute lung injury or ARDS. Giacomini and associates<sup>48</sup> gave enteral vardenafil, a sildenafil analog, to a single patient with ARDS and pulmonary hypertension in whom weaning of inhaled NO had proved impossible. Vardenafil permitted withdrawal of the inhaled NO and was itself eventually tapered. A small number of reports describe positive outcomes with sildenafil therapy for acute right ventricular failure secondary to pulmonary embolism.<sup>49,50</sup> It is unclear whether these results can be replicated in ARDS. Laboratory studies strongly support the potential of sildenafil in the critical care setting. For example, in animal models of septic acute lung injury, PDE-5 inhibition protected against increases in pulmonary vascular resistance<sup>51</sup> and augmented responsiveness to inhaled NO.52

Further work is clearly required to explore the role of sildenafil in the intensive care unit. Its advantages include a synergistic action with inhaled NO and an oral preparation that may permit transition from inhaled therapies in patients ready for separation from mechanical ventilation. Severe systemic hypotension can occur in patients concomitantly receiving nitrates.

#### Levosimendan

Levosimendan is an inodilator. The inotropic effect occurs through sensitization of troponin C in the myocardium. Contractility is improved but uniquely this occurs without a concomitant increse in intracellular calcium or in energy consumption. Vasodilation occurs through activation of potassium–adenosine triphosphate ( $K_{ATP}$ ) channels in the vasculature. Activation of these channels also may account for the cardioprotective effect reported in laboratory<sup>53</sup> and clinical studies.<sup>54</sup> An immunomodulatory effect also has been described,<sup>55</sup> although the mechanism is unknown.

The LIDO study was a double-blind randomized controlled trial that compared levosimendan with dobutamine in cardiogenic shock.<sup>56</sup> Not only were predetermined hemodynamic goals achieved more successfully with levosimendan, but there also was a significant survival benefit. The extreme sensitivity of the right ventricle to modest changes in afterload suggests a particular potential for levosimendan in the treatment of right ventricular failure complicating pulmonary hypertension.

There are several clinical studies describing the use of levosimendan specifically for pulmonary hypertension and right ventricular failure. In a small placebo-controlled trial, Ukkonen and associates<sup>57</sup> reported marked decreases in pulmonary vascular resistance along with improvements in right ventricular mechanical efficiency and cardiac output in patients with severe right heart failure. Morelli and colleagues<sup>58</sup> performed a randomized placebo-controlled trial in 35 patients with ARDS. Levosimendan decreased mean pulmonary artery pressures from  $29 \pm 3$  to  $25 \pm 3$  mmHg while increasing right ventricular ejection fraction from  $45 \pm 10$  to  $59 \pm 10\%$ . Cardiac index and mixed venous oxygen saturations also increased significantly. Finally, intriguing new data point to a benefit of inhaled levosimendan.<sup>55</sup>

# AUTHORS' RECOMMENDATIONS

- Pulmonary hypertension frequently goes unrecognized in ARDS.
- Pulmonary hypertension undoubtedly contributes to poor outcomes in some patients.
- Optimal treatment is unclear. Large randomized controlled trials failed to show survival benefits of pulmonary vasodilators. However, these trials enrolled all ARDS patients, with or without pulmonary hypertension, and primarily targeted oxygenation indices.
- Although unproved, recognition and treatment of pulmonary hypertension in selected patients with ARDS may improve survival.

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# 50 How Does One Manage Postsurgical Patients with Known Coronary Artery Disease in the Intensive Care Unit?

Lee A. Fleisher

Cardiovascular morbidity and mortality represent a significant risk in the patient with known cardiovascular disease undergoing noncardiac surgery. The costs of a perioperative myocardial injury add substantially to the total health care expenditures, with an average increased length of stay of 6.8 days for patients with perioperative myocardial ischemic injury. The implications of perioperative cardiovascular complications, including asymptomatic troponin elevations, not only affect the immediate period but also may influence outcome over the subsequent 1 to 2 years. Over the past three decades, there has been a steady progression of knowledge regarding cardiac risk. This began with identification of those at greatest risk and has progressed to recent randomized trials that identify strategies to reduce perioperative cardiovascular complications. To disseminate best practices, guidelines have been developed to provide information for management of high-risk patients.

All surgical procedures cause a stress response, although the extent of the response depends on the extent of the surgery and reductions from anesthetics and analgesics. The stress response can lead to increases in heart rate and blood pressure. These can precipitate episodes of myocardial ischemia in areas distal to coronary artery stenoses. Prolonged myocardial ischemia (either prolonged individual episodes or cumulative duration of shorter episodes) has been associated with myocardial necrosis and perioperative myocardial infarction and death.<sup>1</sup> Identification of patients with a high risk for coronary artery stenosis because of either history or cardiovascular testing can lead to implementation of strategies to reduce morbidity from supply-demand mismatches.<sup>2</sup> A second major cause of myocardial infarction in the nonoperative setting is rupture of a plaque causing a noncritical coronary stenosis. This may lead to subsequent coronary thrombosis. The perioperative period is marked by tachycardia and a hypercoagulable state that may increase the incidence of plaque disruption and thrombosis. Because the nidus for the thrombosis is a noncritical stenosis, preoperative cardiac evaluation may have failed to identify such a patient before surgery, although control of heart rate may decrease the propensity of the plaque to rupture. The areas distal to the noncritical stenosis would not be expected to have collateral coronary flow, and therefore any acute thrombosis may have a greater detrimental effect than it would in a severely narrowed vessel.

There is some evidence to suggest that both mechanisms are responsible for perioperative myocardial events. Autopsy and postinfarction angiography studies after surgery clearly demonstrate infarction in areas supplied by vessels distal to severe stenoses. In addition, Ellis and colleagues demonstrated that one third of all patients sustained events in areas distal to noncritical stenoses.<sup>3</sup> Dawood and colleagues demonstrated that fatal perioperative myocardial infarction occurs predominantly in patients with multivessel coronary disease, especially when there is left main and three-vessel disease. However, the severity of the preexisting underlying stenosis did not predict the resulting infarct territory.<sup>4</sup> This analysis suggests that fatal events occur primarily in patients with advanced fixed stenoses but that the infarct may be triggered by plaque rupture in a mild or only moderate stenosis of the area of diseased vessel.

# **OPTIONS**

Strategies to reduce cardiac risk for noncardiac surgery in the postoperative period in patients at risk for coronary artery disease (CAD) include pharmacologic treatment to prevent myocardial ischemia and infarction or monitoring for myocardial ischemia and early intervention. Pharmacologic strategies have included  $\beta$ -adrenergic blocker therapy,  $\alpha_2$ -agonists, statins, and nitroglycerin. The monitoring modality most appropriate to detect myocardial ischemia in the intensive care unit (ICU) is continuous ST-segment trending. There are numerous studies that have demonstrated an association between postoperative ST-segment changes and cardiac morbidity and mortality. Prolonged episodes and greater cumulative duration of ST-segment change have been correlated with a greater incidence of infarction. However, there currently are no studies to address the value of acute interventions to treat new STsegment changes. Therefore, this chapter reviews only the evidence for prophylactic strategies that can be implemented in the ICU to reduce cardiac risk for noncardiac surgery.

#### EVIDENCE

Most recent evidence evaluates the relationship between the baseline risk for CAD and various strategies. The identification of perioperative cardiac risk has been an area of active study for three decades, and much of the work has focused on the development of clinical risk indices. The most recent index was developed in a study of 4315 patients aged 50 years or older undergoing elective major noncardiac procedures in a tertiary-care teaching hospital. Six independent predictors of complications were identified. These were used to define a Revised Cardiac Risk Index (RCRI). The indicators were (1) high-risk type of surgery, (2) history of ischemic heart disease, (3) history of congestive heart failure, (4) history of cerebrovascular disease, (5) preoperative treatment with insulin, and (6) preoperative serum creatinine higher than 2.0 mg/dL. An increase in cardiac complication rates was noted with an increasing number of risk factors.<sup>5</sup> The RCRI has become the standard tool in the literature to determine the efficacy of any perioperative management protocol.

#### Surveillance and Implications of Perioperative Cardiac Complications

The optimal and most cost-effective strategy for monitoring high-risk patients for major morbidity after noncardiac surgery is unknown. Myocardial ischemia and infarctions that occur postoperatively most often are silent, perhaps due to the confounding effects of analgesics and postoperative surgical pain. Creatine kinase (CK)-MB is also less specific for myocardial necrosis postoperatively because this marker can rise during aortic surgery and after mesenteric ischemia. Further confounding the issue is the observation that most perioperative myocardial infarctions are non–Q wave in nature and nonspecific ST-T-wave changes are common after surgery with or without myocardial infarction. Therefore, the diagnosis of a perioperative myocardial infarction is particularly difficult using these traditional tools.

The approach to detection of perioperative myocardial infarction has evolved recently with the use of troponin T and I. Adams and associates<sup>6</sup> studied 108 patients undergoing high-risk surgery and obtained measures of CM-MB, total CK, cardiac troponin I, daily electrocardiograms, and preoperative and postoperative echocardiograms. Troponin I had a specificity of 99%, whereas CK-MB had a specificity of 81%. Lee and colleagues measured CK-MB and troponin T levels in 1175 patients undergoing noncardiac surgery and created receiveroperating characteristic curves.<sup>7</sup> They found that troponin T had a similar performance for diagnosing perioperative myocardial infarction but significantly better correlation for major cardiac complications developing after an acute myocardial infarction. Metzler and coworkers examined the sensitivity of troponin assay at variable cut-off levels: a value of 0.6 ng/mL or higher demonstrated a positive predictive value of 87.5% and a negative predictive value of 98%.<sup>8</sup> Le Manach and colleagues studied 1152 consecutive patients who underwent abdominal infrarenal aortic surgery and identified four patterns of cardiac troponin I (cTn-I) release after surgery.9 One group did not have any abnormal levels, whereas a second group had only mild elevations of cTn-I. It is interesting to note that two groups demonstrated elevations of cTn-I consistent with a perioperative myocardial infarction (PMI). One demonstrated acute (<24 hour) and early elevations of cTn-I above threshold, whereas the second was characterized by prolonged depression of cTn-I release followed by a delayed (>24 hour) elevation. The authors suggest that these two different patterns represent two distinct pathophysiologies: acute coronary occlusion for early morbidity and prolonged myocardial ischemia for late events.

Traditionally, perioperative myocardial infarctions were associated with a 30% to 50% short-term mortality. However, recent series have reported a fatality rate at less than 20%.<sup>1</sup> This improvement may be due to more reliable detection of small nonfatal myocardial infarctions. There also appears to be a shift in the timing of a perioperative myocardial infarction. Studies from the 1980s suggested a peak incidence on postoperative days 2 and 3. Badner and associates, using troponin I as a marker for myocardial infarction, suggested that the incidence was at its highest in the immediate postoperative period and the first postoperative day.<sup>10</sup> This has been confirmed in other studies. Again, it is likely that this change relates to more robust surveillance methods and not a fundamental shift in how or when myocardial ischemia or infarct occur.

#### **β-Blocking Agents**

β-Blockers are the best studied medical treatment, and guidelines for their use in the perioperative period have been published. Mangano and colleagues administered atenolol or placebo beginning the morning of surgery and continuing for 7 days after surgery in a cohort of 200 patients with known coronary disease or risk factors for CAD undergoing high-risk noncardiac surgery.<sup>11</sup> They demonstrated a marked reduction in the incidence of perioperative myocardial ischemia but no differences in the rate of perioperative myocardial infarction. Importantly, there was a marked improvement in survival at 6 months in the atenolol group. This trend continued for at least 2 years. The authors speculate that the lower incidence of myocardial ischemia was the result of less plaque destabilization with a resultant reduction in subsequent myocardial infarction or death in the 6 months after noncardiac surgery. There were issues of randomization and uneven distribution of risk factors. Further, treatment at baseline and on discharge with  $\beta$ -blockers may, at least in part, account for the findings. However, Poldermans and colleagues studied the perioperative use of bisoprolol versus routine care in elective major vascular surgery in the DECREASE trial.<sup>12</sup> This medication was started at least 7 days preoperatively, titrated to achieve a resting

heart rate of 60 beats per minute or less and continued postoperatively for 30 days. Of note, the study was confined to patients with at least one clinical marker of cardiac risk (prior myocardial infarction, diabetes, angina pectoris, heart failure, age >70 years, or poor functional status), and evidence of inducible myocardial ischemia on a preoperative dobutamine stress echocardiogram. Patients with extensive regional wall abnormalities (large zones of myocardial ischemia) were excluded. Bisoprolol reduced perioperative myocardial infarction or cardiac death by some 80% in this high-risk population. Because of the selection criteria, the efficacy of bisoprolol in the highest-risk group, those who would be considered for coronary revascularization or modification or cancellation of the surgical procedure, cannot be determined from this trial. However, the event rate in the placebo group (nearly 40%) suggests that all but the highest-risk patients were enrolled in the trial.

Boersma and colleagues reevaluated the value of dobutamine stress echocardiography with respect to the extent of wall motion abnormalities and use of  $\beta$ -blockers during surgery for the entire cohort of patients screened for the DECREASE trial.<sup>13</sup> They assigned one point for each of the following characteristics: age 70 years or older, current angina, myocardial infarction, congestive heart failure, prior cerebrovascular, accident diabetes mellitus, and renal failure. As the total number of clinical risk factors increased, perioperative cardiac event rates increased. When the risk for death from myocardial infarction was stratified by perioperative  $\beta$ -blocker use, there was no significant improvement in those without any of the prior risk factors. In those with a risk factor score between 1 and 3, which represented more than half of all patients, the rate of cardiac events was decreased from 3% to 0.9% by effective  $\beta$ -blockade. Most important, in patients with fewer than three risk factors, comprising 70% of the population,  $\beta$ -blocker therapy was very effective in reducing cardiac events in the presence of new wall motion abnormalities in one to four segments (33% versus 2.8%). This effect was less pronounced in patients without new wall motion abnormalities (5.8% versus 2%). β-Blockers were not protective in patients with new wall motion abnormalities in five segments or more. This group with risk factors and extensive wall motion abnormalities on preoperative stress echo may be appropriate for prophylactic coronary revascularization.

Raby and associates randomized 26 patients to receive continuous intravenous  $\beta$ -blockade with esmolol or placebo plus usual medical therapy, aiming to reduce the postoperative heart rate to 20% below the ischemic threshold.<sup>14</sup> A total of 15 patients were randomized to receive esmolol and 11 to receive placebo. Ischemia persisted in the postoperative period in 8 of 11 placebo patients (73%) but in only 5 of 15 esmolol patients (33%; *P* < .05). There were two postoperative cardiac events among patients who had postoperative ischemia (one placebo, one esmolol) and whose mean heart rates exceeded the ischemic threshold. The study was too small to comment on the incidence of cardiac events.

In a randomized trial by Urban and coworkers, patients undergoing elective knee arthroplasty were randomized to therapy with  $\beta$ -blockers started postoperatively or

placebo therapy.<sup>15</sup> The  $\beta$ -blocker group received postoperative esmolol infusions on the day of surgery and metoprolol for the next 48 hours to maintain a heart rate less than 80 beats/minute. The sample size was too small to detect differences in rate of myocardial infarction or cardiac death but did determine that patients treated with  $\beta$ -blockade had less electrocardiographic evidence of ischemia without any adverse events associated with the  $\beta$ -blocker therapy.

Brady and coworkers randomized 103 patients without previous myocardial infarction who had infrarenal vascular surgery to oral metoprolol or placebo from admission until 7 days after surgery.<sup>16</sup> Perioperative  $\beta$ -blockade with metoprolol did not reduce 30-day cardiovascular events but did decrease the time from surgery to discharge. Lindenauer and coworkers retrospectively reviewed the records of 782,969 patients and identified those who received  $\beta$ -blocker treatment during the first 2 hospital days.<sup>17</sup> The relationship between perioperative  $\beta$ -blocker treatment and the risk for death varied directly with cardiac risk. Among the 580,665 patients with an RCRI of 0 or 1, treatment was associated with no benefit and possible harm. In contrast, among the patients with RCRI of 2, 3, or 4 or more, the adjusted odds ratios for death in the hospital were 0.88 (95% confidence interval [CI], 0.80 to 0.98), 0.71 (95% CI, 0.63 to 0.80), and 0.58 (95% CI, 0.50 to 0.67), respectively.

The Perioperative Beta-Blockade for Patients Undergoing Infra-renal Vascular Surgery (POBBLE) trial involved 103 patients who were randomized to placebo or metoprolol, typically the night before surgery, and then for 7 days after surgery.<sup>16</sup> Patients were excluded if they had a history of myocardial infarction within 2 years of surgery or a history of angina with a positive stress test. There was no statistically significant difference in 30-day cardiovascular morbidity and mortality. Symptomatic bradycardia and hypotension were higher in the study group, with an increased requirement for inotropic support. The Metoprolol after Vascular Surgery (MaVS) trial studied 496 patients undergoing major vascular surgery; 297 of these had an RCRI of 1 (1 point given for undergoing vascular surgery) and 47 patients had an RCRI of 3 or more.<sup>18</sup> Patients were randomized to placebo or metoprolol 2 hours before surgery and then continued for up to 5 days. In patients with an RCRI of 2 or less there was no statistically significant difference in 30-day cardiovascular outcome. Interestingly, in those with an RCRI of 3 or more, the incidence of 30-day complications was higher (7 of 19 versus 4 of 28), although the number of events was too small for significance. Once again, there was a significantly higher incidence of bradycardia and hypotension requiring treatment in the metoprolol group. The Diabetic Postoperative Mortality and Morbidity (DIPOM) trial included 921 patients.<sup>19</sup> Inclusion criteria sought diabetic patients older than 40 years undergoing major surgery, defined as surgery lasting longer than 1 hour. No patient underwent vascular surgery. Patients were excluded if they had medical condithat would indicate outpatient tions β-blocker treatment. Beyond that, there are no details regarding  $\beta$ -blockers. The study drug was metoprolol given the night before surgery and continued for 7 days or until

hospital discharge. There was no statistically significant difference in cardiovascular outcome over the 18-month follow-up period.

After the publication of the 2007 guidelines, the POISE study group published the results of their study.<sup>20</sup> Patients were randomly assigned to receive extendedrelease metoprolol succinate or placebo started 2 to 4 hours before surgery and continued for 30 days. The primary end point was a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal cardiac arrest. Patients were eligible if they were undergoing noncardiac surgery, were 45 years or older, had an expected length of hospital stay of at least 24 hours, and fulfilled any one of the following criteria: history of CAD, peripheral vascular disease, stroke, hospitalization for congestive heart failure within previous 3 years, undergoing major vascular surgery, or any three of seven risk criteria (undergoing intrathoracic or intraperitoneal surgery, history of congestive heart failure, transient ischemic attack, diabetes, serum creatinine >175 µmol/ L, age >70 years, or undergoing emergent or urgent surgery). Patients who had been receiving a  $\beta$ -blocker before randomization or had a coronary artery bypass graft surgery in the preceding 5 years and no cardiac ischemia since were excluded. Patients received the first dose of the study drug metoprolol succinate, 100 mg, 2 to 4 hours before surgery. Study drug administration required a heart rate of 50 beats/minute or more and a systolic blood pressure of 100 mm Hg or greater; these hemodynamics were checked before each administration. If at any time during the first 6 hours after surgery, the heart rate was 80 beats/minute or more and systolic blood pressure was 100 mm Hg or higher, patients received their first postoperative dose (extended-release metoprolol, 100 mg, or matched placebo) orally. If the study drug was not given during the first 6 hours, patients received their first postoperative dose 6 hours after surgery. Twelve hours after the first postoperative dose, patients started taking oral extended-release metoprolol, 200 mg, or placebo every day for 30 days. If a patient's heart rate was consistently below 45 beats/ minute or systolic blood pressure dropped below 100 mm Hg, the study drug was withheld until the heart rate or systolic blood pressure recovered. The study drug was restarted at 100 mg once daily. In patients whose heart rate was consistently 45 to 49 beats/minute and systolic blood pressure exceeded 100 mm Hg, the study drug was delayed for 12 hours. Patients who were unable to take medications orally were excluded. The final analysis included 8351 patients from 190 hospitals in 23 countries with a 30-day follow-up in 8331 participants. Of note, 752 participants at six hospitals in Iran were excluded because of fraudulent activity at their sites. A total of 8331 (99.8%) patients completed the 30day follow-up. Fewer patients in the metoprolol group than in the placebo group reached the primary end point (244 [5.8%] patients in the metoprolol group verus 290 [6.9%] in the placebo group; hazard ratio [HR], 0.84; 95% CI, 0.70 to 0.99; P = .0399). Fewer patients in the metoprolol group than in the placebo group had a myocardial infarction (176 [4.2%] versus 239 [5.7%] patients; HR, 0.73; 95% CI, 0.60 to 0.89; P = .0017).

However, more people receiving metoprolol died than did individuals receiving placebo (HR, 1.33; 95% CI, 1.03 to 1.74; P = .0317; the Kaplan-Meier estimates started separating on day 10. The only reported cause of death for which there was a significant difference between groups was sepsis or infection, which was more common among patients allocated to metoprolol. More patients in the metoprolol group than in the placebo group had a stroke (41 [1.0%] versus 19 [0.5%] patients; HR, 2.17; 95% CI, 1.26 to 3.74; *P* = .0053). Most patients who had a nonfatal stroke subsequently required help to perform everyday activities or were incapacitated. Multiple predefined subgroup analyses were performed, although the study was underpowered to detect modest differences in subgroup effects. Clinically significant hypotension had the largest population attributable risk for death and the largest intraoperative or postoperative risk for stroke.

Bangalore and colleagues performed a meta-analysis of 33 trials encompassing 12,306 patients.<sup>21</sup>  $\beta$ -Blockers were not associated with any significant reduction in the risk for all-cause mortality, cardiovascular mortality, or heart failure but were associated with a decrease (odds ratio [OR], 0.65; 95% CI, 0.54 to 0.79) in nonfatal myocardial infarction (number needed to treat [NNT], 63) and (OR, 0.36; 95% CI, 0.26 to 0.50) in myocardial ischaemia (NNT, 16) at the expense of an increase (OR, 2.01; 95% CI, 1.27 to 3.68) in nonfatal strokes (number needed to harm [NNH], 293). The beneficial effects were driven mainly by trials with high risk for bias. For the safety outcomes,  $\beta$ -blockers were associated with a high risk for perioperative bradycardia requiring treatment (NNH, 22) and perioperative hypotension requiring treatment (NNH, 17).

β-Blockers should be continued in patients currently taking these agents. Hoeks and associates prospectively studied 711 consecutive peripheral vascular surgery patients from 11 hospitals in the Netherlands to determine the impact of perioperative  $\beta$ -blockade.<sup>22</sup> After adjustment for potential confounders and the propensity of use, continuous β-blocker use remained significantly associated with a lower 1-year mortality compared with nonuse (HR, 0.4; 95% CI, 0.2 to 0.7). In contrast,  $\beta$ -blocker withdrawal was associated with an increased risk for 1year mortality compared with nonuse (HR, 2.7; 95% CI, 1.2 to 5.9). Dunkelgrun and colleagues<sup>23</sup> evaluated the effectiveness and safety of beta-blockers and statins for the prevention of perioperative cardiovascular events in intermediate-risk patients undergoing noncardiovascular surgery. Bisoprolol was associated with a significant reduction of 30-day cardiac death and nonfatal MI, while fluvastatin showed a trend for improved outcome.

#### α<sub>2</sub>-Agonists

Several randomized trials have evaluated the value of prophylactic  $\alpha_2$ -agonists as a means of reducing perioperative cardiac morbidity. Wallace and colleagues evaluated  $\alpha_2$ -agonists compared with placebo in high-risk patients undergoing noncardiac surgery.<sup>24</sup> One hundred and ninety patients with or at risk for CAD were prospectively blindly randomized (clonidine, n = 125 versus placebo, n = 65). Clonidine (0.2 mg orally as well as a patch) or

placebo (tablet and patch) was administered the night before surgery, and clonidine (0.2 mg orally) or placebo (tablet) was administered on the morning of surgery. This approach was continued for 4 days and then was stopped. The incidence of perioperative myocardial ischemia was significantly reduced with clonidine (intraoperative and postoperative, 18 of 125 [14%] versus placebo, 20 of 65 [31%]; P = .01). Clonidine reduced the incidence of postoperative mortality for up to 2 years (clonidine, 19 of 125 [15%] versus placebo, 19 of 65 [29%]; relative risk, 0.43; 95% CI, 0.21 to 0.89; P = .035). Licker and colleagues reported on a cardioprotection protocol involving preoperative  $\alpha_2$ -agonist administration and intraoperative and postoperative β-blocker administration.<sup>25</sup> This was compared with historical controls not subjected to preoperative testing and not treated with this pharmacologic protocol. The more contemporary group that employed the cardioprotection protocol had markedly improved perioperative and long-term survival and reduced perioperative troponin levels. A meta-analysis of published studies demonstrated that perioperative clonidine reduced cardiac ischemic episodes in patients with known, or at risk for, CAD without increasing the incidence of bradycardia. However, the studies were underpowered to evaluate the effect on perioperative cardiac morbidity.<sup>26</sup>

### Nitroglycerin

Only two randomized trials have evaluated the protective effect of prophylactic nitroglycerin in reducing perioperative cardiac complications after noncardiac surgery. In a small study by Coriat and colleagues of patients undergoing carotid endarterectomy, high-dose  $(1 \mu g/kg \text{ per minute})$  nitroglycerin was more effective than lower-dose (0.5  $\mu$ g/kg per minute) nitroglycerin in reducing the incidence of myocardial ischemia, but myocardial infarction did not occur in either group.<sup>27</sup> Importantly, the anesthetic used in this study was oxygen-pancuronium-fentanyl, and therefore inhalational agents, which may be cardioprotective and dilate coronary arteries, were not administered. Dodds studied nitroglycerin versus placebo using a balanced anesthetic technique and reported no difference in the rates of myocardial ischemia or infarction.<sup>28</sup> Taken together, the evidence suggests that prophylactic nitroglycerin does not reduce the incidence of perioperative cardiac morbidity, although neither trial was powered to detect modest benefit of nitroglycerin. Because these agents have considerable hemodynamic effects, it would seem prudent to avoid the prophylactic use of nitroglycerin, although there are clear indications for use after myocardial ischemia develops.

# Statin Therapy

In addition to their cholesterol-lowering properties, statins are anti-inflammatory and plaque stabilizing. Given the potential mechanisms that may lead to perioperative myocardial infarctions, statins might be of benefit. Poldermans and associates performed a case-controlled study of 2816 patients who underwent major vascular surgery from 1991 to 2000.<sup>29</sup> Statin therapy

was significantly less common in patients experiencing a postoperative myocardial infarction than in patients without cardiac morbidity (25% versus 8%; P < .001). The adjusted OR for perioperative mortality among statin users compared with nonusers was 0.22 (95% CI, 0.10 to 0.47). Lindenauer and colleagues used administrative data to study a cohort of 780,591 patients; of these, 77,082 patients (9.9%) received lipid-lowering therapy perioperatively, and 23,100 (2.96%) died during the hospitalization.<sup>30</sup> Using multivariate modeling and propensity matching, the NNT with a statin to prevent a postoperative death was 85 (95% CI, 77-98) and varied from 186 among patients at lowest risk to 30 among those with an RCRI score of 4 or more.

In a retrospective study by Kertai and colleagues, 570 patients who underwent AAA surgery were evaluated for risk factors and for statin and  $\beta$ -blocker use.<sup>31</sup> The main outcome studied was a combination of perioperative mortality and myocardial infarction within 30 days of surgery. This outcome occurred in 8.9% of patients but was lower in statin users than nonusers (3.7% versus 11%). Although the statin users had a different clinical risk profile than nonusers, the reduced risk for perioperative events still existed after adjustment for these differences and was independent of  $\beta$ -blocker use.

Durazzo and associates randomized 100 patients to receive 20 mg of atorvastatin or placebo once a day for 45 days.<sup>32</sup> The incidence of cardiac events was more than 3 times higher with placebo (26.0% versus 8.0%; P = .031). Patients given atorvastatin had significantly fewer cardiac events within 6 months of vascular surgery (P = .018). Thus, accumulating evidence suggests that statin therapy should not be discontinued during the perioperative period, and consideration should be given for starting it in high-risk patients, particularly those with established atherosclerosis, because one could argue that the patient should have been taking a statin already. Schouten and colleagues<sup>33</sup> studied a total of 250 intermediate risk patients who were assigned to fluvastatin, and 247 to placebo, a median of 37 days before vascular surgery. Death from cardiovascular causes or myocardial infarction occurred in 12 patients (4.8%) in the fluvastatin group and 25 patients (10.1%) in the placebo group (hazard ratio, 0.47; 95% CI, 0.24 to 0.94; P = 0.03). In patients undergoing vascular surgery, perioperative fluvastatin therapy was associated with an improvement in postoperative cardiac outcome.

#### Areas of Uncertainty

There are several pragmatic considerations in the use of perioperative  $\beta$ -blockers in patients currently not taking these agents. Ideally, the  $\beta$ -blocker therapy should be initiated more than 7 days in advance to allow titration of the agent from low levels to a dose at which heart rate is appropriately decreased. This is important because the POISE study demonstrated the hazards of acute administration at higher doses. If several days of  $\beta$ -blocker therapy is not possible, the potential risks of new-onset  $\beta$ -blocker therapy the morning of surgery. It is currently unknown whether lower doses of  $\beta$ -blockers with tighter heart rate and blood pressure titration will result in a lower risk for death or

Table 50-1Explanation of Class ofRecommendations from the AmericanCollege of Cardiology/American HeartAssociation Guidelines on PerioperativeCardiovascular Evaluation and Care forNoncardiac Surgery

*Class I:* Conditions for which there is evidence for and/or general agreement that the procedure/therapy is useful and effective

- *Class II:* Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of performing the procedure or therapy
- *Class IIa:* Weight of evidence or opinion is in favor of usefulness or efficacy
- *Class Ilb:* Usefulness or efficacy is less well established by evidence or opinion
- *Class III:* Conditions for which there is evidence and/or general agreement that the procedure or therapy is not useful or effective and in some cases may be harmful
- Data from Fleisher LA, Beckman JA, Brown KA, et al. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: A report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). Developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. J Am Coll Cardiol. 2007;50:e159-241.

stroke. The studies of Raby and Urban and their colleagues also demonstrate the utility of initial intravenous titration with short-acting  $\beta$ -blocker agents, although they were underpowered to comment on the risks versus benefits.<sup>14,15</sup>

# GUIDELINES

Guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery were published by the American College of Cardiology and American Heart Association in 2007 and updated in 2009.<sup>34</sup> Recommendations from the guidelines are shown in Tables 50-1 and 50-2.

### AUTHOR'S RECOMMENDATIONS

- Patients currently taking β-blockers should be continued on these agents with titration of heart rate to less than 80 beats/ minute while maintaining blood pressure based upon preoperative levels.
- The overriding theme is that tachycardia caused by perioperative events, such as bleeding, hypovolemia, inadequate control of pain, or infection, should not initially be treated with additional β-blocker therapy.<sup>35</sup> The underlying cause of these conditions should be treated first. If perioperative tachycardia persists, a β-blocker can be used cautiously in high-risk patients with proven or suspected CAD. This is best supervised by physicians with experience in managing perioperative hemodynamics because hypotension

Table 50-2 Recommendations from the American College of Cardiology/American Heart Association Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery

#### RECOMMENDATIONS FOR PERIOPERATIVE BETA-BLOCKER THERAPY

#### Class I

1. Beta blockers should be continued in patients undergoing surgery who are receiving beta blockers for treatment of conditions with ACCF/AHA Class I guideline indications for the drugs. (*Level of Evidence: C*)

#### Class IIa

- 1. Beta blockers titrated to heart rate and blood pressure are probably recommended for patients undergoing vascular surgery who are at high cardiac risk owing to coronary artery disease or the finding of cardiac ischemia on preoperative testing. (*Level of Evidence: B*)
- 2. Beta blockers titrated to heart rate and blood pressure are reasonable for patients in whom preoperative assessment for vascular surgery identifies high cardiac risk, as defined by the presence of more than 1 clinical risk factor. (*Level of Evidence: C*)
- 3. Beta blockers titrated to heart rate and blood pressure are reasonable for patients in whom preoperative assessment identifies coronary artery disease or high cardiac risk, as defined by the presence of more than 1 clinical risk factor, who are undergoing intermediate-risk surgery. (*Level of Evidence: B*)

#### Class IIb

- 1. The usefulness of beta blockers is uncertain for patients who are undergoing either intermediate-risk procedures or vascular surgery in whom preoperative assessment identifies a single clinical risk factor in the absence of coronary artery disease. (*Level of Evidence: C*)
- 2. The usefulness of beta blockers is uncertain in patients undergoing vascular surgery with no clinical risk factors who are not currently taking beta blockers. (*Level of Evidence: B*)

#### Class III

- 1. Beta blockers should not be given to patients undergoing surgery who have absolute contraindications to beta blockade. (*Level of Evidence: C*)
- 2. Routine administration of high-dose beta blockers in the absence of dose titration is not useful and may be harmful to patients not currently taking beta blockers who are undergoing noncardiac surgery. (*Level of Evidence: B*)

 Table 50-2
 Recommendations from the American College of Cardiology/American Heart Association

 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery—Cont'd

#### **RECOMMENDATIONS FOR STATIN THERAPY**

#### Class I

1. For patients currently taking statins and scheduled for noncardiac surgery, statins should be continued (Level of Evidence: B)

#### Class IIa

1. For patients undergoing vascular surgery with or without clinical risk factors, statin use is reasonable (Level of Evidence: B)

#### Class IIb

1. For patients with at least one clinical risk factor who are undergoing intermediate-risk procedures, statins may be considered (*Level of Evidence: C*)

#### RECOMMENDATIONS FOR $\alpha_2$ -AGONISTS

#### Class IIb

1.  $\alpha_2$ -Agonists for perioperative control of hypertension may be considered for patients with known coronary artery disease or at least one clinical risk factor who are undergoing surgery (*Level of Evidence: B*)

#### Class III

1.  $\alpha_2$ -Agonists should not be given to patients undergoing surgery who have contraindications to this medication (Level of Evidence: C)

#### RECOMMENDATION FOR PREOPERATIVE INTENSIVE CARE MONITORING

#### Class IIb

1. Preoperative intensive care monitoring with a pulmonary artery catheter for optimization of hemodynamic status might be considered; however, it is rarely required and should be restricted to a very small number of highly selected patients whose presentation is unstable and who have multiple comorbid conditions (*Level of Evidence: B*)

and other hemodynamic aberrations might increase the incidence of stroke or septic death.

- Clonidine may be a useful alternative to β-blockers for heart rate control, but the absence of a large-scale trial limits our understanding of the risks versus benefits.
- Statins should be continued perioperatively.
- Should statins be indicated independent of noncardiac surgery, initiation before surgery may be of benefit.
- Nitroglycerin has no prophylactic role but may be useful for treatment.

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# 51 What is the value of Non-Dialytic therapy in acute kidney injury?

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Acute kidney injury (AKI) is common in hospitalized patients, especially those in the intensive care unit (ICU). A recent analysis of the National Hospital Discharge Survey of 2001 showed that 1.9% of all discharges included an ICD-9 diagnosis coding for acute renal failure. The presence of AKI was associated with a 2-day increase in length of hospital stay and an adjusted odds ratio (OR) for hospital mortality of 4.1.<sup>1</sup> In a prospective observational multinational study, nearly 6% of patients admitted to the ICU were diagnosed with AKI, and 4% went on to require renal replacement therapy (RRT).<sup>2</sup>

AKI may arise in a variety of clinical settings. It may be caused by prerenal azotemia (due to decreased renal perfusion), acute tubular necrosis (ATN; resulting from ischemic events or a variety of endogenous or exogenous nephrotoxic insults), or less commonly, other intrinsic renal lesions or urinary tract obstruction. A recent review by Esson and Schrier reported that ATN accounted for 38% of AKI in hospitalized patients and 76% of all cases of ICU-associated AKI. Mortality was correspondingly high in those with ATN: 37% of hospitalized patients and 78% of ICU patients. Of all patients with ATN, 5% to 11% required permanent RRT.<sup>3</sup> In an attempt to further understand the pathophysiology of ATN, the disease process has been divided into four phases: initiation, maintenance, recovery, and extension.<sup>4</sup> AKI and its supportive treatment with RRT are both associated with markedly increased morbidity and mortality. Accordingly, many approaches to preventing or treating AKI before RRT have been studied. The results of trials of nondialytic therapeutic interventions attempting to ameliorate the course of AKI will be discussed in this chapter. Success in numerous studies using a variety of agents for prevention or early therapy of AKI in experimental animal models has not been followed by success in human clinical trials. There are several potential reasons for this phenomenon, including deficiencies of experimental models in mirroring clinical AKI, delayed diagnosis of AKI using current clinical tools (azotemia, oliguria), and randomization of patients with severe AKI into clinical trials of agents that had proven preclinical success only in primary or very early secondary prophylaxis. Several of these issues will be further highlighted in subsequent discussion of drug classes.

#### VOLUME RESUSCITATION

Although the effects of colloid or crystalloid administration on morbidity and mortality in critically ill patients have been examined, the choice of fluid to treat AKI has not been studied specifically. In a multicenter randomized double-blind trial, the SAFE study found no differences in mortality, hospital or ICU length of stay, or organ failure rates (including AKI) when 4% albumin versus saline was administered to their cohort of critically ill patients.<sup>5</sup> Furthermore, two meta-analyses (one encompassing 17 trials with 814 patients, with the other including 3082 subjects in 37 trials) could not make a conclusive preferential recommendation for colloids or crystalloids in the resuscitation of hospitalized patients.<sup>6,7</sup> A recent randomized trial using the basic common elements of the Rivers protocol for early goal-directed therapy in severe sepsis found that the rate of AKI was lower compared with the nonprotocol therapy cohort (38.9% versus 55.2%; P = .015), and mortality from multiorgan failure was reduced.<sup>8,9</sup> Specifically, although central lines were placed in all patients, the protocol targeting of therapy with fluids and vasoactive drugs to achieve and maintain central venous pressures of 8 to 12 mm Hg, mean arterial pressures between 65 and 90 mm Hg, and urine output of 0.5 mL/kg per hour or greater improved outcomes compared with the management by physician discretion. Of note, the original Rivers study targeted resuscitation to the above parameters in all subjects and found improved survival in those additionally randomized to target a central venous oxygen saturation above 70%. Unfortunately, the Rivers study report did not include details of renal function. However, a subsequent publication from this group found decreased markers of apoptosis in the group randomized to more aggressive therapy. Specifically, this study showed that caspase-3, a biomarker of apoptosis, was suppressed from 6 to 72 hours in the intervention arm. Thus, it appears likely that apoptotic AKI was reduced by this approach.<sup>10</sup>

#### LOOP DIURETICS

Frequently, hospitalized patients with AKI are administered diuretics to promote increased urine output. "Conversion" from a nonoliguric state can appear to be a harbinger of less severe AKI or improvement of AKI, but the use of diuretics in AKI has not been shown to improve patient outcomes. From a physiologic perspective, the use of loop diuretics inhibits the  $Na^+/K^+$  2Cl<sup>-</sup> transporter in the medullary portion of the thick ascending limb of the loop of Henle. This inhibition of electrolyte transport leads to a decrease in renal oxygen consumption and is hypothesized to be beneficial when renal perfusion is decreased or AKI with tubular injury has developed. However, a number of studies have shown that this presumed physiologic benefit has not translated into improved clinical outcomes. The retrospective observational analysis by the PICARD Study Group demonstrated that the use of diuretics in critically ill patients with AKI was associated with a 68% increase in in-hospital mortality, a 77% increase in the odds of death or nonrecovery of renal function, and an increase in length of hospital stay.<sup>11</sup> Although another recent AKI cohort study did not confirm the association of diuretic use with adverse outcomes in AKI,<sup>12</sup> prospective trials also have failed to demonstrate benefits of diuretic use in AKI. In a randomized doubleblind placebo-controlled multicenter trial comparing highdose intravenous furosemide with oral furosemide and placebo, Cantarovich and colleagues found no benefit in using high-dose intravenous furosemide (25 mg/kg per day) in patients with established AKI receiving RRT.13 This occurred despite a significant decrease in the time to achieve a 2 L/day diuresis with furosemide (5.7 days) compared with placebo (7.8 days; P < .004). Additionally, the investigators found no effect on survival or recovery of renal function. Recently, a meta-analysis analyzing the utility of furosemide for prevention (n = 3) and treatment (n = 6) of AKI was performed.<sup>14</sup> The use of furosemide had no effect on in-hospital mortality (relative risk [RR], 1.11; 95% confidence interval [CI], 0.92 to 1.33; P = .28) or risk for needing renal replacement therapy (RR, 0.99; 95% CI, 0.80 to 1.22; P = .91). Furthermore, another recent randomized placebo-controlled trial studied 92 patients with established AKI for up to 21 days while using torsemide (mean creatinine clearance, 10 mL/minute) or furosemide (8 mL/minute) compared with placebo (7 mL/minute). These investigators found that diuretic use did not affect the need for dialysis (P = .87), recovery from AKI (P = .56), or mortality (P = .73). However, diuretic use did increase urine output in the first 24 hours (P = .02).<sup>15</sup> There are a variety of potential mechanisms for adverse effects of diuretics in AKI. These include precipitation of hypovolemia or electrolyte disorders, renal vasoconstriction with decreased renal blood flow, and perhaps delayed nephrology consultation with late initiation of renal replacement therapy. Nonetheless, on a practical basis, diuretic use in AKI will continue for treatment of fluid overload and hyperkalemia, with less certainty regarding use to treat oliguria and prevent positive fluid balance.

#### NATRIURETIC PEPTIDES

The use of natriuretic peptides for the treatment of established AKI has shown some promising results in small clinical studies but negative results in large-scale clinical trials. In a randomized placebo-controlled trial, Sward and colleagues studied the use of atrial natriuretic peptide (ANP) in postoperative cardiac surgery patients with AKI (defined as  $\geq$ 50% increase in serum creatinine from baseline of <1.8 mg/dL) and showed that ANP use was associated with lower rates of RRT compared with placebo.<sup>16</sup> Sixty-one patients were randomized to receive ANP or placebo until one of the following criteria was met: (1) the serum creatinine decreased below the baseline value at enrollment; (2) the patient died; or (3) RRT was indicated. Patients were excluded if they had oliguria or required intravenous furosemide. The primary end point was the need for RRT within 21 days of enrollment. Twenty-one percent of patients in the ANP arm and 47% in the placebo arm needed renal replacement therapy within the 21 days (hazard ratio [HR], 0.28; 95% CI, 0.10 to 0.73; P = .009). Rates of hypotension were no different in the first 24 hours between groups (59% for ANP group and 52% in placebo group; P = NS). It should be noted that this study was underpowered for the primary end point and thus may be a false-positive study. It also should be noted that the ANP dose used was lower than in prior unsuccessful multicenter clinical trials (perhaps explaining the lower incidence of hypotension) and that this study randomized patients with AKI of far less severity than its predecessors (mean creatinine clearance, 32.1  $\pm$  2.9 mL/minute versus 3  $\pm$  4 mL/minute in a multicenter study of ANP in ATN<sup>17</sup> versus 8.0 mL/minute in a multicenter study of ANP in oliguric ATN.<sup>18</sup>

Urodilatin, another natriuretic peptide (made by renal tubular cells) has been shown to have similar effects as ANP but with a decreased risk for systemic hypotension.<sup>19</sup> Pilot studies show that urodilatin improves AKI in the postoperative period.<sup>20</sup> For example, in a prospective observational phase 2A study, 51 patients undergoing orthotopic heart transplantation were given urodilatin infusion (6 to 20 ng/kg per minute) for a maximum of 96 hours after surgery. AKI incidence was 6% in these patients, compared with 20% in the historical control group. This and other studies suggest a promising role for natriuretic peptides in AKI therapy, but further large-scale clinical trials are needed to establish this indication.

#### DOPAMINE

The endogenous catecholamine dopamine has been used in low doses (2 to 5  $\mu$ g/kg per minute) in many centers for decades because of putative renoprotective effects. In healthy patients, dopamine increases urine output by stimulating the D1, D2, and D4 receptors in the kidney. Dopamine also dilates both the efferent and afferent arterioles and increases renal perfusion. In renal tubular cells, at a dose of 2 to 5  $\mu$ g/kg per minute, the D1 and D2 receptors decrease  $Na^+/K^+$  ATPase activity and promote increased natriuresis.<sup>21</sup> However, at higher doses ( $\geq 5 \ \mu g/kg$  per minute), β-adrenergic effects supplant the dopamine receptor effects, primarily stimulate the heart, and may further increase renal blood flow (by augmenting cardiac output). As a result of these varied physiologic mechanisms, the putative clinical benefits of dopamine have been studied extensively. Despite the overwhelmingly negative results of clinical trials, the use of dopamine remains frequent and often becomes the protocol. The ANZICS Clinical Trials Group performed a randomized double-blind controlled

trial, which compared 2  $\mu$ g/kg per minute infusion of dopamine versus placebo in critically ill patients in 23 different ICUs. This study showed no improvement in the primary end point, which was peak serum creatinine during the study drug infusion (dopamine group peak serum creatinine, 245 mol/L [SD, 144] versus placebo 249 mol/L [SD, 147]; *P* = .93). Similarly, they showed no difference in urine output or the requirement of RRT, length of ICU stay, or hospital mortality.<sup>22</sup>

A number of meta-analyses have also shown negative to marginal benefit of dopamine use for renal protection. Friedrich and colleagues performed a meta-analysis (61 trials with more than 3300 subjects) of the effect of dopamine on renal function, adverse events, or other outcomes.23 They found that dopamine increased urine output by 24% (95% CI, 14% to 35%) on day 1 of use, but no mortality, development of AKI, or the future need for RRT benefit was demonstrated. Of note, a recent retrospective analysis found that after coronary artery bypass graft surgery, the risk for new-onset atrial fibrillation was 74% higher in patients given renal-dose dopamine compared with controls. Furthermore, 56.1% of these episodes occurred within 24 hours of starting the dopamine infusion.<sup>24</sup> Another recent study provided important insight regarding a potential adverse renal effect of dopamine therapy in patients with AKI. Lauschke and colleagues performed a randomized double-blind, placebo-controlled crossover trial using Doppler ultrasound to study the renal vasculature before and after dopamine was administered.<sup>21</sup> In patients with AKI (doubling of baseline serum creatinine or creatinine above 2 mg/dL, dopamine induced vasoconstriction, which was not seen in patients without AKI. This study suggests that low-dose dopamine may further reduce renal perfusion in established AKI and possibly explains the failure of this drug as a renoprotective agent despite apparently favorable physiologic effects. Given the paucity of positive data and emerging evidence of adverse renal and systemic effects, this therapy cannot be recommended for the treatment of AKI.

#### FENOLDOPAM MESYLATE

Fenoldopam mesylate is a benzazepine-derivative pure dopaminergic agonist that is approved by the U.S. Food and Drug Administration for the treatment of severe hypertension. Used intravenously, fenoldopam is a postsynaptic dopamine-1 receptor agonist that increases renal blood flow and decreases systemic vascular resistance.<sup>25</sup> Fenoldopam is thought to be a superior candidate to lowdose dopamine in preventing and treating AKI because it could increase renal blood flow, perhaps with greater renal medullary vasodilation, without systemic adverse effects of stimulating  $\alpha$ - or  $\beta$ -adrenergic receptors. Tumlin and colleagues conducted a prospective, multicenter, doubleblind, placebo-controlled trial of fenoldopam in 155 patients with ICU-associated AKI (defined as  $\geq$ 50%) increase in serum creatinine from admission) with a mean arterial pressure greater than 70 mm Hg.<sup>26</sup> The fenoldopam infusion continued for 72 hours, but it was discontinued if the mean arterial pressure dropped below 70 mm Hg during study drug infusion. This underpowered negative

study showed no difference in the primary end point of 21-day dialysis-free survival. More recently, Brienza and colleagues compared the use of fenoldopam to dopamine in a prospective, randomized controlled trial in 100 critically ill patients with early AKI. AKI was defined as ICU stay less than 1 week, urine output less than 0.5 mL/kg over a 6-hour period, or serum creatinine concentration more than 1.5 mg/dL and less than 3.5 mg/dL. Subjects were randomized to receive either 2  $\mu$ /kg per minute of dopamine or 0.1  $\mu/kg$  per minute of fenoldopam for 4 days. The fenoldopam group had a larger decrease in their "lowest" serum creatinine values (0.53  $\pm$  0.47 versus 0.34  $\pm$ 0.38 mg/dL; P = .027) as well as a significant reduction in serum creatinine at days 2, 3, and 4. No difference was noted in total urinary output, and at day 1, the dopamine group had more urine output than the fenoldopam group.<sup>27</sup> Limitations of this study include the lack of a true control group for comparison, unblinding of investigators, and the nonstandardized definition of AKI. Subsequent to these studies, a meta-analysis of 16 randomized studies involving 1290 critically ill patients found that fenoldopam significantly reduced AKI risk (OR, 0.43; 95% CI, 0.32 to 0.59; *P* < .001), renal replacement need (OR, 0.54; 95% CI, 0.34 to 0.84; P = .007, and in-hospital death (OR, 0.64; 95% CI, 0.45 to 0.91; P = .01).<sup>28</sup> It should be noted that the 16 studies used were individually suboptimal and underpowered for the effect intended to study, and the definition of need for renal replacement therapy was not uniform. It is recognized that fenoldopam has shown promising results in a number of studies; however, until a randomized placebo-controlled trial with adequate power finds similar results, a definitive recommendation for use of fenoldopam for AKI therapy cannot be made.

#### **GROWTH FACTORS**

Novel research investigating the role of growth factors in the treatment of existing AKI has not shown positive results. In a multicenter, randomized placebo-controlled trial, 72 patients with severe acute renal failure (mean glomerular filtration rate, 4.3 mL/minute) were randomized to 12-hour injections of 100  $\mu$ g/kg of insulin-like growth factor-1 (IGF-1) versus placebo.<sup>29</sup> Patients were diagnosed with AKI based on urinary output and iothalmate clearance, with the primary end point being change in glomerular filtration rate from baseline. IGF-1 did not improve the rate of recovery of established AKI. Another study looked at epidermal growth factor, hepatocyte growth factor, IGF-1, and basic fibroblast growth factor and their individual effects on injured human renal thick ascending limb and distal convoluted cells.<sup>30</sup> Of all these growth factors, only epidermal growth factor showed an effect of promoting cell proliferation and growth. These findings must be further tested in human clinical trials.

#### CONTROVERSIES

An area of continued controversy in the field of nephrology is the standardization of the definition of AKI. Through the use of the Acute Dialysis Quality Initiative–initiated risk, injury, failure, loss, and end-stage (RIFLE) classification, there has been an effort to standardize the definition of AKI.<sup>31</sup> This classification has been modified since its initial inception, and an AKI staging system has been created to address even smaller changes in serum creatinine.<sup>32</sup> Many of the studies highlighted in this discussion predate these classification schemas. With the continued controversy of AKI classification, a new area of interest has emerged looking at biomarkers that predict AKI earlier and more reliably than serum creatinine. The utility of testing for proteins such as kidney injury molecule-1 (KIM-1), cystatin C, and neutrophil gelatinase-associated lipocalin (NGAL) has shown promise.<sup>33–35</sup>

#### CONCLUSION

AKI is known to increase the risk for morbidity and mortality in all patients, but particularly in critically ill patients. A number of therapies have been evaluated for both prevention and treatment. There are increasing data that neither diuretics nor dopamine has any beneficial role in improving patient outcomes in either prophylactic or therapeutic treatment of AKI. In point of fact, more recent data may indicate that these therapies are harmful. Volume expansion with protocol-driven management in early sepsis has shown benefit and continues to be a mainstay of treatment. New areas of interest and promise include the use of natriuretic peptides, fenoldopam, and growth factors. Although the physiologic and therapeutic effects of these medications have been beneficial in animal models, these experimental findings have not been translated to successful clinical trials in AKI.

#### AUTHORS' RECOMMENDATIONS

- The morbidity and mortality associated with AKI are significant. Discovery of effective approaches to AKI prevention, early diagnosis, and therapy is imperative, particularly in patients admitted to the ICU.
- In the septic patient, protocol-driven volume resuscitation and vasoactive drugs should be used aggressively to maintain renal perfusion in an attempt to prevent or treat AKI.
- The use of diuretics to treat and prevent AKI is not recommended. In many settings, this therapy may increase the likelihood of AKI development. Diuretic-responsive oliguria may be a sign of less severe AKI, but this should not be a treatment goal. "Renal-dose" dopamine should not be used for the prevention or treatment of AKI.
- Further research is needed to define the roles of natriuretic peptides, fenoldopam, and growth factors in AKI therapy.

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## 52

## How Does One Optimize Care in Patients at Risk for or Presenting with Acute Kidney Injury?

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Acute renal failure (ARF) is common in the intensive care unit (ICU), but its epidemiology and management are difficult to assess owing to the absence of a universally accepted definition. The Acute Kidney Injury Network (AKIN) has proposed a new term, acute kidney injury (AKI), to encompass the entire spectrum of this disorder and proposed new criteria for diagnosis and staging.<sup>1</sup> The definition of acute kidney injury (AKI) is based on evidence that even minor short-term changes in serum creatinine (i.e.,  $\geq 0.3$ mg/dL or 26 µmol/L) are linked to increased morbidity and mortality,<sup>2</sup> and early intervention may be of benefit. Although there currently is no randomized controlled trial (RCT) demonstrating a benefit of early management of AKI, the AKIN criteria suggest that current practice should apply the following measures as soon as a significant increase in creatinine has been detected.

#### PRESERVATION AND OPTIMIZATION OF RENAL FUNCTION

#### **General Measures**

The primary goal is to correct any reversible detrimental factors contributing to AKI. These include volume depletion, hypotension, decreased cardiac output and renal perfusion, obstruction, high intra-abdominal pressure, and nephrotoxic agents. The most common nephrotoxic agents are radiocontrast, nonsteroidal anti-inflammatory drugs (NSAIDs), and antibiotics (aminoglycosides, amphotericin, and vancomycin). These agents should be avoided if possible. Diuretics, angiotensin-receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs) are often incriminated for their nephrotoxic potential, but there is no clear evidence that this is the case. Use of these agents should be avoided in prerenal states.

#### Specific Interventions

#### **Optimizing Volume Status**

Prerenal AKI usually can be corrected with volume expansion if timely and adequate amounts of fluid are infused. In ischemic acute tubular necrosis (ATN),

experimental data suggest that autoregulation is lost and that renal blood flow becomes linearly pressure dependent so that subsequent hypotension and hypoperfusion easily cause new kidney lesions.<sup>3</sup> Thus, maintaining adequate renal perfusion pressure is even more critical in ATN. However, there are no definite measures to determine the optimal fluid and vasopressor therapies.

Based on outcome data detailing mortality in critically ill patients with severe sepsis or septic shock, fluid and pressor therapy might target a mean blood pressure of more than 65 mm Hg, central venous pressure of more than 8 to 12 mm Hg, urine output or 0.5 mL/kg per hour or greater, and central venous oxygen saturation of 70% or greater.<sup>4</sup> However, these studies did not focus on renal outcomes, and the resuscitative strategies may not be applicable for prevention of AKI. Nevertheless, they provide a reference point for future studies in this area.

Urine sodium concentration, fractional excretion of sodium (FeNa), and fractional excretion of urea (FeUN) are common tools to differentiate between prerenal disease and ATN (Table 52-1). The FeUN has been advocated by some as a valuable marker if diuretics are used.<sup>5</sup> Another prospective study did not confirm these findings. An FeNa value below 1% is suggestive of prerenal AKI, and a value higher than 2% typically indicates ATN. A marked decrease in FeNa in patients with ATN can suggest superimposed prerenal disease. However, FeNa can be falsely elevated by diuretics and preexisting chronic kidney disease (CKD) and may be falsely low in congestive heart failure, hepatic failure, severe burns, sepsis, rhabdomyolysis, and contrast nephropathy, among others. FeUN is not altered by prior diuretic use, and a cut-off value of 35% or less is usually consistent with a prerenal state.

Increasing data substantiate the adverse effects of fluid overload in critically ill patients. This may translate to renal function. One recent randomized study comparing two fluid management strategies in acute lung injury (ALI) found that the conservative (restrictive) fluid group had improved lung function and shortened duration of mechanical ventilation without increasing the risk for AKI. There was also a trend toward a reduced need for continuous renal replacement therapy (CRRT).<sup>6</sup> Other studies are required to validate these findings.

Table 52-1 <b>(FeUN)</b>	Fractional Excretion of Sodium (FeNa) and Fractional Excretion of Urea
FeNa, %	Urine sodium concentration × plasma creatinine × 100 Plasma sodium concentration × urine creatinine concentration
FeUN, %	Urine urea nitrogen concentration $\times$ plasma creatinine $\times$ 100 Blood urea nitrogen concentration $\times$ urine creatinine concentration

#### Volume Expanders

The optimal volume expander varies according to the clinical situation, and only limited evidence-based data are available. RCTs have proved the benefit of saline infusions to prevent the nephrotoxicity of radiocontrasts,<sup>7</sup> cisplatin,<sup>8</sup> and amphotericin.<sup>9</sup> Lower levels of evidence support a prompt use of saline for rhabdomyolysis.<sup>10</sup>

In 1998, a Cochrane meta-analysis showed a higher relative risk for death with the use of albumin, and this association remained true even for hypoalbuminemic patients.<sup>11,12</sup> Two subsequent meta-analyses have refuted these findings.<sup>12,13</sup> The most recent RCT, which included 6997 patients in the ICU, did not demonstrate any difference in either mortality or duration of renal replacement therapy (RRT) when the use of 4% albumin was compared with saline.<sup>14</sup> When stratifying these patients post hoc into two groups (those with albumin levels of  $\leq 25 \text{ g/dL}$  versus those with levels > 25 g/dL), no difference was observed in mortality, length of hospital or ICU stay, or duration of RRT, irrespective of the volume expander used.<sup>15</sup> Albumin might be helpful in ALI with the use of a loop diuretic.<sup>16</sup>

The effects of gelatin, dextran, and hydroxyethyl starch (HES) on renal function have been studied in several conditions. One trial randomized 129 patients in severe sepsis or septic shock to receive either 6% HES or 3% fluidmodified gelatin.<sup>17</sup> AKI, defined as a twofold increase in initial serum creatinine or need for RRT, occurred in 42% of patients in the first group and 23% in the second. Multivariate analysis confirmed that HES is an independent risk factor for AKI in severe sepsis or septic shock. Two similar RCTs, which included 40 patients and 60 patients, did not find any difference in renal outcome in elderly patients undergoing cardiac and major abdominal surgery, respectively.<sup>18,19</sup> In the most recent randomized study comparing the same products in 62 patients during aortic aneurysm surgery, HES was associated with improved renal function.<sup>20</sup> Polygeline and urea-linked gelatin were shown to significantly increase serum creatinine compared with albumin in a randomized trial of 105 patients.<sup>21</sup> Another trial showed a nonsignificant increase in creatinine.<sup>22</sup> No randomized data have been found for dextran, but several case reports of AKI have been published.<sup>23</sup> Thus, firm conclusions regarding the safety of synthetic colloids on renal function cannot be made, especially with HES, increasing doses of colloids, and renal dysfunction.

#### Loop Diuretics

A recent meta-analysis did not support the use of loop diuretics to reduce mortality or improve renal recovery in the setting of AKI (Table 52-2).<sup>24</sup> However, a shorter duration of RRT (-1.4 days) was observed with the use of diuretics. Two meta-analyses have confirmed the lack of benefit for in-hospital mortality, the need for RRT, or a reduction in the number of dialysis sessions required,<sup>25</sup> although a trend was seen in one study.<sup>26</sup>

If the benefits of using loop diuretics in AKI are not well defined, is there any danger in prescribing them? Although an initial cohort study of 552 patients suggested that the use of diuretics was associated with increased mortality,<sup>27</sup> a prospective multicenter epidemiologic study of 1743 patients found that diuretic use was not associated with higher mortality rates despite hazard ratios greater than 1.<sup>28</sup> An increased risk for ototoxicity may occur with high doses of diuretics.<sup>25</sup> Despite controversial data, a multinational survey on the clinical use of diuretics in AKI concluded that diuretics are often prescribed in this setting (67.1%) and are most commonly delivered intravenously in bolus.<sup>29</sup> This survey also confirms the need for well-designed trials of diuretics in AKI.

#### Natriuretics

Atrial natriuretic peptide (ANP) has been studied as a treatment for AKI in four randomized controlled trials (Table 52-3).<sup>30–33</sup> The first study was small, and ANP was found to reduce the need for dialysis but did not affect mortality. The largest study showed that ANP did not improve overall dialysis-free survival,<sup>31</sup> except in oliguric patients. A subsequent trial in 222 oliguric patients failed to show any benefit on mortality or dialysis-free survival. Both trials used ANP for 24 hours and at high doses. This could have influenced the results. The most recent study included only 61 patients after cardiac surgery and used a longer treatment period (5.3  $\pm$  0.8 days). These investigators found a decreased probability of dialysis and an improvement in dialysis-free survival.<sup>32</sup> Further studies in larger number of patients are required to determine the value of ANP use in AKI.

#### Vasoactive Agents

The use of "renal-dose" dopamine (0.5 to  $3 \mu g/kg$  per minute) as a specific vasodilator to increase renal blood flow has been the subject of several previous debates. The current evidence does not support the use of dopamine for prevention or treatment of AKI (Table 52-4). In a metaanalysis published in 2005, low-dose dopamine was shown to increase urine output but did not have any effect on renal dysfunction or mortality.<sup>34</sup> Two previous metaanalyses had confirmed these findings, with dopamine having no influence on onset of renal failure, need for Table 52-2 Summary of Meta-Analysis on the Use of Loop Diuretics in Acute Renal Failure

Study	No. of Trials	No. of Subjects (Intervention/ No Intervention)	Intervention	Control	Outcomes
Ho & Sheridan, 2006 <sup>25</sup>	9	416/405	Furosemide	Not defined	In-hospital mortality: RR, 1.11 (95% CI, 0.92-1.33) Risk for requiring RRT: RR, 0.99 (95% CI, 0.80-1.22) Number of dialysis sessions: Mean difference (days) = $-0.48$ ( $-1.45$ to 0.50)
Bagshaw et al, 2007 <sup>24</sup>	5	305/250	Furosemide	Placebo (2/5 trials)	Mortality: OR, 1.28 (95% CI, 0.89- 1.94) Renal recovery: OR, 0.88 (95% CI, 0.59-1.31) Duration of RRT: Mean difference (days) = -1.4 (-0.2 to -2.3)
Sampath et al, 2007 <sup>26</sup>	13	1907/1174	Furosemide	Not defined	Mortality: RR, 1.10 (95% CI, 0.85-1.42) Uremic duration: Mean difference (days) = -1.54 (-5.62 to 2.46)

CI, confidence interval; OR, odds ratio; RR, relative risk; RRT, renal replacement therapy.

Table 52-3 Summary of Randomized Controlled Trials on the Use of Atrial Natriuretic Peptide in Acute Renal Failure

Study	No. of Subjects (Intervention/No Intervention)	Intervention	Control	Outcomes
Rahman et al, 1994 <sup>30</sup>	30/23	ANP for 24 hr with or without diuretic	With or without diuretic	Mortality: 17% vs. 35% ( $P = .11$ ) Need for dialysis: 23% vs. 52% ( $P < .05$ )
Allgren et al, 1997 <sup>31</sup>	243/255	Anaritide for 24 hr	Placebo	Dialysis-free survival at 21 days: 43% vs. 47% ( $P = .35$ ) Dialysis-free survival in oliguric patients: 27% vs. 8% ( $P = .008$ )
Lewis et al, 2000 <sup>33</sup>	108/114	ANP for 24 hr	Placebo	Dialysis-free survival at 21 days: 21% vs. 15% ( $P = .22$ ) Mortality at 60 days: 60% vs. 56% ( $P = .541$ )
Sward et al, 2004 <sup>32</sup>	29/30	ANP for mean duration of $5.3 \pm 0.8$ days	Placebo for 4.3 $\pm$ 0.7 days	Dialysis on or before day 21: 21% vs 47% ( $P = .009$ ) Dialysis or death before or at day 21: 28% vs. 57% ( $P = .017$ )

ANP, atrial natriuretic peptide.

dialysis,<sup>35</sup> or absolute change in serum creatinine.<sup>36</sup> Some concerns focus on its detrimental effect on the immune system, gut ischemia, cardiac arrhythmias, endocrine status, myocardial ischemia, and ventilator weaning.<sup>36</sup>

Vasopressors often are considered detrimental to organ perfusion. Contrary to this belief, however, a small prospective study in 14 patients with sepsis revealed that norepinephrine had beneficial effects on creatinine clearance when raising mean arterial pressure over 70 mm Hg, compared with 12 nonseptic patients.<sup>37</sup> However, another small RCT including 28 patients did not demonstrate any benefit on creatinine or creatinine clearance by increasing mean arterial pressure from 65 to 85 mm Hg.<sup>38</sup>

A recent meta-analysis found that fenoldopam, a dopamine receptor-1 agonist that increases blood flow to the renal cortex and outer medulla, reduced the risk for

Study	No. of Trials	No. of Subjects (Intervention/No Intervention)	Intervention	Control	Outcomes
Kellum et al, 2001 <sup>35</sup>	17	295/251 (mortality) 418/324 (hemodialysis) 303/286 (renal failure)	Dopamine <5 μg/kg/ min	Not defined	Mortality: RR, 0.90 (95% CI, 0.44-1.83) Onset of AKI: RR, 0.81 (95% CI, 0.55-1.19) Need for dialysis: RR, 0.83 (95% CI, 0.55-1.24)
Marik, 2002 <sup>36</sup>	15	436/524 (change creatinine) 358/360 (acute renal dysfunction)	Dopamine 2-5 μg/kg/min	Not defined	Absolute change in serum creatinine: 0.06 mg/dL (95% CI, -0.07 to 0.19) Acute renal dysfunction: RR, 1.01 (95% CI, 0.79-1.28)
Friedrich et al, 2005 <sup>24</sup>	61	701/686 (mortality) 606/610 (RRT)	Dopamine ≤5 µg/kg/min	Placebo or no therapy	Mortality: RR, 0.96 (95% CI, 0.78-1.19) Need for RRT: RR, 0.93 (95% CI, 0.76-1.15) Adverse events: RR, 1.13 (95% CI, 0.90-1.41)

Table 52-4 Summary of Meta-Analysis on the Use of Dopamine in Acute Renal Failure

AKI, acute kidney injury; CI, confidence interval; RR, relative risk; RRT, renal replacement therapy.

AKI, the need for RRT (6.5% versus 10.4%; 95% confidence interval [CI], 0.34 to 0.84), and in-hospital mortality (15.1% versus 18.9%; 95% CI, 0.45 to 0.91) in postoperative or ICU patients.<sup>39</sup> However, several limitations were present in this study. These included lack of standardized criteria for initiation of RRT, heterogeneity of populations, multiple definitions of AKI, variance in dosage and duration of treatments, and absence of an independent measure of glomerular filtration rate (GFR). Concerns focus on the hypotensive properties of fenoldopam in the "real world," the suboptimal quality of the studies, and the vasodilation properties previously shown not to be beneficial in studies on dopamine, ANP, and insulin-like growth factor-1.<sup>39</sup> No single prospective study has shown that fenoldopam can reduce the need for RRT. These results need to be confirmed with an adequately powered trial before the use of fenoldopam is promoted widely.

In an RCT, the use of fenoldopam has not been shown to reduce contrast-induced nephropathy.<sup>40</sup> Targeted renal delivery of fenoldopam may benefit kidney function in patients undergoing contrast procedures compared with intravenous fenoldopam.<sup>41</sup> RCTs are needed to support these preliminary results.

#### Other Agents

In a secondary outcome of an often-cited 2001 study on the use of intensive insulin therapy, the need for RRT was reduced by 41%. In 2007, a meta-analysis examining the effect of insulin on the prevention of AKI pointed toward a reduction in the incidence of AKI in both the medical and surgical ICU.<sup>42</sup> However, a more recent meta-analysis showed that tight glucose control did not improve mortality or new need for dialysis.<sup>43</sup>

Although N-acetylcysteine is commonly used in the prevention of radiocontrast AKI owing to its safety

and low cost, multiple RCTs that included patients at risk for or with early ATN indicate that this drug is not effective in preventing AKI.<sup>44–49</sup> Calcium channel blockers were studied in small RCTs that demonstrated some benefits on renal clearance, although no convincing data are available for the incidence of AKI or need for RRT.<sup>50</sup> Neither thyroid hormone nor insulin-like growth factor-1 provided benefit in AKI patients in RCTs.<sup>51,52</sup>

#### CORRECTION OF ELECTROLYTE, ACID-BASE, AND MINERAL HOMEOSTASIS

AKI limits the ability of the kidneys to maintain acid-base and electrolyte balance. In oliguric states, this equilibrium is even more difficult to achieve, justifying frequent monitoring of electrolytes in order to avoid severe and sometimes fatal hyperkalemia. It is a standard of care to administer calcium, ion-exchange resins, glucose and insulin, bicarbonate, and possibly diuretics or salbutamol to treat acute, severe hyperkalemia. A recent Cochrane meta-analysis supported the use of salbutamol and intravenous insulin and glucose alone or in combination.53 Even though there are no RCTs to support the use of ion-exchange resins and chloride calcium, ion-exchange resins were recommended in the absence of gastrointestinal disease and intravenous calcium in the presence of electrocardiogram changes or arrhythmias.<sup>53</sup> Most nephrologists will initiate hemodialysis if (1) hyperkalemia is severe or accompanied by arrhythmias, (2) moderate to severe hyperkalemia is refractory to medical treatment or present in a dialysis patient, or (3) there is marked tissue breakdown and release of potassium from cells (e.g., tumor lysis syndrome).

Metabolic acidosis is the most frequent acid-base disturbance in critically ill patients suffering from AKI.<sup>54</sup> The treatment of metabolic acidosis in AKI has never been the subject of randomized trials, and the consequences of metabolic acidosis in AKI patients are not clear. Therefore, the bicarbonate level to target is unknown. Some experts have recommended that a pH value below 7.2 serve as a threshold to administer bicarbonate.<sup>55</sup> In patients with CKD, it is recommended to maintain serum bicarbonate levels above 22 mEq/L owing to detrimental effects of acidosis on protein catabolism.<sup>56</sup>

Hypocalcemia and hyperphosphatemia are common in AKI. However, no randomized study has evaluated the benefits of treating these disorders. Hyperphosphatemia caused by oral phosphorus-containing medications<sup>57</sup> and tumor lysis syndrome<sup>58</sup> has been proposed as an etiologic factor for AKI. Thus severe hyperphosphatemia should be avoided to prevent further damage. Calcium-based phosphate binders and other phosphate binders can be used in this setting along with a low-phosphate diet.

#### MINIMIZATION OF CONSEQUENCES DUE TO ACUTE KIDNEY INJURY

#### Secondary Organ Damage

There is a common belief that because AKI can be treated with RRT, patients will not die of AKI but rather of their underlying disease.<sup>59</sup> However, AKI has a profound influence on prognosis because it causes multiple systemic disturbances. Patients with AKI are prone to infection because of the effect of AKI on immunocompetence, and many do succumb to infections.<sup>60</sup> Moreover, AKI is implicated in insulin resistance, hepatic gluconeogenesis, protein catabolism, bleeding diathesis, respiratory failure, and inflammation.<sup>59,61</sup> These consequences reinforce adequate preventive and treatment measures for AKI.

#### Medication Dose Adjustments

Many drugs are metabolized and excreted by the kidneys. In AKI, some drug dosages need to be adjusted to prevent accumulation and toxicity.<sup>62</sup> Drug elimination correlates with the GFR. One key but often misunderstood concept is that it is inappropriate to use the Cockcroft-Gault (CG) equation<sup>63</sup> to estimate the GFR in the presence of AKI. For example, with total renal shutdown, the creatinine level will increase by 1 to 1.5 mg/dL per day. Therefore, a normal creatinine might increase from 1 to 2.5 mg/dL.<sup>64</sup> The calculated GFR with the CG equation would be 30 mL/minute. However, the "true" GFR in this condition is 0 mL/minute. Thus, when adjusting medications for a patient with progressive AKI, the predicted GFR should be minimized in order to reflect the real GFR. This concept also applies for the administration of gadolinium (see next section).

Other pharmacokinetic parameters are altered in renal failure. These include drug absorption, volume of distribution, protein binding, and hepatic biotransformation.<sup>63</sup> Thus, dosage may be altered by factors other than GFR, and adjustments must reflect this.

#### **Gadolinium-Based Contrast Agents**

Gadolinium-based contrast agents are commonly used for magnetic resonance imaging. These agents have been linked to nephrogenic systemic fibrosis (NSF). NSF is a systemic disorder with scleromyxedema-like cutaneous manifestations that occur only in patients with severe renal insufficiency.<sup>65</sup> In addition, gadolinium chelates may cause pseudohypocalcemia and may be nephrotoxic, especially in CKD.<sup>66</sup> At the present time, we do not know whether gadolinium nephrotoxicity is related to free gadolinium or gadolinium chelates. In May 2007, the U.S. Food and Drug Administration (FDA) cautioned that gadolinium be avoided in patients with acute or chronic renal insufficiency (defined as GFR < 30 mL/ minute per 1.73 m<sup>2</sup>) unless the diagnostic information to be obtained is essential. In addition, the FDA advised that gadolinium be avoided in patients with AKI due to hepatorenal syndrome or in the perioperative liver transplantation period irrespective of the GFR value. Updated information is available on the FDA website at http:// www.fda.gov/.

### Prevention of Progression to Chronic Kidney Disease

There is increasing interest in the effect of AKI on the development of end-stage renal disease (ESRD). The U.S. Renal Data System listed ATN as the cause of ESRD in 1.7% of patients from 1999 to 2003.<sup>67</sup> What percentage of AKI patients subsequently develop CKD and ESRD is currently unclear because of varied AKI definitions. Improving the prognosis of AKI patients might reduce the incidence of CKD and ERSD. No study has evaluated the use of drugs to reduce the incidence of progressive CKD after AKI, although three cohort trials showed that the use of CRRT reduced dialysis dependence when compared with intermittent hemodialysis.<sup>68–70</sup> However, in four RCTs and one recent meta-analysis, the use of CRRT did not reduce the rate of dialysis dependence at hospital discharge.<sup>71–75</sup>

#### CONCLUSION

Evidence-based management of AKI is compromised by a lack of clear definition, heterogeneity of patients and underlying conditions, and a lack of clear end points for trials. However, given that minor short-term changes in serum creatinine are linked to increased morbidity and mortality, any reversible detrimental factor contributing to AKI should be corrected promptly. Many different drugs have been tried to prevent or treat AKI, with mixed results. The use of fenoldopam and insulin might be valuable, although further data are needed before promoting their use on a large scale. The consequences of acute renal dysfunction on other organs, drug elimination, and progression of CKD should also be considered in the management of patients suffering from AKI.

#### **AUTHORS' RECOMMENDATIONS**

- Minor short-term changes in serum creatinine are related to increased morbidity and mortality. Therefore, preventive and treatment measures should be applied as soon as there is a significant increase in creatinine.
- The first goal of therapy is to correct any reversible detrimental factor contributing to AKI. These include volume depletion, hypotension, decreased cardiac output, obstruction, high intraabdominal pressure, and nephrotoxic agents.
- Neither loop diuretics nor dopamine should be used to prevent AKI, reduce mortality, or improve renal recovery during AKI.
- New studies are needed to assess the benefits of ANP, fenoldopam, and insulin in AKI.
- A high suspicion of infection, adjustments in drug dosing, and avoiding gadolinium use in severe AKI are essential parts of the management of AKI in order to avoid harmful complications.

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## 53

## What Is the Role of Renal Replacement Therapy in the Intensive Care Unit?

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This chapter aims to review the evidence surrounding decisions to commence renal replacement therapy (RRT) in the intensive care unit (ICU). It examines the conventional indications for emergency RRT and assesses the emerging evidence for both earlier commencement of RRT and the expanded role of RRT in the management of sepsis and multiorgan failure (MOF).

#### WHAT ARE THE CONVENTIONAL INDICATIONS FOR COMMENCING RENAL REPLACEMENT IN ACUTE KIDNEY INJURY?

There are wide variations in RRT prescribing practice, reflecting the lack of consensus guidelines internationally. However, some pathophysiologic states are generally considered absolute indications for this intervention (Table 53-1).

#### Intravascular Volume Overload and Pulmonary Edema Unresponsive to Diuretic Therapy

The role of negative or neutral fluid balance in acute kidney injury (AKI) with pulmonary edema but without acute lung injury (ALI) is unclear. Studies carried out in critically ill children with AKI after cardiac surgery suggested that early institution of continuous renal replacement therapy (CRRT) improved respiratory parameters with associated improvement in multiple clinical outcomes.<sup>1–3</sup> Randomized controlled trials (RCTs) in adults are lacking, although observational data indicate that a positive fluid balance in critically ill patients with AKI is independently associated with a higher 60-day mortality rate (hazard ratio [HR], 1.21; P < .001).<sup>4</sup>

There is no evidence to support the common practice of trial of diuresis in AKI-associated pulmonary edema. Indeed, the use of diuretic therapy may increase the probability of nonrecovery of renal function.<sup>5–8</sup> In addition, studies in animal models suggest that ultrafiltration is more effective than diuresis in reducing extravascular lung water in ALI.<sup>9</sup> In conclusion, RRT should be considered early in patients with AKI complicated by refractory pulmonary edema.

#### Metabolic Acidosis Refractory to Medical Management

Metabolic acidosis is a common complication of AKI, resulting from a combination of chloride-rich fluid resuscitation and the accumulation of lactate, phosphate, and unexcreted metabolic acids. RRT can be highly effective in correcting this acidosis.<sup>10,11</sup> CRRT as a modality may be superior to intermittent hemodiafiltration (IHD) in terms of duration of treatment effect.<sup>12</sup> Importantly, RRT avoids systemic administration of sodium bicarbonate therapy with its associated risk for exacerbating fluid overload and hypernatremia. The threshold pH or base deficit at which to commence RRT has not been established. Because a pH lower than 7.1 is associated with negative inotropic and metabolic effects, in general, one would consider intervening before this level is reached.

## Hyperkalemia Refractory to Medical Management

No specific treatment threshold has been established for when to treat hyperkalemia with RRT. In general, myocardial toxicity is considered unlikely when the serum potassium concentration is less than 6.5 mmol/L. Potassium excretion by diuresis is generally ineffective in renal failure. For this reason, the threshold for commencing RRT in AKI might be lowered further, particularly if there is minimal response to initial emergency treatment (insulin-glucose, inhaled  $\beta$ -agonist, exchange resins).<sup>13</sup>

#### **The Uremic State**

Manifestations of the "uremic state" include encephalopathy, pericarditis, and bleeding diathesis. Both mental status changes and bleeding propensity can be multifactorial in the septic, critically ill patient and can be difficult to attribute solely to renal failure. Uremic pericarditis requires urgent initiation of renal support once it is detected because it carries a high risk for intrapericardial hemorrhage and tamponade.

### Table 53-1 Conventional Indications for RenalReplacement Therapy

- 1.1. Intravascular volume overload unresponsive to diuretic therapy
- 1.2. Metabolic acidosis (pH < 7.1) refractory to medical management
- 1.3. Hyperkalemia (K > 6.5 mEq/L) refractory to medical management
- 1.4. Uremic state (encephalopathy, pericarditis, bleeding diathesis)
- 1.5. Intoxication with a dialyzable drug or toxin
- 1.6. Hyperthermia refractory to conventional cooling techniques
- 1.7. Severe electrolyte derangements in the setting of acute kidney injury
- 1.8. Progressive azotemia or oliguria unresponsive to fluid administration

#### Intoxication with a Dialyzable Drug or Toxin

Toxins of low molecular weight residing in the extracellular space, which have little or no protein-binding properties, can be effectively removed by RRT. In general, IHD is preferable to CRRT for this purpose as it clears solute more rapidly. A review of the U.S. Poison Center's "Toxic Exposure Surveillance System" records, from 1985 to 2005, found that 19,351 cases received extracorporeal toxin removal over this time period.<sup>14</sup> IHD was most commonly used for the treatment of lithium, ethylene glycol, salicylate, valproate, acetaminophen, methanol, ethanol, and theophylline poisoning, although some cases of IHD used for removal of methotrexate and phenobarbital were reported. Hemoperfusion techniques were most commonly used for treatment of theophylline, carbamazepine, and paraquat poisoning.

#### Severe Electrolyte Derangements

AKI can be associated with an array of electrolyte disturbances, including hyponatremia, hypernatremia, hyperphosphatemia, hypocalcemia, hypercalcemia, and hypermagnesemia. CRRT may be helpful in the management of many of these disorders.<sup>12</sup>

#### Progressive Azotemia or Oliguria Unresponsive to Fluid Administration

In the modern era, RRT is most often initiated before sufficient time has passed for the previously discussed complications to develop. Instead, the decision to commence treatment is made when urea and creatinine levels climb, or urine output falls, despite conservative measures. The threshold values of these parameters that should trigger a decision to commence RRT have not been established and are discussed later.

#### SHOULD RENAL REPLACEMENT THERAPY BE INITIATED IN ACUTE KIDNEY INJURY BEFORE COMPLICATIONS HAVE DEVELOPED?

Although undisputed indications generally point to RRT as being a "rescue remedy," employed when other measures have failed, a number of studies have examined the value of earlier commencement of therapy in improving patient outcomes (Table 53-2).

From the outset, one should note that there is no clear consensus on what is meant by "earlier" initiation of renal replacement therapy; initiation at lower urea and creatinine levels,<sup>15,16</sup> initiation closer to the time of renal injury,<sup>17</sup> initiation sooner after urine output is noted to fall,<sup>18,19</sup> and initiation sooner after admission to the ICU have all been studied (see Table 53-2). This makes study comparison and meta-analysis difficult. In addition, the effect of earlier initiation of RRT is likely to be influenced by the etiology of the AKI; thus, the heterogeneity of populations studied renders meaningful meta-analysis even more difficult.

A small and retrospective study in posttraumatic AKI using a blood urea nitrogen (BUN) threshold for early initiation of RRT of 60 mg/dL demonstrated a significantly lower mortality rate for the early compared with the delayed RRT cohort (relative risk [RR] for death, 0.77; 95% confidence interval [CI], 0.58 to 1.0; P = .04).<sup>15</sup> These results suggest that the BUN threshold for considering the initiation of RRT should be lowered to at least 60 mg/dL.

Further support for a strategy of earlier initiation of RRT was provided by retrospective studies in the postoperative coronary artery bypass graft (CABG) patient population.<sup>18,19</sup> These studies used reduced urine output (<100 mL within 8 hours consecutively after surgery, despite furosemide administration) as their criterion for early initiation of CRRT. The attainment of specified BUN, serum creatinine, or potassium thresholds was the trigger for late commencement of therapy. The first of these studies examined the outcomes of 64 patients with a high baseline prevalence of class 3 or 4 heart failure and chronic kidney disease (CKD). It reported a survival rate of 78% in the early initiation group, compared with 57% in the late initiation group (P < .05).<sup>18</sup> The early initiation group was also found to have had a significantly shorter ICU stay (12.5 versus 8.5 days; P < .05), shorter hospital stay (20.9 versus 15.4 days; P < .05), and lower rate of multiorgan failure (MOF) (19% versus 29%; P = .01). The second study, a retrospective analysis of post-CABG AKI using a historical control group, again showed significantly improved survival (77% versus 45%; P = .016), shorter length of ICU stay (12 versus 8 days; P = .0001), and shorter length of hospital stay (30 versus 15 days) in the early treatment group.<sup>1</sup>

Clinical benefit of early initiation of RRT was also reported in a secondary analysis of a prospectively collected AKI database.<sup>16</sup> Despite there being, on average, more failed organ systems in the early intervention group, the relative risk for death associated with delayed initiation was 1.85 (95% CI, 1.16 to 2.96) after covariate adjustment for age, hepatic failure, sepsis, thrombocytopenia, serum creatinine, study site, and initial dialysis modality.

#### Table 53-2 Studies Evaluating the Timing of Initiation of RRT

				GROUP DEFINITION			<b>IVAL</b>
Study	Mode	Design	No. of Patients	Early	Late	Early	Late
Teschan, 1960 <sup>47</sup>	IHD	Case series	15	<100 mg/dL	_	33%	_
Parsons, 1961 <sup>48</sup>	IHD	Single-arm (historical control)	33	BUN reaching 120-150 mg/dL	Clinical deterioration or BUN 200 mg/dL	75%	12%
Fischer, 1966 <sup>49</sup>	IHD	Retrospective cohort study	162	Clinical deterioration or BUN increase to about 150 mg/dL	Hyperkalemia, BUN about 200 mg/dL	43%	26%
Kleinknecht, 1972 <sup>50</sup>	IHD	Retrospective cohort study	500	To maintain BUN < 93 mg/dL (blood urea < 200 mg/dL)	BUN > 163 mg/dL (blood urea > 350 mg/dL) or severe electrolyte disturbance	73%	58%
Conger, 1975 <sup>51</sup>	IHD	RCT	18	BUN < 70 mg/dL or sCr < 5 mg/dL	BUN about 150 mg/dL, sCr 10 mg/dL or clinical indication	64%	20%
Gillum, 1986 <sup>52</sup>	IHD	RCT	34	Maintenance of BUN < 60 mg/dL	Maintenance of BUN about 100 mg/dL	41%	53%
Gettings et al, 1999 <sup>15</sup>	CRRT	Retrospective cohort study	100	BUN < 60 mg/dL (mean 42.6 mg/dL)	$\begin{array}{l} \text{BUN} \geq 60 \ \text{mg/dL} \\ \text{(mean, 94.5 mg/dL)} \end{array}$	39%	20%
Elahi et al, 2004 <sup>18</sup>	CVVH	Retrospective cohort study	64	UO < 100 mL over 8 hr after surgery, despite furosemide infusion	BUN > 84 mg/dL, sCr > 2.8 mg/dL, or sK > 6 mEq/L	78%	57%
Demirkilic et al, <sup>19</sup>	CVVHDF	Retrospective cohort study	61	UO < 100 mL over 8 hr after surgery, despite furosemide bolus	$sCr > 5 mg/dL \text{ or} \\ sK > 5.5 mEq/L$	77%	45%
Liu et al, 2006 <sup>16</sup>	IHD, CRRT	Prospective cohort study	243	$BUN < 76 \ mg/dL$	BUN > 76 mg/dL	65%	59%
Bouman et al, 2002 <sup>17</sup>	CVVH	RCT	106	Within 12 hr of developing UO < 20 mL/hr and Cr clearance < 20 mL/min	Urea > 40 mmol/L (BUN >112 mg/dL), sK > 6.5 mEq/L (>6.5 mmol/L) or severe pulmonary edema	69%	75%

BUN, blood urea nitrogen; Cr, creatinine; CRRT, continuous renal replacement therapy; CVVH; continuous venovenous hemofiltration; CVVHDF; continuous venovenous hemodiafiltration; IHD, intermittent hemodiafiltration; RCT, randomized controlled trial; sCr, serum creatinine; sK, serum potassium; UO, urine output.

Although these observational studies generally support earlier commencement of RRT, available higherlevel evidence is less convincing. In a prospective RCT of 106 patients examining the effects of both timing of initiation of dialysis and dose of dialysis on 28-day survival rates in AKI, there was no survival advantage to early initiation of RRT (survival, 69% in the early low-volume group versus 75% in the late low-volume group, nonsignificant).<sup>17</sup> In addition, and of particular interest, the authors did not find a survival advantage to higher-dose therapy compared with lower-dose therapy (survival, 74% in the high-volume group versus 69% in the low-volume group, nonsignificant). In this trial, patients were randomized to three different treatment groups: an early high-volume hemofiltration group, an early low-volume hemofiltration group, and a late low-volume hemofiltration group. "Early treatment" was defined by treatment initiation within 12 hours of meeting the study's AKI definition, whereas "late treatment" was initiated only when the patient's BUN was higher than 112 mg/dL or hyperkalemia (>6.5 mmol/ L) or pulmonary edema developed. Mean BUN in the early treatment group was 48 mg/dL, compared with a mean BUN of 105 mg/dL in the late treatment group. Unfortunately, however, this study was underpowered to detect a clinically significant treatment effect, and outcomes in this relatively small patient population may have been skewed by the fact that six patients in the late group did not require dialysis because they recovered renal function or died.

A recent meta-analysis evaluated the evidence for and against early initiation of RRT in AKI.<sup>20</sup> Two main questions were asked: (1) Does early RRT improve survival? (2) Is early initiation of RRT associated with improved renal recovery? Marked heterogeneity was noted among study groups in terms of population settings, baseline disease severity, cut-off value definitions of early compared with late initiation, dialysis technique, and duration of study follow-up. The overall study method quality scores were low, and most trials (78%) were observational in nature. Primary analysis of the five included randomized trials concluded that early RRT was associated with a 36% mortality risk reduction (approaching significance, P = .08). A secondary analysis of nonrandomized trials also supported this hypothesis (26% mortality risk reduction; P < .001). The meta-analysis of renal recovery included two RCTs and five comparative cohort studies and found a nonsignificant higher likelihood of recovery among the early initiation groups.

These suggestive findings have yet to be confirmed by a large multicenter RCT. Furthermore, the development of novel biomarkers that might estimate severity of renal injury more accurately than current methods (creatinine, urea, urine output) and better predict likelihood of spontaneous renal recovery would assist greatly in informing the decision to commence early RRT.

Until such time as more definitive evidence is available to confirm the role of earlier initiation of RRT in improving outcome, clinicians must carry out a risk-to-benefit analysis for each patient on a case-by-case basis. Decisions can be aided by management guidelines, such as the U.K. Renal Association Clinical Practice Guidelines relating to timing of initiation of renal replacement treatment in AKI (Table 53-3).

Table 53-3 Renal Association Clinical PracticeGuidelines on Acute Kidney Injury: Timing ofInitiation of Renal Replacement Treatment

- **Guideline 9.1.** The decision to start renal replacement therapy (RRT) in patients with acute kidney injury (AKI) should remain a clinical decision based on fluid, electrolyte, and metabolic status of each individual patient.
- **Guideline 9.2.** RRT should be initiated once AKI is established and unavoidable but before overt complications have developed.
- **Guideline 9.3.** The threshold for initiating RRT should be lowered when AKI occurs as part of multiorgan failure.
- **Guideline 9.4.** The initiation of RRT may be deferred if the underlying clinical condition is improving and there are early signs of renal recovery.

**Guideline 9.5.** An improvement in the clinical condition and urine output would justify temporary discontinuation of ongoing renal support to determine whether AKI is recovering.

#### WHAT IS THE ROLE OF RENAL REPLACEMENT THERAPY IN THE MANAGEMENT OF PATIENTS WITH THE SYSTEMIC INFLAMMATORY RESPONSE SYNDROME IN THE SETTING OF SEPSIS OR MULTIORGAN FAILURE?

The most common contributing factor to AKI in the modern ICU setting is septic shock.<sup>21</sup> Septic AKI carries a significantly increased mortality when compared with other forms of AKI<sup>21,22</sup> and is often associated with concurrent failure of multiple other organs.<sup>21,22</sup> For these reasons, a significant amount of research has been carried out to specifically investigate the role of RRT in managing the patient with sepsis or MOF. A number of key questions have been raised:

- Can extracorporeal "blood purification" alter the systemic inflammatory response?
- Should higher doses of ultrafiltration than are conventionally used be prescribed in cases of septic AKI?
- Is CRRT superior to IHD when AKI occurs in the setting of sepsis or MOF?
- Can ultrafiltration serve as a means of support for organs other than the kidney?

#### CAN EXTRACORPOREAL BLOOD PURIFICATION ALTER THE SYSTEMIC INFLAMMATORY RESPONSE THAT OCCURS IN SEPSIS AND MULTIORGAN FAILURE?

It is widely believed that hemofiltration removes, or alters the production of, inflammatory mediators and thereby restores immune homeostasis.<sup>23</sup> Adsorption of inflammatory mediators onto the surface of hemofilters, in particular, polyacrylonitrile (PAN) filters,<sup>24</sup> plays a complementary role to simple convection in this process. Furthermore, in light of the fact that the molecular weight of many inflammatory mediators exceeds the cut-off value of standard hemofilters, "high-flux" membranes have been developed to further enhance clearance, and their use has been associated with positive hemodynamic effects.<sup>25</sup>

#### SHOULD HIGHER DOSES OF ULTRAFILTRATION THAN ARE CONVENTIONALLY USED BE PRESCRIBED IN CASES OF SEPTIC ACUTE KIDNEY INJURY?

The question of whether higher-intensity RRT is associated with improved AKI outcomes, when compared with standard-intensity RRT, has been a matter of debate for many years. The recent landmark Veterans Affairs/ National Institutes of Health (VA/NIH) Acute Renal Failure Trial Network study, the largest and highest quality RCT to date investigating intensity of renal support in AKI, has helped clarify the situation.<sup>26</sup> This study group

From Davenport A, Kanagasundaram S, Lewington A, Stevens P. The Renal Association Clinical Practice Guidelines Module 5 – Acute Kidney Injury. http://www.renal.org/guidelines/module5.html

defined high-intensity RRT as (1) IHD or slow, lowefficiency dialysis (SLED) 6 times per week in hemodynamically stable patients; or (2) continuous venovenous hemodiafiltration (CVVHDF) at a rate of 35 mL/kg per hour in hemodynamically unstable patients. Standard intensity treatment was defined as three intermittent treatment sessions per week or CVVHDF at 20 mL/kg per hour, respectively. This study found that higher-intensity treatment was not associated with reduced mortality, improved renal recovery, or reduced rate of nonrenal organ failure when compared with less intensive therapy.

Specific to AKI in the setting of sepsis and MOF, however, an argument may still be made that higher-dose ultrafiltration can clear inflammatory mediators better than standard-dose ultrafiltration.<sup>27</sup> Although this may not necessarily hasten renal recovery, or even improve survival, it may have a positive effect on the patient's overall clinical condition and vasopressor requirement.<sup>26–28</sup>

For this reason, despite the findings of the VA/NIH trial, a strategy of somewhat higher-volume ultrafiltration than is conventionally prescribed may be reasonable when specifically treating sepsis-associated AKI. The U.K. Renal Association Clinical Guidelines for AKI<sup>29</sup>, updated in light of the results of the VA/NIH trial, state the following:

- Patients with AKI and MOF treated by CRRT should receive treatment doses equivalent to ultrafiltration rates ≥ 20 mL/kg per hour.
- Patients with AKI and MOF treated by IHD should receive either alternate-day hemodialysis with at least the minimal dose considered appropriate for endstage renal disease (urea reduction ration >65%, or equivalent Kt/V > 1.2) or daily hemodialysis.

There has been no convincing evidence to date to support the use of RRT in the management of sepsis in the absence of coexisting AKI. Therefore its use, at present, cannot be advocated.

#### IS CONTINUOUS RENAL REPLACEMENT THERAPY SUPERIOR TO INTERMITTENT HEMODIALYSIS WHEN ACUTE KIDNEY INJURY OCCURS IN THE SETTING OF SEPSIS OR MULTIORGAN FAILURE?

Advocates of CRRT propose that its use is associated with less hemodynamic instability than is seen with IHD, an important consideration in the septic patient with MOF. A second potential advantage to this method is that it may increase rates of dialysis independence at hospital discharge when compared with IHD,<sup>30,31</sup> although all reported studies supporting this association have been observational in nature. On the contrary, the body of RCTs exploring this issue have failed to find any significant difference in terms of hemodynamic effects or survival between the two methods.<sup>32–34</sup> Meta-analyses have found both IHD and CRRT to have comparable mortality outcomes.<sup>35,36</sup> Indeed, it is likely that even critically ill patients can be safely treated with IHD.<sup>35</sup>

On balance, it appears that CRRT and IHD are equally effective in the management of AKI in terms of patient survival and renal recovery, a point reinforced by the fact that the theoretical concern for increased hemodynamic instability during IHD has not been confirmed in clinical trials. Nevertheless, in some specific clinical scenarios, CRRT may still be preferable to IHD:

- AKI in the setting of cerebral edema: the slower and more gradual reduction in plasma osmolality seen with CRRT can prevent dialysis dysequilibrium and has been associated with improved hemodynamic stability and better preserved cerebral perfusion pressure in patients with AKI and cerebral edema.<sup>37</sup>
- AKI in the setting of hypercatabolism: CRRT facilitates delivery of full-dose nutrition. CRRT may also be preferable for patients requiring high-volume intravenous fluids (blood products, antibiotics). These are nearly universal scenarios in the ICU, where CRRT ensures tight hour-by-hour control of volume.
- AKI in the setting of congestive heart failure: although CRRT has been shown to improve cardiac function (see earlier), it has not been proved to be superior to IHD in this context. CRRT does, however, have the theoretical advantage of being associated with fewer hemodynamic alterations, which may be preferable in the individual patient with reduced cardiac index.

#### CAN ULTRAFILTRATION SERVE AS A MEANS OF SUPPORT FOR ORGANS OTHER THAN THE KIDNEY?

In the intensive care setting, AKI occurs in 20% to 40% of patients with ARDS,<sup>38</sup> 33% of patients with cardiogenic shock,<sup>39</sup> and 55% of patients with fulminant hepatic failure.<sup>40</sup> Experience using CRRT in the management of these patients has generated interest in whether this intervention can improve outcomes even in patients without AKI, that is, whether CRRT has a supportive role in the management of heart, lung, or liver failure.

#### **Cardiac Support**

In an RCT of patients with decompensated heart failure, continuous ultrafiltration was reported to produce greater weight and fluid loss than intravenous diuretics, in addition to reducing patient rehospitalization rates.<sup>41</sup> Another older study, this time observational, again found that, in patients with diuretic-resistant congestive cardiac failure, hemofiltration can restore dry body weight, improve urinary output, decrease neurohumoral activation, and prolong symptom-free and edema-free time.<sup>42</sup> This benefit appears greater than that which would be expected due to fluid removal alone and may be related to the removal of myocardial depressant factors from the circulation.<sup>43</sup>

#### Lung Support

As previously mentioned, ultrafiltration with continuous arteriovenous hemofiltration for oleic acid–induced pulmonary edema in dogs was more effective than diuresis in reducing extravascular lung water.<sup>2</sup> This was despite significantly less overall fluid loss, suggesting an additional role of RRT over and above simple fluid removal. In light of the fact that ARDS is believed to be a manifestation of the systemic inflammatory response, as suggested by the increased levels of tumor necrosis factor- $\alpha$ , IL-1 $\beta$ , and IL-6 found in the bronchoalveolar lavage fluid of affected patients, this advantage of CRRT over diuretics may be related to the removal of humoral mediators of lung injury from the circulation. There are no human studies showing clear benefit when CRRT is used in the management of acute respiratory distress syndrome. Presently, CRRT is only indicated for patients with ARDS who have coexisting AKI.

#### Liver Support

Application of blood purification strategies to humans with liver failure has mainly occurred in trial settings and is not yet common practice. Experimental approaches have included hemodiabsorption<sup>44</sup> and the molecular adsorbent recirculating system (MARS).<sup>45,46</sup> Small studies using these techniques in the management of hepatic failure showed benefit in patients with acute-on-chronic hepatic failure,<sup>44</sup> the hepatorenal syndrome,<sup>45</sup> and even fulminant hepatic failure.<sup>46</sup> In the absence of more robust evidence to confirm these findings, however, no recommendation can be given to support their routine use in clinical practice.

#### AUTHORS' RECOMMENDATIONS

There are no universally accepted criteria for the commencement of renal replacement therapies in patients with AKI.

- Widely used indications include a BUN higher than 60 mg/dL, uremia defined by pericarditis, platelet dysfunction and neuropathy, pulmonary edema, hyperkalemia, metabolic acidosis, hyperthermia, and intoxication.
- There are no current data to support the use of CRRT over IHD in the critical care setting for control of uremia.
- The major advantage of CRRT is the ability to control circulating volume on a minute-by-minute basis.
- CRRT may be a better choice than IHD in the setting of brain injury or severe congestive heart failure.
- Current literature supports ultrafiltration rates of 20 to 25 mL/kg per minute.
- Although widely reported, there are few data to support the use of CRRT in the management of sepsis or for external organ support, for example, in liver failure, heart failure, or ALI.

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## Do Renal Replacement Therapy Strategies in the Intensive Care Unit Affect Clinical Outcomes?

Shigehiko Uchino, Rinaldo Bellomo

Acute kidney injury (AKI) is a common complication of critical illness. In severe cases, renal replacement therapy (RRT) is required. The incidence of RRT for severe AKI in the intensive care unit (ICU) is about 4%, and the hospital mortality rate among patients who require RRT is more than 60%.<sup>1</sup> RRT can be life-saving. Indeed, its powerful impact and complexity; the variability in dose, intensity, timing of application, and technology; and its known complications make it likely that RRT is a significant modulator of patient outcome.

There are several forms of RRT. These include peritoneal dialysis (PD), intermittent RRT (IRRT) (including conventional intermittent hemodialysis and slow extended daily dialysis), and continuous RRT (CRRT). There are also many variations in the way each form of RRT is administered, including major differences in intensity and timing. These variations also might affect patient and kidney outcome. In this chapter, we discuss some of these variations and their possible impact on outcome, with a strong focus on dose and the comparison between IRRT and CRRT.

#### INTENSITY OF RENAL REPLACEMENT THERAPY

The term *dose* used here is defined as the amount of RRT delivered to control uremic toxins. This dose is typically measured using the single pool urea kinetic concept of Kt/V. This concept combines the K (clearance or intensity of blood purification per unit of time) multiplied by the time (t) during which this intensity is applied, all divided by the volume of distribution of the target solute (V). A greater dose of RRT might improve patient and kidney outcome. However, greater dose requires greater cost. It might also cause some side effects (e.g., bleeding related to more anticoagulation use, electrolyte abnormalities, keeping the patient immobile for longer). Therefore, the issue of RRT dose has been one of the most important controversies in this field, and several randomized controlled trials (RCTs) comparing different doses of RRT have been conducted to address this issue.

Schiffl and colleagues compared conventional alternate-day intermittent hemodialysis (IHD) with daily IHD in 160 patients with AKI.<sup>2</sup> Daily IHD resulted in better control of uremia, fewer hypotensive episodes during hemodialysis, and more rapid resolution of AKI than did alternate-day IHD. The 14-day mortality rate was 28% for daily IHD and 46% for alternate-day IHD (P = .01).

Phu and associates compared PD and continuous venovenous hemofiltration (CVVH) in patients with severe malaria (48 patients) and sepsis (22 patients): 36 were assigned to PD and 34 to CVVH.<sup>3</sup> Patients with CVVH received a higher dose of RRT, had better control in acidosis and serum creatinine level, and required RRT for a shorter period compared with PD. The mortality rate was 15% for CVVH and 47% for PD (P = .005).

Different doses of CRRT have also been compared in four controlled studies. Storck and associates compared spontaneous continuous arteriovenous hemofiltration (CAVH) and pump-driven CVVH for postsurgical patients with severe AKI.<sup>4</sup> Because these investigators had only one pump for CVVH, they used CVVH when there was only one patient requiring RRT, and any other patients were treated with CAVH. The daily ultrafiltrate volume was significantly higher with CVVH than CAVH (15.7 versus 7.0 L), indicating a higher dose of RRT. The survival rate was also higher in CVVH compared with CAVH (29.4% versus 12.5%; P = .04).

Ronco and associates compared three different doses of CRRT using CVVH: 20 mL/kg per hour (group 1, n = 146), 35 mL/kg per hour (group 2, n = 139), and 45 mL/kg per hour (group 3, n = 140).<sup>5</sup> The survival rate in group 1 was significantly lower compared with the other two groups (41%, 57%, and 58%). The authors recommended that ultra-filtration should be prescribed according to patient body weight and that it should reach at least 35 mL/kg hour. In daily Kt/V terms, such a dose would be about 1.6.

Bouman and associates compared early high-volume CVVH (EHV group, 48.2 mL/kg hour, n = 35), early low-volume CVVH (ELV group, 20.1 mL/kg hour, n = 35), and late low-volume CVVH (LLV group, 19 mL/kg per hour, n = 36) in mechanically ventilated patients with severe AKI.<sup>6</sup> CVVH was started 7 hours after study inclusion in the EHV and ELV groups and 42 hours after inclusion in the LLV group. The 28-day survival rate was similar in the three groups (EHV, 25.7%; ELV, 31.2%; LLV, 25.0%; P = .80). The high survival rate in this study compared with other studies is probably due to the fact that more

than half of patients had undergone cardiac surgery, which might have affected the findings.

Saudan and coworkers compared CVVH (1 to 2.5 L/hour replacement fluid rate according to patient's body weight; n = 102) and continuous venovenous hemodiafiltration (CVVHDF, 1 to 2.5 L/hour replacement fluid rate and the addition of 1 to 1.5 L/hour dialysate according to body weight; n = 104).<sup>7</sup> The mean prescribed dose was 25 mL/kg per hour in the CVVH group and 42 mL/kg per hour in the CVVHDF group. The 28-day survival rate was significantly higher in the CVVHDF group compared with the CVVH group (59% versus 39%; P = .03).

Therefore, although studies also compared different RRT modalities, several of the RCTs published in the past 20 years have shown that increasing intensity can improve outcome of patients with severe AKI requiring RRT. However, all these studies were single-center studies, making the associated level of evidence lower and decreasing external validity. Large multicenter RCTs comparing different doses, especially for CRRT, are now required to confirm these findings.

#### INTERMITTENT VERSUS CONTINUOUS RENAL REPLACEMENT THERAPY

Another important controversy concerning RRT relates to modality. In particular, there is uncertainty as to whether the choice of CRRT or IRRT can affect outcome. CRRT has been reported to offer potential physiologic advantages over IRRT. These include greater hemodynamic stability,<sup>8</sup> better solute clearance,<sup>9,10</sup> easier fluid management,<sup>11</sup> and stable intracranial pressure.<sup>12</sup> In a mathematic model, Clark and associates calculated that a patient with a body weight greater than 80 kg could not achieve blood urea nitrogen control to 60 mg/dL even with daily conventional IRRT, whereas this could be easily achieved with 1.5 L/hour of CRRT dose.<sup>13</sup> Whether these potential physiologic advantages would result in a survival benefit remains unknown.

To date, five published RCTs have compared IRRT and CRRT.<sup>14–18</sup> Among them, two studies were multicenter in design.<sup>14,15</sup> In the first of these, Mehta and colleagues randomized 166 patients in four centers to receive CVVHDF or conventional IHD.<sup>14</sup> Despite randomization, there were significant differences in gender, hepatic failure, Acute Physiology and Chronic Health Evaluation (APACHE) II and III scores, and the number of failed organ systems. Each biased the results in favor of the IHD group. Although blood urea nitrogen and serum creatinine levels were lower in the CVVHDF group, the crude hospital

mortality was higher in these patients (65.5% versus 47.6%; P < .02). However, using multivariate logistic regression analysis, the odds ratio (OR) for hospital mortality with CVVHDF was not increased.

In the second multicenter study, Vinsonneau and associates randomized 359 patients in 21 centers to receive CVVHDF or IHD.<sup>15</sup> The mean urea level was similar between the two groups (15.7 and 14.8 mmol/L). There was also no difference in 60-day mortality (primary end point) between the two groups (32.6% versus 31.5%; P = .98). However, there was an unexpected and unexplained significant improvement in survival rates in the IHD group over time that was not observed in the CVVHDF group. In addition, the dose of IHD was relatively high and that of CVVHDF relatively low. The remaining three single-center studies also failed to show any outcome benefits of CRRT.<sup>16–18</sup>

Two meta-analyses have been conducted on this issue<sup>19,20</sup> (Table 54-1). Kellum and associates included 13 studies, 3 of which were RCTs.<sup>19</sup> They found that overall mortality was not different between the two modalities. However, they also found that study quality was poor and that only 6 studies compared groups of equal severity of illness at baseline. Adjusting for study quality and severity of illness, mortality was significantly lower in patients treated with CRRT (risk ratio, 0.72). On the other hand, Tonelli and colleagues included RCTs only (6 studies) for their meta-analysis and found no difference in mortality between the two modalities.<sup>20</sup>

Therefore, all RCTs published so far have shown no benefit of CRRT over IRRT in terms of survival. However, these studies are small or contain significant flaws. Nonetheless, even if there was outcome difference between the two modalities, such difference seems to be relatively small (<20% relative risk reduction). Accordingly, a large (>1000 patients) multicenter study would be required to have enough power to detect such difference.

#### RENAL RECOVERY

Although CRRT has not shown survival benefits over IRRT, this preliminary finding does not necessarily imply that IRRT and CRRT deliver equal outcomes. Renal recovery is another important patient-centered outcome in AKI and might be affected differently by IRRT and CRRT. In theory, owing to rapid changes in fluid status and plasma osmolality, IRRT might induce a decrease in venous return, blood pressure, and cardiac index. Therefore, there is a possibility that IRRT might cause subclinical renal ischemia and delay renal recovery after AKI.

 Table 54-1 Summary of Meta-Analyses on Comparison of Intermittent and Continuous Renal

 Replacement Therapy

Study	No. of Trials	No. of Subjects (IRRT/CRRT)	Mortality (Risk Ratio for CRRT)	Dialysis Dependence (Risk Ratio for CRRT)
Kellum et al, 2002 <sup>19</sup>	3 RCTs + 10 non-RCTs	1400	0.93 (0.79-1.09)	_
Tonelli et al, 2002 <sup>20</sup>	6 RCTs	624 (307/617)	1.04 (0.93-1.18)	0.84 (0.44-1.61)

CRRT, continuous renal replacement therapy; IRRT, intermittent renal replacement therapy; RCT, randomized controlled trial.

Among RCTs comparing CRRT and IRRT, four studies have reported the incidence of renal recovery.<sup>14,15,17,18</sup> Two are the multicenter studies mentioned previously. In the study by Mehta and associates,<sup>14</sup> 7% of surviving patients in the IHD group and 14% of those in the CVVHDF group remained on dialysis at hospital discharge (not significant). However, patients with hemodynamic instability (mean arterial pressure < 70 mm Hg) were excluded from the study. This excludes the patients in whom the advantages of CRRT should be most evident. Furthermore, CVVHDF was associated with a significantly higher rate of complete renal recovery in surviving patients who received an adequate trial of therapy with no crossover (92.3% versus 59.4%; *P* < .01).

In the study by Vinsonneau and coworkers,<sup>15</sup> only one patient among all included patients was dialysis dependent at hospital discharge. Unfortunately, this study excluded patients with chronic renal impairment. This is the group at highest risk for dialysis dependence after RRT and perhaps the most likely to benefit from CRRT.

One of the two meta-analyses of IRRT versus CRRT analyzed dialysis dependence among survivors<sup>20</sup> (see Table 54-1). The authors found a lower but not significantly different risk ratio for CRRT at 0.84. Excluding the study by Mehta<sup>14</sup> because of the significant baseline differences, the risk ratio for nonrecovery with CRRT decreased to 0.60 (P = .19).

Recently, two large epidemiologic studies reporting renal recovery comparisons of CRRT and IRRT have been published.<sup>21,22</sup> Uchino and associates compared CRRT and IRRT using the BEST kidney database.<sup>21</sup> The BEST kidney study is a multinational, prospective epidemiologic study of AKI in the ICU. The database includes more than 1700 patients at 54 centers in 23 countries.<sup>1</sup> We examined data from 1218 patients treated with CRRT (n = 1006) or IRRT (n = 212) from this large international cohort. Patients treated first with CRRT required vasopressor drugs and mechanical ventilation more frequently (P < .0001), and unadjusted hospital survival was lower (35.8% versus 51.9%; P < .0001) compared with those receiving IRRT. However, multivariable logistic regression analysis showed that choice of CRRT was not an independent predictor of hospital survival. Unadjusted dialysis independence at hospital discharge was higher after CRRT (85.5% versus 66.2%; P < .0001) (Fig. 54-1), and the choice of CRRT was an independent predictor of a survivor being dialysis free at hospital discharge (OR, 3.333; 95% confidence interval [CI], 1.845 to 6.024; P < .0001). Further adjustment using a propensity score did not significantly change these results.

Bell and associates retrospectively collected data from 2202 patients treated with RRT for AKI from 32 ICUs in Sweden.<sup>22</sup> CRRT was used for 1911 patients and IHD for 291. There were no differences between CRRT and IHD regarding baseline characteristics, such as age, sex, and comorbidities. The 90-day mortality rates were not significantly different (45.7% versus 50.6%) between the two groups. Among 944 survivors treated with CRRT, 8.3% never recovered their renal function and became dialysis dependent. On the other hand, the proportion was significantly higher among IHD patients, and 26 patients out of 158 survivors (16.5%) became dialysis dependent. Multivariate analysis showed that the adjusted OR for dialysis



Figure 54-1. Recovery rate from dialysis dependence.

dependence in IHD patients was 2.60, compared with CRRT. These ORs are remarkably similar to those found in the BEST kidney study.

Therefore, there is some (nonrandomized) evidence that CRRT and IRRT affect renal recovery differently, with CRRT being associated with a greater chance of recovery. Multicenter RCTs will be needed to confirm such observational findings.

#### MORE RECENT EVIDENCE

Three important randomized controlled trials dealing with the issue of dose of RRT have been recently reported in the literature. In another single-center study at the University of Alabama, Tolwani and coworkers compared standarddose (20 mL/kg per hour) and high-dose (35 mL/kg per hour) CVVHDF in 200 ICU patients with acute kidney injury.<sup>23</sup> Contrary to previous findings, they did not detect a statistically significant difference in survival or renal recovery with higher dose treatment. The Veterans Affaires/National Institutes of Health (VA/NIH) Acute Renal Failure Trial Network reported the findings of the large multicenter randomized controlled trial of RRT dose.<sup>24</sup> These investigators randomized patients to two different doses (intensive versus less intensive) of RRT using both IHD and CVVHF as modalities depending on the patient's hemodynamic state. They studied 1124 patients in 29 hospitals and found that increasing the intensity of dialysis dose did not affect all-cause 60-day mortality (53.6% for intensive RRT versus 51.5% for less intensive RRT). No other significant differences were found in clinically relevant end points. Another large randomized controlled trial (The Randomized Evaluation of Normal versus Augmented Level (RENAL) Replacement Therapy Study) was also reported recently.<sup>25</sup> They randomly assigned 1508 patients to CVVHDF with an effluent flow of either 40 mL/kg per hour (higher intensity) or 25 mL/kg per hour (lower intensity). At 90 days after randomization, 322 deaths had occurred in the higher-intensity group and 332 deaths in the lower-intensity group, for a mortality of 44.7% in each group. Hypophosphatemia was more common in the higher-intensity group than in the lower-intensity group (65% vs. 54%). These findings have provided further strong evidence against the initially optimistic reports of a beneficial effect of increasing RRT dose on patient outcome.

#### CONCLUSION

The available evidence does not suggest that increasing the intensity of RRT improves survival of patients with AKI once a dose of 20 to 25 mL/kg per hour is delivered with CRRT, or a Kt/V of between 1.2 and 1.4 is prescribed for IHD. Although CRRT might often deliver a higher dose than conventional IRRT, there is no clear evidence to suggest that CRRT carries a survival benefit over IRRT. However, evidence derived mainly from observational studies suggests that, in survivors, CRRT might allow renal recovery more frequently than IRRT.

#### AUTHORS' RECOMMENDATIONS

- Clinicians need to make decisions on how to conduct RRT, including modality (peritoneal dialysis, IRRT, CRRT) and dose (clearance x time/volume of distribution of target solute [Kt/V]).
- There is no clear evidence to suggest that CRRT has a survival benefit over IRRT.
- Mainly from observational studies, patients who survive AKI and are treated with CRRT might be more likely than after IRRT to be dialysis free at hospital discharge.
- Current evidence is insufficient to support any specific dose of RRT above a CRRT effluent rate of 20 mL/kg per hour or IHD with a prescribed Kt/V of between 1.2 and 1.4.

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## 55 Can Radiographic Contrast Nephropathy Be Prevented?

Lynn Redahan, Donal Reddan

Contrast-induced nephropathy (CIN) describes deterioration in renal function, after the administration of radiographic contrast media. It is defined as impairment in renal function occurring within 3 days after administration of contrast media in the absence of an alternative etiology. Diagnostic criteria include a 25% or higher increase in serum creatinine concentration from baseline value, or an absolute increment in serum creatinine of at least 0.5 mg/dL (44.2 mol/L).<sup>1</sup> CIN is associated with increased morbidity and discharge delay.<sup>2–5</sup> It is relatively common, accounting for 10% to 12% of acute kidney injury (AKI) in the hospital setting.<sup>6</sup> Critically ill patients are frequently exposed to radiographic contrast media and, owing to dysregulation of renal blood flow and other risk factors, are particularly vulnerable. AKI requiring renal replacement therapy in the critically ill patient is associated with more than 60% hospital mortality.<sup>7</sup>

CIN is a potentially avoidable cause of AKI, and it is therefore crucial to implement management strategies to prevent it when possible. Despite evidence supporting prophylactic measures for CIN, these are not uniformly employed. Weisbord and colleagues demonstrated that among patients with a glomerular filtration rate (GFR) of less than 60 mL/1.73 m<sup>2</sup> per minute receiving intravenous contrast before and after hydration was administered in only 40%, *N*-acetylcysteine (NAC) was given to 39.2% of patients, and only 6.8% of patients were advised to discontinue nonsteroidal anti-inflammatory drugs (NSAIDs) before contrast exposure.<sup>8</sup>

#### EPIDEMIOLOGY

The estimated incidence of CIN varies from less than 5% to as much as 50%. This variation is most likely due to differences in study populations, the type of radiographic media used, the radiographic procedure performed, and differences in the definition of CIN. CIN is becoming more prevalent. An increasing number of radiographic procedures requiring contrast media are being performed, and the role of computed tomography (CT) and CT angiography in patient assessment is becoming increasingly important.<sup>9</sup> Also, as more interventional radiographic procedures are performed, the exposure to radiographic contrast media increases. The prevalence of chronic kidney disease (CKD), the most important risk factor for CIN, also appears to be increasing and has recently been

reported to be as high as 13.1% for the U.S. population as a whole.<sup>10</sup> As the population of the world ages and becomes progressively more obese, the prevalence of metabolic disorders, cardiovascular disease, and diabetes mellitus will increase.

#### **RISK FACTORS**

There are several well-recognized risk factors for the development of contrast nephropathy (Table 55-1). These factors relate to both the patient and the contrast administered. Identifying the high-risk patient is the first step in preventing CIN. The presence of underlying CKD is the strongest risk factor. The risk for contrast nephropathy is negligible among patients with normal renal function.<sup>11</sup> The coexistence of CKD and diabetes mellitus (DM) dramatically increases the risk for CIN, and incidences of up to 50% have been reported.<sup>12</sup> Whether the presence of DM with normal renal function is a risk factor is controversial, but recent small studies suggest that such patients may also be at risk.<sup>13,14</sup> Other well-accepted risk factors include advancing age, concomitant use of nephrotoxic medications, and the presence of any factor causing reduced renal perfusion such as hypovolemia, hypotension, and congestive cardiac failure. Many of these factors coalesce in the critically ill patient. Hyperuricemia and the metabolic syndrome are also recently recognized risk factors.<sup>15</sup> It is important to review the patient's medications before contrast media exposure. Patients taking metformin are at risk for developing metformin-associated lactic acidosis (MALA) after exposure to radiographic contrast media, and almost all cases of MALA reported have occurred in patients with underlying renal insufficiency.<sup>16</sup> Although recommendations vary, it is advisable to discontinue metformin for 48 hours before and after contrast exposure.

There are factors relating to the contrast administration that are associated with an increased risk for CIN. The risk for contrast nephropathy is increased with the use of higher doses of contrast and the repeated administration of contrast media within a 72-hour period.<sup>17</sup> Intra-arterial injection of contrast may be associated with a higher risk for CIN than intravenous injection. The type of iodinated contrast medium used is also relevant. Agents with a high osmolality are associated with a greater risk for CIN than those with low osmolality contrast media.<sup>18</sup>

### Table 55-1 Risk Factors for the Development of Contrast-Induced Nephropathy

Administration of radiographic contrast				
Chronic kidney disease				
Diabetes mellitus				
Advancing age				
Concomitant use of nephrotoxic drugs				
<ul> <li>Nonsteroidal anti-inflammatory drugs</li> </ul>				
Aminoglycosides				
Amphotericin				
<ul> <li>Glycopeptides</li> </ul>				
Hypovolemia				
Sepsis				
Congestive heart failure				
Metabolic syndrome				
Hyperuricemia				

#### STRATEGIES TO PREVENT CONTRAST-INDUCED NEPHROPATHY

Considerable research effort has gone into developing effective CIN prophylactic strategies. Most protocols currently in use include pharmacologic agents and a volume repletion regime. The role of renal replacement therapy has also been studied. Consideration should be given to the choice of radiographic contrast medium used. General measures such as stopping nephrotoxic medications, minimizing the dose of contrast administered, and avoiding contrast altogether (if possible) are vitally important. We will address each of these strategies separately.

#### PHARMACOLOGIC THERAPY

The precise pathogenesis of CIN is poorly understood. The effects of iodinated contrast media on the kidney may include generation of free oxygen radicals,<sup>19</sup> renal vasoconstriction,<sup>20</sup> and apoptosis.<sup>21</sup> A variety of pharma-cologic interventions designed to target these processes have been studied. Agents such as furosemide, mannitol, statins, NAC, dopamine, fenoldopam, theophylline, and endothelin receptor antagonists have been attempted, and all have been proved unsuccessful.<sup>22</sup> Dopamine and fenoldopam increase renal blood flow, yet they have been found to be ineffective in preventing CIN.<sup>23,24</sup> Neither furosemide nor mannitol is beneficial.<sup>25</sup>

Adenosine is an important mediator of CIN and, as theophylline, is an adenosine antagonist. Several studies have investigated the effect of theophylline on CIN prevention. Huber and associates compared theophylline to placebo in the prevention of contrast nephropathy and found a reduced incidence of CIN in the patients who had received theophylline.<sup>26</sup> A further study in 2007 found theophylline to be superior to NAC in the prevention of CIN.<sup>27</sup> Theophylline may offer some protection against CIN, but no single study has clearly demonstrated its efficacy over hydration alone. In view of its potentially serious adverse effects, theophylline is not currently recommended in the prophylaxis of CIN.

Statins have also been studied for any potential role in CIN prophylaxis At least two observational studies have suggested a benefit,<sup>28,29</sup> but a more recent double-blind placebo-controlled study was negative.<sup>30</sup>

NAC has been studied extensively and is widely used for CIN prevention. Acetylcysteine is inexpensive and has minimal or no adverse effects. The presumed mechanism of action of NAC is as an antioxidant. Tepal and colleagues studied 83 patients with chronic renal insufficiency (mean serum creatinine concentration, 2.4 mg/dL) who were undergoing CT and receiving nonionic radiographic contrast.<sup>31</sup> Patients were randomly assigned either to receive the antioxidant acetylcysteine (600 mg orally twice daily) and 0.45% saline intravenously, before and after administration of the contrast agent, or to receive placebo and saline. The incidence of worsening renal dysfunction, as determined by a rise in serum creatinine by 0.5 mg/dL over the next 48 hours, was 2% in the acetylcysteine group and 21% in the control group (adjusted relative risk, 19%; number needed to treat (NNT), 5; P = .01; relative risk [RR], 0.1; 95% confidence interval [CI], 0.02 to 0.9). Interestingly, in the acetylcysteine group, the mean creatinine concentration actually fell significantly but was statistically unchanged in the control group.

Several criticisms were made of this study, not least the use of serum creatinine as the principal marker of renal function. It has been suggested that NAC may pharmacologically lower serum creatinine independent of renal function. Hoffman and colleagues studied 50 volunteers who had neither renal dysfunction nor were to receive radiographic contrast.<sup>32</sup> NAC was administered orally at a dose of 600 mg every 12 hours, for a total of four doses. Surrogate markers of renal function, such as serum creatinine, urea, albumin, and cystatin C levels, were measured, and estimated GFR (eGFR) was assessed immediately before the administration of NAC and 4 and 48 hours after the last dose. There was a significant decrease in the mean serum creatinine concentration (P < .05) and a significant increase in the eGFR (P < .02) 4 hours after the last dose of NAC. The cystatin C concentrations did not change significantly. Hasse and colleagues refuted this.<sup>33</sup> Their study included 110 cardiac surgical patients who were randomly allocated to perioperative infusion of a lower dose of NAC (300 mg/kg over 24 hours, n = 30) or placebo (n = 80). They were unable to demonstrate a significant difference in the plasma creatinine-to-plasma cystatin C ratio for the NAC and placebo group either during or after NAC infusion at 24 hours (1.03 versus 1.00; P = .78) and 72 hours (0.94 versus 0.89; P = .09). Similar results were reported in a cohort of patients with CKD who were administered 1200 mg of NAC.34

Other studies of NAC for CIN have produced conflicting results. For example, Durham and colleagues<sup>35</sup> looked at high-risk patients undergoing coronary angiography. Patients with serum creatinine (sCr) levels higher than 1.7 mg/dL were randomized to double-blind administration of placebo or NAC, 1200 mg orally, with doses 1 hour before the procedure and 3 hours afterward. *Acute renal failure* was defined as an increase in sCr of 0.5 mg/dL. They found no significant difference in the rate of CIN between the NAC and placebo groups (26.3% versus 22.0%). Kay and associates found opposite results,<sup>36</sup> as did Shyu and colleagues<sup>37</sup> and Diaz-Sandoval and coworkers.<sup>38</sup> If one looks at the positive data for the four trials by Tepel and colleagues,<sup>31</sup> Shyu and colleagues,<sup>37</sup> Kay and associates,<sup>36</sup> and Diaz-Sandoval and coworkers,<sup>3</sup> the reported reduction in the risk for CIN by NAC was 90.5%, 86.6%, 67.7%, and 82.2%, respectively. This is a remarkable treatment effect for any intervention in clinical medicine, particularly in light of the number of negative trials that have been published on the same therapy.<sup>39</sup> There is an excess in the number of negative trials over positive ones. A study of 354 patients undergoing primary angioplasty after myocardial infarction, by Marenzi and colleagues<sup>40</sup> demonstrated not only a dramatic reduction of up to 75.8% (using a double dose of 1200 mg NAC) in the risk for CIN, but NAC was also found to reduce the risk for death by an absolute amount of up to 13% (5% versus 18%; P = .002; high-dose NAC versus placebo). Conversely, a larger study by Webb and associates<sup>41</sup> was stopped after 500 patients for futility; there was no measurable benefit to NAC.

Because all the studies on NAC and CIN have been relatively small, a series of meta-analyses have attempted to clarify the situation. For example, a meta-analysis published in 2007 by Gonzales and colleagues<sup>42</sup> included 22 studies and 2746 patients. Remarkable heterogeneity was found, and the studies we grouped into two clusters. Cluster 1 studies (n = 18; 2445 patients) showed no benefit (RR, 0.87; 95% CI, 0.68 to 1.12; P = 0.28), whereas cluster 2 studies (n = 4; 301 patients) indicated that NAC was highly beneficial (RR, 0.15; 95% CI, 0.07 to 0.33; P <.0001). Benefit in cluster 2 was unexpectedly associated with NAC-induced decreases in creatinine from baseline (P = .07). Cluster 2 studies were relatively early, small, and of lower quality compared with cluster 1 studies (P = .01 for the three factors combined). Overall, their interpretation of the literature did not support the use of NAC in reducing the rates of CIN. Similar results have been reported in other systematic reviews and metaanalyses.43,4

We cannot recommend the use of NAC for the prevention of contrast nephropathy based on current evidence.

Table 55-2 outlines a summary of the findings with regard to various potential pharmacologic preventative strategies.

#### **VOLUME-REPLETION STRATEGIES**

Although the use of adjunct therapy for CIN such as NAC remains extremely controversial, there is universal agreement about the value of prehydration with fluid. The choice of solution, the volume to be infused, and the infusion timing remain controversial. Three intravenous solutions have been tested and compared by numerous studies: 0.9% sodium chloride, 0.45% sodium chloride, and sodium bicarbonate. Strangely, balanced salt solutions have not been investigated, despite their ubiquitous role in fluid resuscitation. Significant controversy remains regarding fluid volume versus fluid content.<sup>45</sup> In addition, there is controversy regarding the effectiveness or otherwise of the oral route of rehydration.<sup>46,47</sup>

#### Table 55-2 Summary of Data for Various Pharmacologic Agents

Pharmacologic Agent	Summary of Data
Dopamine and fenoldopam	Ineffective or only marginally beneficial
Diuretics	No significant benefit over hydration alone
Theophylline	May have a role in the prevention of contrast-induced nephropathy (CIN); however, its use is limited owing to its potentially serious side effects
Statins	Studies have failed to demonstrate any benefit in the prevention of CIN
Endothelin receptor antagonist	Endothelin antagonist was associated with an increased incidence of CIN

#### **Saline Solutions**

Much of the reverence to prehydration is derived from a retrospective study by Eisenberg and colleagues that evaluated hydration with 550 mL normal saline (NS) plus 250 mL heparinized saline flush per hour.<sup>48</sup> They claim to have prevented CIN in 100% of 537 patients undergoing cerebral, abdominal, or peripheral angiography with the use of high-osmolar contrast media. There was no control group. Few data have been published to contradict these findings; there have been no prospective randomized controlled trials to compare hydration with no intervention. However, extrapolation of data from studies comparing oral to intravenous hydration appears to support the hydration hypothesis. An example of a prehydration regime is an infusion of isotonic crystalloid at a rate of 1 mL/kg per hour for 12 hours before and 12 hours after contrast administration. Hypotonic saline (0.45% sodium chloride) is widely used as an alternative to 0.9% sodium chloride; it has a significantly larger volume of distribution and a shorter plasma retention time. Mueller and colleagues compared 0.45% saline with 0.9% saline in one of the larger trials (n = 1620) in this field.<sup>49</sup> In this study, there was a 1.7% incidence of CIN in the 0.9% saline group versus a 2.0% incidence in the 0.45% saline group (P = .042). These data, although far from compelling, suggest that isotonic crystalloid should be administered as the prehydration strategy of choice.

#### **Sodium Bicarbonate**

NS is a slightly isotonic solution that contains equimolar concentration of sodium and chloride. Each liter of fluid administered results in a net gain of chloride into the extracellular space, and this is known to result in hyperchloremic acidosis.<sup>50,51</sup> In the human diet, sodium and chloride are ingested in roughly equimolar concentrations, but the serum concentration of the two is maintained at a relative ratio of roughly 1.4:1. A major component of renal function is the excretion of relatively more chloride than sodium. Hence, chloride in and of itself, when delivered to an injured or ischemic kidney, may act as a nephrotoxin. There are some data to support this case.<sup>50,52,53</sup> Early data suggested that sodium bicarbonate rather than isotonic saline may be beneficial in the prevention of CIN.<sup>54</sup> Haase and colleagues<sup>55</sup> compared perioperative NaHCO<sub>3</sub> or normal saline (4 mmol/kg over 24 hours) in patients undergoing cardiac surgery. There was a 20% absolute risk increase of renal dysfunction in the patients receiving NS (odds ratio, 0.43; 95% CI, 0.19 to 0.98; P = .043).

Merten and colleagues demonstrated an 11.9% (NNT, 8) ARR for patients prehydrated with 154 mmol/L NaHCO3 versus 0.9% isotonic saline.<sup>56</sup> Ozcan and associates compared sodium bicarbonate to saline and saline plus NAC (NS-NAC).<sup>57</sup> They reported a 9.1% absolute reduction when NaHCO<sub>3</sub> was administered versus saline (P = .036), but there was no statistically significant difference compared with the NS-NAC combination. The REMEDIAL study looked at 351 patients with a GFR less than 40 mL/minute.<sup>58</sup> The patients received either intravenous NS-NAC, intravenous NaHCO3 with NAC, or intravenous NS with intravenous ascorbic acid and NAC. CIN occurred in 11 of 111 patients (9.9%) in the NS-NAC group, in 2 of 108 (1.9%) in the NaHCO<sub>3</sub>-NAC group (P = .019 by Fisher exact test versus saline plus NAC group), and in 11 of 107 (10.3%) in the NS plus ascorbic acid plus NAC group (P = 1.00 versus saline plus NAC group). Thus, there was a substantial risk reduction in this series with NaHCO<sub>3</sub>. Adolf and colleagues compared NaHCO<sub>3</sub> with NS in 145 patients in a single-blind trial of patients undergoing coronary angiography.<sup>59</sup> The patients in this REINFORCE study had mildly elevated levels of serum creatinine at baseline and had a remarkably low incidence of CIN (4.2% in sodium bicarbonate group versus 2.7% in sodium chloride group; P = .614), suggesting that the study was underpowered and the severity of renal function inadequate to find a difference between the groups. The combination of NaHCO<sub>3</sub> plus NAC is superior to NS alone.<sup>60</sup> But what of NS plus NAC? In a study of 500 patients, all with estimated GFR of less than 60 mL/min NaHCO<sub>3</sub> plus NAC was not superior to NS plus NAC (CIN, 10.8% versus 11.5%; P = .6). These data are supported by two meta-analyses: sodium bicarbonate is superior to saline alone, but not when saline is combined with NAC.<sup>61,62</sup>

Therefore, no clear data are available supporting one approach—hydration, NAC, or NaHCO<sub>3</sub>—versus another. It is important to note that most of these studies involved patients undergoing coronary angiography, receiving radiographic contrast from cardiologists rather than radiologists, with extensive cardiovascular disease. How these data apply to critically ill patients undergoing imaging during early sepsis or acute respiratory distress syndrome, in which organ failure is imminent or established, is unclear. Indeed, by their very nature, critically ill patients are likely to be managed differently from patients undergoing elective coronary angiography. For example, it is possible to plan, in advance, hydration strategies. Intensivists are likely to administer larger volumes of prehydration than cardiologists, owing to the ability to more aggressively deal with the consequences in the intensive care unit (ICU). Further, the volume of radiographic contrast may be substantially lower when administered by radiologists than cardiologists. Finally, the concern for CIN in this patient population must be weighed against the importance of uncovering the diagnosis, resulting in source control and recovery.

#### CHOICE OF CONTRAST MEDIUM

For angiography and CT, iodine is used as it enhances brightly when exposed to ionizing radiation. For magnetic resonance imaging, gadolinium is used. All radiologic contrasts are weak acids that ionize in acidic conditions.

Iodinated contrast media are classified according to their iodine content, their osmolality, and their ionization in solution. High-osmolality contrast media (HOCM) are associated with greater risk of CIN. These agents are the older generation of iodinated contrast media and include agents such as diatrizoate and iothalamate. The osmolality of these agents is much higher than that of human plasma (1400 to 1800 mOsm/kg).

So called low-osmolality agents have a lower density than the older HOCM; however, they are still hyperosmolar relative to plasma (500 to 850 mOsm/kg). Low-osmolality contrast media (LOCM) include iohexol, iopamidol, iomeprol, ioxaglate, and iopromide. Iodixanol is classed as an iso-osmolar contrast media (IOCM). HOCM are no longer used in clinical practice. Iodixanol has been demonstrated to be associated with a lower incidence of CIN than low osmolar agents in high-risk patients,<sup>63–65</sup> but this has not been a universal finding in that no difference between iodixanol and LOCM have been demonstrated in other studies;<sup>66–68</sup> indeed, one study suggested that there were more cases of CIN with iodixanol when compared with an LOCM.<sup>69</sup>

There have also been conflicting meta-analyses. McCullough and colleagues using pooled data from 2727 patients in 16 trials demonstrated that use of the IOCM iodixanol was associated with lower rates of CIN than LOCM, especially in patients with CKD or the combination of CKD and diabetes.<sup>70</sup> A subsequent meta-analysis of 25 studies found no significant reduction in the risk for CIN with iodixanol compared with the LOCM pooled together but iodixanol was associated with a reduced risk for CIN compared specifically with the LOCM iohexol among patients with intra-arterial administration and renal insufficiency,<sup>71</sup>

It is generally accepted that the volume of contrast administered should be kept to a minimum because the incidence of CIN correlates with the volume of contrast.<sup>72</sup> There is no definite value for a "safe" dose of iodinated contrast; however, the recommendation is to use less than 100 mL of contrast agent in high-risk patients.<sup>72</sup> High doses of contrast have been associated with a greater risk for developing nephropathy requiring dialysis.<sup>73</sup>

#### HEMODIALYSIS AND HEMOFILTRATION

Hemodialysis effectively removes iodinated contrast media from the circulation.<sup>74</sup> However, several studies have failed to show a significant benefit of hemodialysis in the prevention of CIN.<sup>74,75</sup> Indeed, it has been

suggested that hemodialysis in this situation may be potentially harmful.<sup>76</sup> At present, the use of hemodialysis in the prevention of CIN is controversial, and further research is required before it can be recommended.

In the ICU, hemofiltration is widely used as a component of continuous renal replacement therapy. Hemofiltration before and after contrast exposure may have potential in preventing CIN.<sup>77</sup> Marenzi and colleagues<sup>77</sup> studied 114 consecutive patients with chronic kidney injury (serum creatinine concentration, >2 mg/dL [176.8 mol/L]) who were undergoing coronary interventions. The patients were randomly assigned to either hemofiltration in an ICU (58 patients, with a mean  $[\pm SD]$  serum creatinine concentration of  $3.0 \pm 1.0 \text{ mg/dL} [265.2 \pm 88.4 \text{ mol/L}])$ or isotonic-saline hydration at a rate of 1 mL/kg body weight per hour given in a step-down unit (56 patients, with a mean serum creatinine concentration of  $3.1 \pm 1.0$ mg/dL [274.0  $\pm$  88.4 mol/L]). Hemofiltration (fluid replacement rate, 1000 mL/hour without weight loss) and saline hydration were initiated 4 to 8 hours before the coronary intervention and were continued for 18 to 24 hours after the procedure was completed. Although a variety of outcome measures were used, renal indices were likely biased by the effect of hemofiltration. However, in-hospital mortality rates were 2% in the hemofiltration group and 14% in the control group (P = .02), and the cumulative 1-year mortality rates were 10% and 30%, respectively (P = .01; ARR, 20%; NNT, 5). This study has not been validated by follow-up, and there remains a suspicion that confounders-intensive care, the use of anticoagulants, differences in the severity of cardiac disease-may have accounted for the different outcomes. Based on a single study, with an abundance of negative data for intermittent hemodialysis, we cannot recommend hemofiltration for avoidance of CIN, but it is an option that intensivists should consider in high-risk patients.

#### **AUTHORS' RECOMMENDATIONS**

- The first step in preventing CIN is to identify the patients who are at high risk.
- Exposure to contrast media in high-risk patient populations should, ideally, be carefully planned.
- The patient's medication should be reviewed, and nephrotoxic agents should be stopped.
- Hydration should be carried out both before and after the procedure. Isotonic crystalloid or isotonic sodium bicarbonate should be used.
- The role of NAC is controversial. It is unclear whether efficacy should be balanced against low toxic potential. The dose is 600 to 1200 mg twice daily orally for 24 hours before and after contrast exposure.
- The lowest possible dose of low-osmolality nonionic contrast must be used, and it is recommended that the repeated administration of contrast within a 72-hour time period should be avoided.
- There are currently insufficient data to support the use of hemodialysis in the prevention of CIN.
- Hemofiltration may be of benefit in high-risk critically ill patients who require angiography or CT and are at risk for CIN.

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## 56 How Should Acid-Base Disorders Be Diagnosed and Managed?

Patrick J. Neligan, Rory O'Donoghue

This chapter reviews the current state of knowledge of acid-base chemistry in critical care. We look at the physiochemical principles underlying acid-base disturbances and then review the analytical tools used to identify and treat them.

#### SCIENTIFIC BACKGROUND

The revolutionary theory of Svante Arrhenius (1859-1927) in 1903 established the foundations of acid-base chemistry. In an aqueous solution, an Arrhenius acid is any substance that delivers a hydrogen ion into the solution.<sup>1</sup> A base is any substance that delivers a hydroxyl ion into the solution. Water is a highly ionizing solution, on account of its high dielectric constant, so that substances with polar bonds, immersed in water, will dissociate into their component parts (dissolve). Thus, hydrogen chloride (HCl) is an acid, and potassium hydroxide (KOH) is a base.

The degree of dissociation of substances in water determines whether they are strong acids or strong bases. Thus, lactic acid, which has an ion dissociation constant (pKa) of 3.4, is completely dissociated at physiologic pH and is a strong acid. Conversely, carbonic acid, which has a pKa of 6.4, is incompletely dissociated and is a weak acid. Similarly, ions, such as sodium, potassium, and chloride, that do not easily bind other molecules, are considered strong ions: they exist free in physiologic fluids. In any solution, the ion dissociation constant for water, Kw', dictates that the relative ratio of H<sup>+</sup> to OH<sup>-</sup> must always be constant, and electrical neutrality must always hold. Consequently, strong cations (Na<sup>+</sup>, K<sup>+</sup>,  $Ca^{2+}$ ,  $Mg^{2+}$ ) will act as Arrhenius bases (because they will drive hydroxyl out of, and hydrogen into, solution, to maintain electrical neutrality), and strong anions (Cl-, LA-, ketones, sulfate, and formate) will act as Arrhenius acids.

In 1923, Brønsted and Lowry proposed an expanded theory of acids and bases. They defined acids as proton donors and bases as proton acceptors. All Arrhenius acids and bases are thus also Brønsted-Lowry acids and bases.

#### Strong lons

Strong ions are completely dissociated at physiologic pH. The most abundant strong ions in the extracellular space are Na<sup>+</sup> and Cl<sup>-</sup>. Other important strong ions include  $K^+$ , SO<sub>4</sub><sup>2-</sup>, Mg<sup>2+</sup>, and Ca<sup>2+</sup>. Each applies a direct electrochemical and osmotic effect.

In the extracellular space, the difference between the charge carried on strong cations and strong anions is calculated as follows:

$$SID = (Na^{+} + K^{+} + Ca^{2+} + Mg^{2+}) - (Cl^{-} + [other strong anions: A^{-}]] = 40 - 44 \text{ mEq}$$

This excess of positive charge, called the *strong ion difference* (SID) by Stewart,<sup>2</sup> is always positive and is balanced by an equal amount of buffer base, principally in the form of phosphate, albumin, and bicarbonate.<sup>3</sup> SID independently influences water dissociation, determined by electrical neutrality and mass conservation. If all other factors (Pco<sub>2</sub>, albumin, and phosphate) are kept constant, an increase in SID will decrease hydrogen ion liberation from water (and increase hydroxyl ion liberation), causing alkalosis. A decrease in SID increases hydrogen ion liberation to maintain electrical neutrality, causing acidosis.

The chief determinant of SID is the relationship between the relative concentration of sodium, chloride, and free water in extracellular fluid (ECF). The normal ratio of sodium to chloride is about1.4:1. Any process that reduces that ratio reduces SID and leads to acidosis (sodium loss, chloride gain, or free water gain). Any process that increases that ratio increases SID and leads to alkalosis (sodium gain, chloride loss, or free water gain).

#### Weak Acids

Albumin and phosphate are weak acids, whose degree of dissociation is related to temperature and pH. Weak acids, represented by the symbol A<sub>TOT</sub>, independently influence acid-base balance, depending on absolute quantity and dissociation equilibria.<sup>2,4</sup>

The principal limitation of traditional approaches to acid-base balance has been the limited attention paid to changes in A<sub>TOT</sub>.<sup>5</sup> Although this may be valid in otherwise healthy patients, perioperative care and critical illness cause hypoalbuminemia due to crystalloid administration,

hepatic prioritization, and capillary leak.<sup>6</sup> A reduction in serum albumin or phosphate leads to metabolic alkalosis.<sup>7</sup> Hypophosphatemia is associated with malnutrition, refeeding, diuresis, and hemodilution. Hyperphosphatemia occurs in renal failure. Hyperphosphatemia leads to metabolic acidosis.

#### Carbon Dioxide

Aerobic metabolism results in the production of large quantities of carbon dioxide. Carbon dioxide is hydrated by carbonic anhydrase in red cell erythrocytes to carbonic acid. This liberates the equivalent of 12,500 mEq of H<sup>+</sup> per day. Hydrogen ions bind to histidine residues on deoxyhemoglobin, and bicarbonate is actively pumped out of the cell. Carbon dioxide exists in four forms: carbon dioxide [denoted  $CO_2(d)$ ], carbonic acid (H<sub>2</sub>CO<sub>3</sub>), bicarbonate ions (HCO<sub>3</sub><sup>-</sup>), and carbonate ions  $CO_3^{2-}$ . The principal mechanism of excretion is through alveolar ventilation, although some  $CO_2$  is excreted from the kidney as bicarbonate as part of a sodium-chloride cotransporter.

Chronic respiratory acidosis is associated with increase in total-body CO<sub>2</sub> content, reflected principally by an increase in serum bicarbonate. Mathematically,  $\triangle HCO_3^-$ = 0.5  $\triangle PacO_2^8$  (Table 56-1). It is important that this is not confused with *metabolic compensation for hypercarbia*, a relatively slow process that reduces SID by increase urinary chloride excretion.<sup>9</sup>

#### ACID-BASE DISTURBANCES

Acid-base disturbances are an important part of clinical and laboratory investigation of perioperative and critically ill patients.

There are six primary acid-base abnormalities (see Table 56-1):

- 1. Acidosis due to increased Paco<sub>2</sub>
- 2. Acidosis due to decreased SID
- Increased chloride (hyperchloremic); reduced sodium (dilutional) and increased free water
- 3. Acidosis due to increased  $A_{TOT}$
- Hyperphosphatemia, hyperproteinemia
- 4. Alkalosis due to decreased Paco<sub>2</sub>

#### Table 56-1 Relative changes in Serum Bicarbonate and PaCO<sub>2</sub> in different acid-base scenarios

Disturbance	$HCO_3^-$ vs. $Paco_2$
Acute respiratory acidosis	$\Delta HCO_3^- = 0.2 \Delta Paco_2$
Acute respiratory alkalosis	$\Delta H \text{co}_3{}^- = 0.2 \ \Delta P \text{aco}_2$
Chronic respiratory acidosis	$\Delta H \text{co}_3{}^- = 0.5 \; \Delta P \text{aco}_2$
Metabolic acidosis	$\Delta Paco_2 = 1.3 \ \Delta HCO_3^{-}$
Metabolic alkalosis	$\Delta Paco_2 = 0.75 \ \Delta HCO_3^{-1}$

Modified from Narins RB, Emmett M: Simple and mixed acid-base disorders: A practical approach. *Medicine*. 1980;59:161-187.

- 5. Alkalosis due to increased SID
  - Decreased chloride (hypochloremic); increased sodium and decreased free water (contractional)
- 6. Alkalosis due to decreased  $A_{TOT}$ 
  - Hypophosphatemia, hypoalbuminemia

#### ACUTE RESPIRATORY ACIDOSIS AND ALKALOSIS

Acute respiratory acidosis results from hypoventilation, due to loss of respiratory drive, neuromuscular or chest wall disorders, or rapid-shallow breathing, which increases the fraction of dead space ventilation. Acute respiratory acidosis is often associated with a precipitous reduction in pH due to the absence of a rapid buffering system for large quantities of carbon dioxide (see later). Acute respiratory alkalosis (pH > 7.5) is caused by hyperventilation due to anxiety, central respiratory stimulation (as occurs early in salicylate poisoning), or excessive artificial ventilation. Acute respiratory alkalosis usually accompanies acute metabolic acidosis (pH < 7.35), in which case the reduction in Pco<sub>2</sub> from baseline (usually 40 mmHg) is equal to the magnitude of the base deficit (BD; see later). For example, in a patient with lactic acidosis, with a lactate level of 10 mEq/L, the BD should be -10, and the Pco<sub>2</sub>, 30 mm Hg. If the Pco<sub>2</sub> is higher than expected, there is a problem with the respiratory apparatus. This is seen, for example, in a multitrauma patient, in whom there is massive blood loss, causing lactic acidosis, plus a flail chest, causing respiratory acidosis.

#### ACUTE METABOLIC ACIDOSIS

Acute metabolic acidosis is caused by an alteration in SID or  $A_{TOT}$ . SID is changed by an alteration in the relative quantity of strong anions to strong cations. This can be caused by anion gain, as occurs with lactic acidosis, renal acidosis, ketoacidosis, and hyperchloremic acidosis, or cation loss, as occurs with severe diarrhea. Acidosis also results from increased free water relative to strong ions: dilutional acidosis, which results from excessive hypotonic fluid intake; certain poisonings (methanol, ethylene glycol, or isopropyl alcohol); or hyperglycemia.

#### Metabolic Acidosis due to Unmeasured Anions

In acute metabolic acidosis, three diagnoses should be immediately investigated: lactic acidosis (serum lactate level should mirror the magnitude of BD), ketoacidosis due to diabetes (the patient should be hyperglycemic and have positive urinary ketones), and acute renal failure, demonstrated by high serum urea and creatinine and low total CO<sub>2</sub>. The latter is a diagnosis of exclusion. The presence of a low serum sodium (<135 mEq/L) should alert the clinician to the possibility of a dilutional acidosis, caused by alcohol poisoning. Alcohols such as ethanol, methanol, isopropyl alcohol, and ethylene glycol are osmotically active molecules that expand extracellular water (glucose and mannitol have the same effect but also promote diuresis because the molecules are small enough to be filtered by the kidney). Alcohol poisoning is suspected by the presence of an osmolar gap; a difference between the measured and calculated serum osmolality of greater than 12 mOsm demonstrates the presence of unmeasured osmoles. Toxicology laboratories can investigate for the presence of various toxic alcohols.

#### Hyperchloremic and Dilutional Acidosis Associated with Intravenous Fluids

The administration of intravenous fluids to patients has significant impact on acid-base balance. There are changes in free water volume, SID, and A<sub>TOT</sub> (principally albumin). Dilutional acidosis results from administration of pure water to extracellular fluid (which is alkaline).<sup>10</sup> This can occur with large volume administration of any fluid whose SID is 0, including 5% dextrose and other hypotonic saline infusions. The administration of each liter of 0.9% saline (normal saline contains 154 mEq of both Na<sup>+</sup> and Cl<sup>+</sup>) results in net ECF gain of 50 mEq/L chloride or, put another way, hydrochloric acid. This "hyperchloremic" acidosis is frequently seen in the operating suite following large volume administration of 0.9% saline solution or 6% hetastarch (both formulated in normal saline), hypertonic saline, or gelatin-based solutions.<sup>11–17</sup> Kellum<sup>18</sup> has shown that, in an experimental model of sepsis, dogs treated with lactated Ringer solution and 5% hydroxyethyl starch diluted in lactated ringers (Hextend), both with a SID of 20, had less acidosis and longer survival than those treated with normal saline. The administration of albumin results in metabolic acidosis due to an increase in A<sub>TOT</sub>.<sup>19,20</sup>

#### **Renal Tubular Acidosis**

In metabolic acidosis, chloride is preferentially excreted by the kidney. Indeed, this is the resting state of renal physiology because sodium and chloride are absorbed in the diet in relatively equal quantities. In metabolic alkalosis, chloride is retained, and sodium and potassium are excreted. Acetazolamide corrects metabolic alkalosis by increasing SID secondary to reduced chloride excretion.<sup>21</sup>

Abnormalities in the renal handling of chloride may be responsible for several inherited acid-base disturbances. In renal tubular acidosis, there is inability to excrete Cl<sup>-</sup> in proportion to Na<sup>+</sup>.<sup>22</sup> Similarly, pseudohypoaldosteronism appears to be due to high reabsorption of chloride.<sup>23</sup> Bartter syndrome is caused by a mutation in the gene encoding the chloride channel, CLCNKB, which regulates the Na<sup>+</sup>-K<sup>+</sup> 2Cl cotransporter (NKCC2).<sup>24</sup>

#### Clinical Relevance of Hyperchloremic Acidosis

What is the clinical relevance hyperchloremic acidosis? Brill and colleagues found that acidosis due to hyperchloremia was associated with better outcomes than lactic acidosis or ketoacidosis.<sup>25</sup> This supports the contention that it is the underlying problem that increases patient risk. Nonetheless, metabolic acidosis, regardless of origin,

can depress myocardial contractility, reduce cardiac output, and reduce tissue perfusion. Acidosis inactivates membrane calcium channels and inhibits the release of norepinephrine from sympathetic nerve fibers, leading to vasodilation and maldistribution of blood flow. Additionally, metabolic acidosis is associated with an increased incidence of postoperative nausea and emesis.<sup>26</sup> In the human diet, sodium and chloride are ingested in roughly equimolar concentrations, but the serum concentration of the two is maintained at a relative ratio of roughly 1.4:1. A major component of renal function is the excretion of relatively more chloride than sodium. Hence, chloride in and of itself, when delivered to an injured or ischemic kidney, may act as a nephrotoxin. Plasma chloride levels affect afferent arteriolar tone through calcium-activated chloride channels and modulate the release of rennin.<sup>2</sup> Hyperchloremia can reduce renal blood flow and glomerular filtration rate.<sup>28</sup> Hyperchloremia reduces splanchnic blood flow.<sup>29</sup> In a study of healthy volunteers, normal saline was associated with reduced urinary output compared with lactated Ringer solution.<sup>30</sup> In a study of fluid prehydration to prevent contrast nephropathy, the use of sodium bicarbonate was associated with an 11.9% absolute reduction in the risk for renal injury (defined as a 25% increase in creatinine).<sup>31</sup> Hasse and colleagues compared perioperative NaHCO<sub>3</sub> or normal saline (4 mmol/kg over 24 hours) in patients undergoing cardiac surgery.<sup>32</sup> There was a 20% absolute risk increase of renal dysfunction in the patients receiving normal saline (odds ratio, 0.43; 95% confidence interval, 0.19 to 0.98; P = .043).

#### Renal Acidosis and the Impact of Dialysis

Renal acidosis is widely believed to be caused by accumulation of strong ion products of metabolism excreted exclusively by the kidney. These include sulphate and formate. In addition, there is accumulation of a weak acid, phosphate. However, hyperchloremia has been found to be the major cause of strong ion gain.<sup>33,34</sup> Moreover, free water gain results in a concomitant hyponatremic dilutional acidosis.<sup>35</sup>

Continuous renal replacement therapy (CRRT) is used in critical illness to hemofiltrate and hemodialyze patients who are hemodynamically unstable. Rocktaschel and colleagues have demonstrated that CRRT resolves the acidosis of acute renal failure by removing strong ions and phosphate.<sup>36</sup> However, metabolic alkalosis ensued because of the unmasking of metabolic alkalosis due to hypoalbuminemia. Serum lactate goes up, but this does not result in acidosis.<sup>17</sup> In the setting of severe hepatic failure, weak acids are no longer effectively removed by the liver, and metabolic acidosis will require more aggressive dialysis to resolve.<sup>37</sup>

#### ACUTE METABOLIC ALKALOSIS

Perioperative metabolic alkalosis is usually of iatrogenic origin. Hyperventilation of patients with chronic respiratory failure results in acute metabolic alkalosis due to chronic compensatory alkalosis associated with chloride loss in urine. More frequently, metabolic alkalosis is associated with increased SID due to sodium gain. This results from administration of fluids in which sodium is "buffered" by weak ions, citrate (in blood products), acetate (in parenteral nutrition), and, of course, bicarbonate. In each of these situations, the anion is converted to carbon dioxide (usually by hepatic metabolism) and excreted through respiration; net sodium gain follows as a result of mass conservation.

The most frequent single disturbance in acid-base chemistry in perioperative and critically ill patients is hypoalbuminemia. This is ubiquitous and causes an unpredictable metabolic alkalosis. This may mask significant alterations in SID, such as lactic acidosis. All intravenous fluids that do not contain albumin are alkalizing. Thus, all patients who receive significant volumes of intravenous fluid in the operating room develop a hypoalbuminemic alkalosis. It is unknown whether this anomaly has any clinical significance. Morgan and colleagues, in a series of elegant studies, have determined that the optimal SID of resuscitation fluid should be 24 mEq/L, rather than 40 mEq/L.<sup>10,38</sup> The reason is that progressive dilution of albumin is alkalinizing; thus, net chloride gain is required to maintain the normal balance between SID and  $A_{TOT}$ .<sup>39</sup>

#### OTHER ACID-BASE PROBLEMS IN CRITICAL ILLNESS

Critically ill patients are vulnerable to significant changes in SID and free water. Nasogastric suctioning causes chloride loss; diarrhea leads to sodium and potassium loss. Surgical drains placed in tissue beds may remove fluids with varying electrolyte concentrations (the pancreatic bed, for example, secretes fluid rich in sodium). Fever, sweating, oozing tissues, and inadequately humidified ventilator circuits lead to large volume insensible loss and contraction alkalosis. Loop diuretics and polyuric renal failure may be associated with significant contraction alkalosis due to loss of chloride and free water.

Parenteral infusions may be responsible for stealth alterations in serum chemistry. Many antibiotics, such as piperacillin-tazobactam, are diluted in sodium rich solutions. Others, such as vancomycin, are administered in large volumes of free water (5% dextrose). Lorazepam is diluted in propylene glycol, large volumes of which will cause metabolic acidosis similar to that seen with ethylene glycol.<sup>40</sup> Mannitol may cause metabolic acidosis by the same mechanism.<sup>41</sup>

#### ANALYTIC TOOLS USED IN ACID-BASE CHEMISTRY

In this section, we consider some of the tools that have evolved over the past 60 years to assist our interpretation of acid-base conundrums.

#### The CO<sub>2</sub>-Bicarbonate (Boston) Approach

Schwartz and colleagues, at Tufts University in Boston, developed an approach to acid-base chemistry using acid-base maps and the mathematical relationship

#### Table 56-2 Changes in Standardized Base Deficit or Excess (BDE) in Response to Acute and Chronic Acid-Base Disturbances

Disturbance	BDE vs. Paco <sub>2</sub>
Acute respiratory acidosis	$\Delta BDE = 0$
Acute respiratory alkalosis	$\Delta BDE = 0$
Chronic respiratory acidosis	$\Delta BDE = 0.4 \ \Delta Paco_2$
Metabolic acidosis	$\Delta Paco_2 = \Delta BDE$
Metabolic alkalosis	$\Delta Paco_2 = 0.6 \Delta BDE$

Modified from Narins RB, Emmett M. Simple and mixed acid-base disorders: A practical approach. *Medicine*. 1980;59:161-187.

between carbon dioxide tension and serum bicarbonate (or total CO<sub>2</sub>), derived from the Henderson-Hasselbalch equation, to predict the nature of acid-base disturbances (Table 56-2).<sup>42</sup> A number of patients with known acid-base disturbances, at steady states of compensation, were evaluated. The degree of compensation, from what was considered normal, was measured for each disease state. The investigators were able to describe six primary states of acid-base imbalance, using linear equations or maps, relating hydrogen ion concentration to PaCO<sub>2</sub> for respiratory disturbances, and PaCO<sub>2</sub> to HCO<sub>3</sub><sup>-</sup> concentration, for metabolic disturbances (see Table 56-1). For any given acid-base disturbance, an expected HCO<sub>3</sub><sup>-</sup> concentration was determined. The major drawback of this approach is that it treats HCO<sub>3</sub><sup>-</sup> and CO2 as independent rather than interdependent variables.

#### The Base Deficit Excess (Copenhagen) Approach

Singer and Hastings pioneered an alternative approach to acid-base chemistry in 1948 by moving away from Henderson-Hasselbalch toward quantifying the metabolic component.<sup>3</sup> They proposed that the whole blood buffer base (BB) could be used for this purpose. The BB represented the sum of the bicarbonate and the nonvolatile buffer ions (essentially the serum albumin, phosphate, and hemoglobin). Applying the law of electrical neutrality, the BB was forced to equal the electrical charge difference between strong (fully dissociated) ions. Thus, normally  $BB = Na^+$  $+ K^{+} - Cl^{-}$ . Alterations in BB represented changes, essentially, in strong ion concentrations (which could not be easily measured in 1948). BB increases in metabolic alkalosis and decreases in metabolic acidosis. The major drawback of the use of BB measurements is the potential for changes in buffering capacity associated with alterations in hemoglobin concentration.

Siggard-Anderson, in 1958, developed a simpler measure of metabolic acid-base activity, the base deficit excess (BDE).<sup>43</sup> This, they defined, is the amount of strong acid or base required to return the pH of 1 L of blood to 7.4, assuming a PaCO<sub>2</sub> of 40 mm Hg and temperature of 38°C. The initial use of whole blood base excess was criticized owing to the dynamic activity of red cells within the acid-base paradigm: gas and electrolyte exchange. This approach was modified in the 1960s to use only serum base excess, and the calculation became the *standardized* base excess (SBE). Current algorithms for computing the SBE are derived from the van Slyke equation (1977).<sup>44</sup> The BDE approach to acid-base chemistry has been successfully validated by Schlitig and colleagues<sup>45</sup> and Morgan and associates.<sup>46</sup>

Simple mathematical rules can be applied using the BDE in each of the common acid-base disturbances (Table 56-2). For example, in acute respiratory acidosis or alkalosis, BDE does not change. Conversely, in acute metabolic acidosis, the magnitude of change of the  $Pco_2$  (in mm Hg) is the same as that of the BDE (in mEq/L), and the change in BDE represents the overall sum total of all acidifying and alkalinizing effects. This makes interpretation of acid-base abnormalities simple, but misleading.

The BD approach has two significant limitations. First, it does not account for changes in acid-base chemistry associated with hypoproteinemia; indeed, the van Slyke equation assumes normal serum proteins, which is not the case in critical illness.<sup>7</sup> The second limitation is that this approach does not distinguish between metabolic acidosis associated with hyperchloremia and that associated with unmeasured anions.

#### Anion Gap Approach

To address the primary limitation of the Boston and Copenhagen approaches, the anion gap (AG) was developed by Emmit and Narins in 1975.<sup>47</sup> This is based on the law of electrical neutrality and is entirely consistent with the work of Stewart and Fencl. The sum of the difference in charge of the common extracellular ions reveals an unaccounted for "gap" of -12 to -16 mEq/L (anion gap = Na<sup>+</sup> + K<sup>+</sup> - CL<sup>-</sup> + HCO<sub>3</sub><sup>-</sup>) (Fig. 56-1). If the patient develops a metabolic acidosis, and the gap widens to, for example -20 mEq/L (due to consumption of bicarbonate), the acidosis is caused by unmeasured anions: lactate or ketones. If the gap does not widen, the anions *are* being measured, and the acidosis has been caused by hyperchloremia (bicarbonate cannot independently influence acid-base status).

Although this is a useful tool, it is weakened by the assumption of what is or is not a normal gap. Like the BD, the AG frequently underestimates the extent of the metabolic disturbance. Most critically ill patients are hypoalbuminemic, and many are also hypophosphatemic.<sup>48</sup>



**Figure 56-1.** The Anion Gap. This accounts for anionic (A<sup>-</sup>) charge carried by albumin, phosphate and unmeasured anions (UMA).

Consequently, the gap may be normal in the presence of unmeasured anions. Figge and colleagues have provided us with a useful variant known as the *corrected* (for albumin) *anion gap*  $(AGC)^{49}$ :

AGC = calculated AG + 2.5 (normal albumin [g/dL])- observed albumin [g/dL])

The AGC has been validated and appears accurate in a variety of settings.<sup>50</sup>

#### Stewart-Fencl Approach

A more accurate reflection of true acid-base status can be derived using the Stewart-Fencl approach.<sup>1,51</sup> This, like the anion gap, is based on the concept of electrical neutrality. There exists, in plasma, an SID ( $[Na^+ + Mg^{2+} + Ca^{2+} = K^+] - [Cl^- + A^-]$ ) of 40 to 44 mEq/L, balanced by the negative charge on bicarbonate and  $A_{TOT}$  (the BB). There is a small difference between the apparent SID and weak acid buffers (effective SID). This represents a strong ion gap (SIG, Fig. 56-2), which quantifies the amount of unmeasured anion present:

Apparent SID = 
$$(Na^+ + K^+ + Mg^{2+} + Ca^{2+}) - Cl^-$$
  
Effective SID =  $HCO_3^- + [charge \text{ on albumin}] + [charge \text{ on Pi}] (in mmol/L)$ 

Weak acids' degree of ionization is pH dependent, so one must calculate for this:

$$[alb-] = [alb g/L] \times (0.123 \times pH - 0.631)$$
$$[Pi] (in mg/dL) = [Pi]/10 \times pH - 0.47.$$
$$SIG = apparent SID - effective SID$$

The BDE and SIG approaches are consistent with one another and can be derived from a master equation.<sup>52</sup> The Stewart approach more accurately measures the contribution of charge from weak acids that change with temperature and pH.

The weakness of this system is that the SIG does not necessarily represent unmeasured strong anions, merely all anions that are unmeasured. Further, SID changes

#### STRONG ION GAP



**Figure 56-2.** The Strong Ion Gap. A<sub>TOT</sub>, weak acids; SIDa, apparent strong ion difference; SIDe, effective strong ion difference; UMA, unmeasured anion.

quantitatively in absolute and relative terms, when there are changes in plasma water concentration. Fencl and associates<sup>53</sup> addressed this by correcting the chloride concentration for free water (Cl<sup>-</sup>*corr*) using the following equation:

 $Cl^- corr = Cl^- observed \times (Na^+ normal/Na^+ observed)$ 

This corrected chloride concentration may be then inserted into the apparent SID equation above. Likewise, the derived value for unmeasured anions (UMAs) should also be corrected for free water using UMA instead of Cl<sup>-</sup> in the above equation.<sup>53</sup> In a series of nine normal subjects, Fencl and associates estimated the "normal" SIG as  $8 \pm 2\text{mEq/L}.^{53}$ 

Although accurate, the SIG is cumbersome and expensive, requiring measurement of multiple ions and albumin. An alternative approach, used by Gilfix and colleagues,<sup>54</sup> and subsequently by Balasubramanyan and associates<sup>55</sup> and Story and coworkers,<sup>56</sup> is to calculate the base deficit excess gap (BEG; Table 56-3). This allows recalculation of BDE using strong ions, free water, and albumin. The resulting BEG should mirror the SIG and, indeed, the AG.

#### Acid-Base Tools and Outcome Prediction

Lactic acidosis on admission to the emergency room is a marker of severity of illness. The magnitude of acidosis and the degree of elevation of serum lactate correlate well with patient outcomes.<sup>57</sup> Also, the speed of clearance of lactate from the circulation is a known prognostic indicator.<sup>58,59</sup> BD does not reliably reflect lactate in the emergency setting.<sup>60,61</sup> Kaplan and Kellum looked at a variety of acid-base measurements in the acute trauma setting.<sup>62</sup> SIG was superior at predicting outcome versus all other measures. Only one survivor (2% of total) had an SIG greater than 5 mEq/L, and only two nonsurvivors (7%) had an SIG less than 5 mEq/L. Admission pH, HCO<sub>3</sub><sup>-</sup>, and lactate were poor predictors of hospital mortality after trauma.

To date, studies of critically ill patients have failed to demonstrate that SIG predicts outcomes.<sup>63,64</sup> This may be due to the array of different acid-base disturbances that are going on simultaneously. For example, Moviat and colleagues found that unmeasured strong anions

Table 56-3 Calculation of Base Deficit Excess of Sodium, Chloride, and Free Water and Albumin

 $BDE_{NaCl} = ([Na^+] - [Cl^-]) - 38$ 

 $BDE_{Alb}=0.25 \ (42-albumin \ g/L)$ 

 $BDE_{NaCl} - BDE_{Alb} = BDE_{calc}$ 

 $BDE - BDE_{calc} = BDE$  gap = the effect of unmeasured anions or cations

This approach involves calculating the base deficit excess for sodium, chloride, and free water (BDE<sub>NaCl</sub>) and that for albumin (BDE<sub>Alb</sub>). The result is the calculated BDE (BDE<sub>calc</sub>). This is subtracted from the measured BDE to find the BDE gap.

were present in 98%, hyperchloremia was present in 80%, and elevated lactate levels were present in 62% of patients.  $^{65}$ 

#### CONCLUSION

Much of the confusion regarding acid-base chemistry relates to the attempt to apply observational approaches, such as that of Schwartz and Brackett, to the entire spectrum of pathophysiologic processes. The use of physical chemistry principles has improved our ability to teach, understand, and diagnose acid-base abnormalities. All acid-base disorders can be explained in terms of SID,  $A_{TOT}$ , and  $Pco_2$ . This is important to intensivists, who are routinely faced with complex acid-base abnormalities in practice.

#### **AUTHORS' RECOMMENDATIONS**

- A significant acid-base abnormality often signals a sinister underlying problem.
- All acid-base abnormalities result from alterations in the dissociation of water.
- $\bullet\,$  Only three factors independently affect acid-base balance: Pco\_2, SID, and A\_{TOT}.
- Respiratory acidosis and alkalosis are caused by hypercarbia and hypocarbia, respectively.
- Metabolic acidosis is caused by decreased SID or increased A<sub>TOT</sub>. Decreased SID results from accumulation of metabolic anions (i.e., shock, ketoacidosis, and renal failure), hyperchloremia, and free water excess. Increased A<sub>TOT</sub> results from hyperphosphatemia.
- Metabolic alkalosis is caused by increased SID or decreased A<sub>TOT</sub>. The SID increases because of sodium gain, chloride loss, or free water deficit. A<sub>TOT</sub> decreases in hypoalbuminemia and hypophosphatemia. This condition is particularly common in critical illness.
- The AG is accurate only if corrected for albumin.
- The BD and SIG are accurate measures of metabolic acid activity.
- The SIG and BD predict outcomes in emergency medicine and trauma but not critical illness.

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# What Are the Etiology, Pathogenesis, and Pathophysiology of Elevated Intracranial Pressure?

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Intracranial pressure (ICP) refers to the pressure within the cranial vault relative to the ambient atmospheric pressure. Elevated ICP is a common complication of severe brain injury, including traumatic brain injury (TBI), ischemic or hemorrhagic stroke, subarachnoid hemorrhage (SAH), brain tumors, hydrocephalus, and infection. Studies in patients with a number of these conditions demonstrate that ICP is associated with outcome.<sup>1-4</sup> Therefore, ICP monitoring and control are central to the intensive care management of brain-injured patients. However, most management recommendations are based on clinical experience rather than randomized trials. In addition, although several observational or clinical studies demonstrate that ICP control may benefit patient outcome and reduce mortality, the value of an ICP monitor or therapy has yet to be tested in a randomized clinical trial. Given these caveats, it is important to understand ICP physiology and pathophysiology to target appropriate therapy. This chapter reviews ICP physiology; the etiology and pathophysiology of increased ICP, including waveform analysis, compliance, and pressure reactivity; and the pathogenesis of brain edema.

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#### PHYSIOLOGY

#### **Normal Values**

"Normal values" for ICP depend on age, body posture, and clinical conditions. Normal ICP in healthy adults ranges between 7 and 15 mm Hg (i.e., <20 cm H<sub>2</sub>O) in the horizontal position and 10 mm Hg in the vertical position. Values for children are not as well established. Normal values are less than 10 to 15 mm Hg for older children, 3 to 7 mm Hg for young children, and 1.5 to 6 mm Hg for term infants. ICP may be subatmospheric in newborns.<sup>5</sup>

### Intracranial Compartments and the Monro-Kellie Doctrine

In most cases, the location of an organ system has little effect on perfusion and is coupled to atmospheric pressure. The brain differs in this respect because it is surrounded and protected by a noncompliant skull. The cranial vault, once the fontanelles have closed, is a fixed space that contains brain tissue, cerebrospinal fluid (CSF), extracellular fluid, and blood. In the average adult, the skull encloses a total volume of 1475 mL. This includes 1300 mL of brain parenchyma, 65 mL of CSF, and 110 mL of blood. From a simplified standpoint, intracranial volume can be considered brain parenchyma (80% of volume), blood (10% of volume), and CSF (10% of volume).<sup>6</sup> Because brain parenchyma is almost incompressible, the volume of the blood in the cranial cavity remains nearly constant. Therefore, continuous venous outflow is required to make room for entering arterial blood. CSF also drains into the venous system through the arachnoid villi and granulations. Normally, there is little to impede this outflow. As a result, central venous pressure can influence ICP in healthy patients. If the CSF in the vertebral canal also is considered, the entire system has limited capacitance.

ICP is the pressure exerted by the cranial contents on the dura mater. Pressure is built up by arterial influx and depends on the volume, and hence partial pressure (P), of each component of the skull's contents. ICP therefore is calculated as follows:

$$ICP = P_{brain} + P_{blood} + P_{CSF}$$

When one pressure increases (e.g., when cerebral edema occurs and P<sub>brain</sub> increases), the other pressures will change in the opposite direction to keep ICP constant. This is known as the *Monro-Kellie doctrine*. In the normal adult, ICP can and often does transiently increase, such as during coughing or other Valsalva maneuvers. These increases are not considered pathologic, and several compensatory mechanisms keep ICP within normal limits:

- Shift of CSF from the ventricular or the subarachnoid space into the spinal compartment
- · Removal of blood from the cerebral venous vessels
- Increased CSF absorption

If the limits of these compensatory mechanisms are exceeded by an increase in the pressure in one of the three compartments (brain, blood, CSF), ICP increases. Only a few milliliters increase in the volume of any compartment



**Figure 57-1.** Intracranial compartments. CSF, cerebrospinal fluid; ICP, intracranial pressure.

may elevate ICP (Fig. 57-1). This relation is reflected in the pressure-volume curve (see later) or elastance ( $\Delta P/\Delta V$ ). This curve is exponential and the reciprocal of compliance ( $\Delta V/\Delta P$ ). Elastance is greatest in children and lowest in old adults.

#### **Increased Intracranial Pressure**

ICP thresholds above which therapy is started depend on age and disease. They may vary from 15 (e.g., hydrocephalus) to 25 mm Hg. There is no level I evidence that one single ICP threshold should be used to initiate therapy. However, an ICP greater than 20 mm Hg that persists for 5 minutes or more is a generally accepted threshold.<sup>7</sup> Most bedside ICP monitors display the mean ICP numerically or display a pulse waveform. This information is used to guide ICP treatment or treatment protocols (e.g., the Lund concept<sup>8</sup> or a cerebral perfusion pressure [CPP]-based protocol<sup>9</sup>). Recent advances in data processing and computerized multimodal bedside monitoring have made it possible to perform online, real-time analysis of the interdependence between the dynamic behaviors of the regulatory processes of ICP. Accordingly, ICP is now considered "more than a number," and secondary ICP variables such as pulse amplitude, index of compensatory reserve, or pressure-reactivity index (PRx) can be used to guide therapy even when the numerical value of ICP is normal. Finally, it is important to realize that ICP is not always homogeneous within the skull because of anatomic compartmentalization. The falx cerebri and the tentorium cerebelli may prevent even distribution of the pressure exerted by mass lesions. The subsequent pressure gradients may be as great as 30 mm Hg and may produce herniation.

Several pathologic conditions (e.g., brain edema, spaceoccupying lesion, obstruction of CSF pathway) that disturb intracranial volume or circulation may provoke an increase in ICP (Table 57-1; see Fig. 57-1). These can occur individually or in various combinations. In general, there are two components to increased ICP:

• Vascular component of ICP ≈ mean arterial pressure (MAP) and cerebral venous outflow

#### Table 57-1 Causes of Increased Intracranial Pressure

#### **INTRACRANIAL (PRIMARY)**

Trauma

Mass lesion (e.g., epidural or subdural hematomas, hemorrhagic contusions) Depressed skull fracture Brain edema Hyperemia (vasomotor paralysis or loss of autoregulation) Hydrocephalus Extracranial causes (see below) Nontraumatic intracranial hemorrhage Intracerebral Subarachnoid Ischemic stroke Hydrocephalus Communicating Obstructive Brain tumor Seizures Cerebral vasospasm Infection (e.g., meningitis, abscess, or subdural empyema) Pseudotumor cerebri Idiopathic intracranial hypertension EXTRACRANIAL (SECONDARY)

#### Airway obstruction Hypoventilation Hypoxia Hypercarbia (cerebral vasodilation) Hypertension Head position or posture Venous outflow obstruction Hyperpyrexia Agitation, pain Increased intrathoracic or intra-abdominal pressure (e.g., multicompartment syndrome, Valsalva maneuvers) Liver failure Altered sodium balance Hypoglycemia or hyperglycemia High altitude sickness (brain edema) Drugs (e.g., lead intoxication, tetracycline)

• CSF component of ICP  $\approx$  resistance to CSF outflow  $\times$  CSF formation

Intracranial pressure also may be increased after neurosurgical procedures. This may occur because of a postoperative hematoma, exacerbation of brain edema, disturbance of CSF flow, hyperemia (vasodilation or normal perfusion pressure breakthrough), seizures, or a variety of extracranial causes (see Table 57-1).

Intracranial regulatory processes for ICP are complex and dynamic. However, an understanding of this pathophysiology is important for appropriate ICP treatment, to avoid excessive vasopressor use in CPP-oriented therapy, or to better predict outcome after TBI. In 1960, Lundberg<sup>10</sup> introduced ICP waveform analysis and described slow ICP waves and their pathologic significance. Several years later, Langfitt and colleagues<sup>11</sup> and Lofgren and associates<sup>12</sup> developed the pressurevolume curve and the concept of compensatory reserve. This led to an understanding of brain compliance<sup>13,14</sup> and the development of derived indices of cerebrovascular reactivity (PRx) and cerebrospinal compensatory reserve (RAP).<sup>15,16</sup> These indices provide an approximation of the cerebrovascular autoregulatory reserve.<sup>17</sup> Each of these various measures provides insight into a patient's reserve or how "sick" the brain is. For example, a patient with an ICP of 20 mm Hg, a high RAP index (+1; low compensatory reserve), and a high PRx (>0.3; impaired pressure reactivity) is at much greater risk than a patient with the same ICP but normal indices and waveform. These pathophysiologic differences may be reflected in the therapeutic intensity level (TIL), which is a quantitative measure of what management is required to control ICP.<sup>18</sup> The greater the TIL, the "more" therapy and more complex therapies are required to control ICP (i.e., the "sicker" the patient). This information is important because every aspect of ICP management has potential deleterious side effects. Thus, selecting a therapy that does not cause extracranial complications (e.g., lung injury) may become critical.

#### **Intracranial Pressure Waveform Analysis**

The ICP waveform is made up of three distinct quasiperiodic components: heart (pulse) rate, respiratory waves, and slow vasogenic waves. The ICP fluctuates with the hemodynamic cycle because of arterial perfusion. In ventilated patients, this is superimposed on the pressure cycle produced by the ventilator. The displayed ICP number on a monitor is the mean pressure. Depending on the software used, it is calculated over one or more hemodynamic and ventilatory cycles. It is the mean value of a complex, cyclic waveform, and although the three waveform components overlap on a background of randomly changing mean ICP, they can be isolated and quantified using spectral analysis.

The ICP pulse waveform (Fig. 57-2) has a fundamental frequency equivalent to the heart rate (i.e., vascular origins) and several harmonic components. Over time, on a monitor, there are three different typical patterns: spontaneous changes, A waves and B waves, and induced changes.



Figure 57-2. Intracranial pressure pulse waveform.

#### Spontaneous Changes

Many patients have a relatively low and stable ICP. However, stable but elevated ICP can be seen most of the time in brain-injured patients. "A" waves or plateau waves comprise a steep increase in ICP (ICP spikes) from near-normal values to 40 mm Hg or more persisting for 5 to 20 minutes. These waves reflect poor compensatory reserve and limited intracranial compliance. In general, they are ominous. "B" waves are short-lasting ICP oscillations that occur at 0.5 to 2 waves/minute; at ICP greater than 20 mm Hg, they are related to changes in vascular tone. Although B waves are more benign than A waves, they also indicate that intracranial compliance reserves are compromised.

#### Induced Changes

ICP changes may occur secondary to changes in MAP, cerebral blood flow (CBF), or cerebral blood volume (CBV). In addition, changes in abdominal or thoracic pressure may alter CBV and therefore induce ICP changes. Finally, pain and agitation are important contributors to ICP elevations.

#### **Intracranial Compliance**

Intracranial compliance is defined as the change in volume (V) over the change in pressure (P),  $\Delta V/\Delta P$ . The relationship between ICP and intracranial volume is expressed by the nonlinear pressure-volume curve (Fig. 57-3). Compliance decreases as intracranial volume increases. Three zones can be described:

 Good compensatory reserve (flat part of the P-V curve): a volume change produces no or very little pressure change because CSF is displaced into the spinal thecal sac and blood is decompressed from distensible cerebral veins to compensate for the added volume.



**Figure 57-3.** Pressure-volume curve (brain compliance =  $\Delta V / \Delta P$ ).

- 2. *Poor* compensatory reserve (steep part of the P-V curve): any further increase in volume, however small, may produce a rapid increase in ICP because the compensatory mechanisms are depleted.
- 3. *Exhausted* compensatory reserve: critical ICP, corresponding to a terminal disturbance in cerebro-vascular response at very high ICP, where ICP equals MAP.

The amplitude and shape of the ICP pulse wave may provide a clue that compliance is reduced. As compliance decreases, the ICP pulse amplitude increases. In addition, the normal waveform (amplitude of P1>P2>P3) is changed, and P2 amplitude becomes larger (see Fig. 57-2). Simple bedside tests, such as gentle pressure on the abdomen, that are associated with an increase in P2 amplitude or mean ICP suggest reduced compliance.

### Pressure-Volume Compensatory Reserve and RAP Index

The compensatory reserve of the intracranial compartment can be examined using the relationship between the mean ICP and changes in volume of the intracerebral space, or pressure-volume curve. This relationship is known as RAP (correlation coefficient [R] between the amplitude of the fundamental component [A] and mean pressure [P]) and is derived by calculating the linear correlation between consecutive, time-averaged (6- to 10second) data points of the amplitude of the fundamental component and ICP (about 40 samples). RAP and the pressure-volume index are not one and the same thing. The pressure-volume index characterizes the steepness of the pressure-volume curve whereas the RAP indicates where on the curve (i.e., on its flat or steep part) the system works.

When the RAP coefficient is near 0, there is a good pressure-volume compensatory reserve at low ICP, and a volume change produces no or very little ICP change. When the RAP increases to +1, the compensatory reserve is low; therefore, any further volume increase may produce a rapid ICP increase. When ICP increases, RAP values can be less than 0. This occurs when the cerebral autoregulatory capacity is compromised. A low RAP at

an ICP of greater than 20 mm Hg often indicates terminal cerebrovascular disturbance and pulse pressure transmission from the arterial bed to the intracranial compartment. During plateau waves, when maximal vasodilation occurs, RAP decreases from +1 to 0 or less, indicating a state of cerebrovascular deterioration.<sup>15</sup> Similarly, during refractory intracranial hypertension, switching from positive to low or negative RAP values indicates that the critical level of ICP has been exceeded. Above this threshold, normal cerebrovascular mechanisms fail, and cerebral ischemia may cause irreversible brain damage.<sup>19</sup> After successful decompressive craniotomy, a decrease in RAP (from about +1 to 0) indicates recovery of good compensatory reserve.<sup>20</sup> Increased ICP (>20 to 25 mm Hg) can be associated with fatal outcome.<sup>21</sup> Similarly, low average RAP is associated with worse outcome, independent of ICP.<sup>15</sup> The product of the mean ICP  $\times$  (1 – RAP) also is thought to be an indicator of dangerous intracranial hypertension. The relationship of ICP  $\times$  (1 – RAP) and outcome appears to be stronger than ICP and RAP alone.<sup>22</sup>

### Cerebral Perfusion Pressure and Cerebral Autoregulation

The main untoward consequence of increased ICP is reduced CPP. This will reduce CBF and may lead to secondary hypoxic-ischemic injury. CPP is calculated as MAP minus ICP:

CPP = MAP – ICP, where MAP  
= 
$$\frac{1}{3}$$
 systolic blood pressure (BP) +  $\frac{2}{3}$  diastolic BP

CPP can be reduced by an increase in ICP, a decrease in blood pressure, or a combination of both factors. In turn, CPP is the pressure gradient across the cerebrovascular bed and so is an important determinant of CBF regulation. Normally, autoregulation of the cerebral vasculature maintains CBF at a constant level between CPP of 50 and 150 mm Hg (i.e., *normal cerebral autoregulation*). However, when CPP is less than 50 mm Hg, the brain may not be able to compensate adequately, and CBF falls passively with CPP.

Brain injury can impair autoregulation and cause the CPP/CBF relationship to approach linearity; that is, CBF may become *dependent* on CPP. When this occurs, CBF can passively follow changes in CPP even within a normal range of CPP. Any reduction of CPP (caused by an increase of ICP or a decrease of MAP) then may induce a critical reduction of CBF, ultimately leading to ischemia and cerebral infarction. Although the optimal CPP for each patient may vary, it is suggested that, in general, CPP should be greater than 50 to 60 mm Hg (to avert ischemia) and less than 110 mm Hg (to avoid break-through hyperperfusion and cerebral edema). Current TBI guidelines suggest that the optimal CPP is between 50 and 70 mm Hg.<sup>23</sup>

Normal autoregulation means that an increase of MAP results in a decrease of ICP, whereas the opposite is true in conditions of impaired autoregulation, such as after severe brain injury. When CPP is within the normal autoregulatory range (50 to 150 mm Hg), the ability of

the brain to pressure-autoregulate also affects the response of ICP to a change in CPP.<sup>24–26</sup> When pressure autoregulation is intact, decreasing CPP results in vasodilation of cerebral vessels, allowing CBF to remain unchanged. The vasodilation can result in an increase in ICP that further decreases CPP. This response has been called the *vasodilatory cascade*. Similarly, an increase in CPP results in vasoconstriction of cerebral vessels and may reduce ICP. When pressure autoregulation is impaired or absent, ICP decreases and increases with changes in CPP.

#### Cerebrovascular Reactivity and the Pressure-Reactivity Index

Cerebrovascular regulation and reactivity can be assessed at the bedside by the PRx, another ICP-derived index. PRx is a simple continuous dynamic index that quantifies cerebrovascular reactivity and approximates global cerebral autoregulatory reserve by observing the response of ICP to slow spontaneous changes in MAP.<sup>16,17</sup> That is, PRx makes use of existing physiologic parameters (MAP and ICP) that are routinely monitored in the intensive care unit. PRx is determined by calculating the correlation coefficient between 30 and 40 consecutive time-averaged ICP and MAP data points obtained at 10-second intervals. To do this requires similar computational methods to those used to derive RAP.

PRx ranges between 1 and -1. A negative (-1 to 0) PRx indicates no correlation between ICP and MAP (preserved autoregulation), whereas a positive (0 to 1) PRx indicates a positive correlation between ICP and MAP (impaired autoregulation). A PRx of 0.3 is the critical value above which pressure reactivity is impaired.<sup>25</sup> Several clinical studies demonstrate that PRx correlates well with transcranial Doppler-based indices of autoregulation or positron emission tomography-assessed measures of CBF or cerebral metabolic rate of oxygen (CMRO<sub>2</sub>).<sup>27</sup> Abnormal PRx values are associated with poor outcome after TBI and may be independent of mean ICP and injury severity.<sup>19</sup> The PRx indicates that pressure-reactivity information provided the pressure-volume curve has an exponential shape. Consequently, in some patients after decompressive craniectomy, the PRx may deteriorate because the P-V curve becomes flat.<sup>28</sup> Usually, PRx is impaired (>0.3) when ICP is elevated. After surgical decompression for intractable ICP, the mean PRx returns to autoregulatory values. The improvement generally is greater among patients who have a favorable outcome.<sup>29</sup>

#### Brain Edema

Brain edema is a common feature in patients with severe brain injury of various causes. Pappius<sup>30</sup> defined brain edema as an increase in net brain water content that causes an increase in tissue (i.e., intracranial) volume. This swelling is a major underlying pathophysiologic mechanism of intracranial hypertension. The ICP increase may contribute to death and poor prognosis among survivors of severe brain injury.<sup>1,4,31–37</sup> In TBI, brain swelling is classified into four grades of severity based on the initial head computed tomography (CT) finding.<sup>31,32</sup> The severity of swelling observed on the first head CT scan is associated with outcome in large part because of the exponential relationship between ICP and brain water content.<sup>33,34</sup> Hence, it is important to understand the pathogenesis of cerebral edema to better control and treat ICP.

Brain edema can be classified into four principal types:

- *Vasogenic*, due to increased permeability of capillary endothelial cells and blood-brain barrier disruption, resulting in extracellular water accumulation
- *Cytotoxic*, due to increased sodium and potassium permeability in astrocytic and neuronal cell membranes and cell energy depletion, leading to sustained intracellular water accumulation
- *Osmotic*, due to osmotic imbalance of active electrolytes between blood and tissue, such as syndrome of inappropriate antidiuretic hormone
- *Hydrocephalic/interstitial,* related to an obstruction of CSF outflow

After brain ischemia or trauma, vasogenic and cytotoxic edema are observed most often.<sup>38,39</sup> The cause of brain edema after intracerebral hemorrhage, however, remains uncertain. Recent studies using magnetic resonance imaging have attempted to characterize the predominant cause of brain edema according to the primary brain injury. After ischemic injury, brain edema characteristically is greatest 24 to 72 hours after the inciting event. Cytotoxic edema is seen first and is associated with cell energy failure that results in intracellular fluid accumulation. This results in shifts in sodium and potassium between intracellular and extracellular brain compartments. Eventually, with ongoing ischemia, the blood-brain barrier is disrupted, and vasogenic edema develops. Edema after TBI was thought to be vasogenic in origin and to be associated with blood-brain barrier opening. However, recent clinical and experimental studies indicate that cellular (cytotoxic) edema is predominant after TBI.40 Trauma leads to a cascade of events that include mechanical deformation, neurotransmitter release, mitochondrial dysfunction, and membrane depolarization. These events lead to loss of ionic homeostasis with an increase in extracellular K<sup>+</sup> and a decrease in extracellular Na<sup>+</sup>, Ca<sup>2+</sup>, and Cl<sup>-</sup>. The movement of Na<sup>+</sup> and Ca<sup>2+</sup> is followed by passive Cl<sup>-</sup> and water diffusion to maintain ionic and osmotic balance. If this disturbance in ionic homeostasis persists, cellular swelling and cytotoxic edema result.

Treating cellular edema is problematic because we are only beginning to understand exactly how water enters the cell. However, a better understanding of the underlying mechanisms of brain edema may provide new and more effective treatments (e.g., hypothermia, decompressive craniectomy). This improved understanding also may explain why drugs that attenuate vasogenic brain edema (e.g., corticosteroids) are beneficial in certain conditions<sup>41</sup> but not in others (e.g., TBI).<sup>42</sup> The recent discovery of aquaporins, a family of water-conducting ubiquitously distributed protein-based channels, may provide a mechanistic insight.<sup>43</sup> Approaches that focus on the aquaporins may open new therapies to attenuate brain edema<sup>44</sup> and thus increased ICP.

#### **AUTHORS' RECOMMENDATIONS**

- ICP is the pressure within the cranial vault and is related to the volume of brain tissue, CSF, extracellular fluid, and blood in the skull.
- Elevated ICP is a common complication of several neurologic disorders and if untreated can cause herniation and death.
- ICP is a complex parameter that, when carefully analyzed, contains information about cerebral compensatory mechanisms and mechanisms that contribute to CBF regulation.
- ICP control requires continuous ICP monitoring and integration of the additional information contained in the ICP waveform and its relationship to MAP.
- An understanding of the underlying pathophysiology of elevated ICP may improve the clinical management and outcomes of brain-injured patients.

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# B How Should Traumatic Brain Injury Be Managed?

Larami MacKenzie, W. Andrew Kofke

Traumatic brain injury (TBI) affects about 1.5 million Americans annually. This involves 1.2 million emergency department visits, 290,000 hospitalizations, and a mortality rate of nearly 51,000.<sup>1</sup> Of those who survive, a substantial proportion are left with significant disability. Thus, nearly 5.3 million people alive today in the United States have TBI-related disability. TBI is a growing problem worldwide, with motor vehicle crashes predicted to become the third leading cause of global burden of disease and injury by 2020, in part owing to the increasing use of motor vehicles in low- and middle-income countries.<sup>2,3</sup> In richer countries where safety measures such as speed limits and safety belts have become a major public safety initiative, TBI still is a leading cause of death and disability among young people. The elderly population is increasingly at risk for TBI due to falls. Prompt diagnosis, treatment of secondary processes, and anticipation of complications may improve outcome. This possibility is reflected in the progressive reduction in TBI mortality from 50% to less than 25% during the past 3 decades.<sup>4</sup>

This chapter reviews major clinical management points and discusses the relevant literature. We follow and summarize the general format of the Brain Trauma Foundation (BTF) management guidelines,<sup>5</sup> briefly reviewing multiple aspects of TBI management. Those specific studies that are included were evaluated using GRADE criteria, as detailed in Table 58-1.

# PATHOPHYSIOLOGY AND MECHANISM OF ACTION

The pathophysiology of TBI and intracranial hypertension is reviewed elsewhere in this book (see Chapter 57). Briefly, in TBI, there are two main sources of injury: the initial mechanical impact, torsion, and shear injury and the secondary injury processes. These include swelling that raises the intracranial pressure (ICP) and threatens to oppose perfusion. Diminished perfusion leads to ischemia. The principal therapeutic strategies described later focus on maintaining perfusion and oxygenation as well as reducing ICP and preventing or attenuating additional complications and tertiary injury (e.g., seizures, malnutrition, and venous thrombosis) related to critical illness and immobility.

#### **BLOOD PRESSURE AND OXYGENATION**

#### Background

Secondary processes after injury are major contributors to outcome after TBI.<sup>6,7</sup> Both hypotension and hypoxemia contribute to poor outcome post injury. Prehospital studies report that hypoxemia is associated with a significantly (14.3% to 50%) increased mortality and disability in survivors.<sup>8,9</sup> An in-hospital study reported that hypoxemia was an independent predictor of mortality.<sup>7</sup> Similar results have been reported with prehospital and in-hospital hypotension.<sup>10</sup> A single episode of hypotension with a systolic blood pressure lower than 90 mm Hg was associated with increased morbidity and doubled mortality.<sup>8</sup>

#### Evidence

A series of prospective studies by Vassar and colleagues<sup>11</sup> evaluating resuscitative fluids used before hospital admission in hypotensive trauma patients demonstrated that hyperosmolar fluid resuscitation (7.5% hypertonic saline [HTS]  $\pm$  Dextran) more effectively raised blood pressure than isotonic solutions, and patients who received hyperosmolar resuscitation had better outcomes than predicted. In the subset of trauma patients with a Glasgow Coma Scale (GCS) score of 8 or less, the hyperosmolar treatment group fared significantly better than the isotonic group. A follow-up prospective study looking specifically at prehospital resuscitation of hypotensive TBI patients did not confirm the observation that hyperosmolar therapy improved neurologic outcome.<sup>12</sup>

#### Recommendations

Hypoxemia and hypotension are significant comorbid risks associated with TBI. GRADE B evidence supports a threshold value of 90 mm Hg systolic and  $Pao_2$  mm Hg less than 60 with  $O_2$  saturation less than 90%, respectively.

#### HYPEROSMOLAR THERAPY

#### Background

Mannitol is the prototypical agent used for hyperosmolar therapy to reduce intracranial hypertension and increase

## Table 58-1The GRADE System: Determinationof the Quality of Evidence

#### UNDERLYING METHODOLOGY

А	RCT					
В	Downgraded RCT or upgraded observational studies					
С	Well-done observational studies					
D	Case series or expert opinion					
FACTOR OF EV	RS THAT MAY DECREASE THE STRENGTH					
1	Poor quality of planning and implementation of available RCTs suggesting high likelihood of bias					
2	Inconsistency of results (including problems with subgroup analyses)					
3	Indirectness of evidence (differing population, intervention, control, outcomes, comparison)					
4	Imprecision of results					
5	High likelihood of reporting bias					
MAIN FACTORS THAT MAY INCREASE THE STRENGTH OF EVIDENCE						
1	Large magnitude of effect (direct evidence, $RR \ge 2$ with no plausible confounders)					
2	Very large magnitude of effect with $RR \ge 5$ and no threats to validity (by two levels)					
3	Dose-response gradient					

RCT, randomized controlled trial; RR, relative risk.

cerebral perfusion pressure (CPP).<sup>13</sup> Various mechanisms of action have been suggested. HTS is another useful hyperosmolar therapy. Its primary mechanism of action also is thought to be mobilization of fluid across the intact blood-brain barrier to reduce cerebral water content and thus decrease ICP. The novel agent hypertonic sodium lactate (HTSL) should work through a mechanism similar to hypertonic saline.<sup>14</sup>

#### **Evidence**

Although there are few trials comparing these therapies head to head in equiosmolar doses, it is generally held that mannitol, HTS, and HTSL effectively reduce ICP in TBI. Compared with pentobarbital coma, 20% mannitol given as an initial bolus of 1 g/kg and repeated as necessary to keep ICP < 20 mm Hg and osmolality less than 320 mOsm/L more effectively controlled CPP, ICP, and mortality (GRADE C), especially in cases of diffuse brain injury (i.e., no evacuable hematoma).<sup>15</sup> Some guidelines suggest that intermittent bolus therapy of mannitol is superior to continuous infusion. However, data are inadequate to make a firm conclusion regarding the two infusion schedules.<sup>13,16,17</sup> Several studies report efficacy of HTS in decreasing ICP, notably being effective as rescue therapy in cases in which ICP is refractory to mannitol.<sup>18,19</sup> A trial evaluating equiosmolar doses of mannitol and 3% HTS in the operating room revealed equivalent effect on "brain relaxation," suggesting equivalent ICP reduction with equiosmolar therapy.<sup>20</sup>

A small but well-designed trial of 34 patients comparing boluses of 1.5 mL/kg of half-molar HTSL with 20% mannitol (in equiosmolar doses of 1100 or 1160 mOsm/L, respectively) suggested that HTSL provides a larger and more prolonged decrease in ICP in TBI patients as well as a better neurologic outcome at 1 year (P = .024).<sup>14</sup> Another prospective randomized study of 20 TBI patients looked at the effect of equivalent volumes of 7.5% HTS and 20% mannitol (2400 mOsm/kg HTS, 1160 mOsm/kg mannitol), showing a lower incidence of treatment failure with HTS.<sup>21</sup> A recent study using brain tissue oxygen monitoring in TBI found that, compared with 0.75 g/kg 20% mannitol, 7.5% HTS boluses were associated with lower ICP and higher CPP and cardiac output. They concluded that in patients with severe TBI and elevated ICP refractory to previous mannitol treatment, 7.5% hypertonic saline administered as second-tier therapy is associated with a significant increase of brain oxygenation and improved cerebral and systemic hemodynamics.<sup>22</sup>

#### Recommendations

Mannitol, HTS, and HTSL are effective in reducing elevated ICP (GRADE C evidence, strong recommendation).

Small studies suggest superiority of HTS (GRADE C) and HTSL (GRADE B) in terms of ICP reducing efficacy. Nonetheless, the critical question remains of whether one hyperosmolar therapy is superior to another, or whether more therapeutic osmoles are simply better than fewer. To date, no large randomized studies have compared equiosmolar doses of the different osmolar treatments and their impact on overall outcome such that recommendations regarding relative merits of the agents can be confidently made. GRADE C evidence supports the use of HTS when mannitol fails.

#### SURGICAL DECOMPRESSIVE THERAPY

#### Background

The use of decompressive craniectomy to control elevated ICP has a long history dating to the early 20th century.<sup>23–25</sup> Only recently has the procedure started to undergo scrutiny for impact on outcome.

#### Evidence

Decompressive hemicraniectomy or bifrontal craniectomy (Kjellberg procedure) is a relatively simple procedure involving removal of a portion of the skull without replacement of the bone flap. It is logical that removal of a unilateral or bilateral bone flap ought to control ICP in TBI, and there is clinical evidence that ICP decreases significantly after decompression.<sup>26–28</sup> Recently, three randomized controlled trials (RCTs) were combined and subjected to meta-analysis. This supported decompressive craniectomy for malignant edema after ischemic stroke.<sup>29</sup>

However, there is a dearth of published controlled trials evaluating decompression after TBI in adults.<sup>30</sup> There is a single randomized trial of early decompressive craniectomy in children with TBI. This revealed a relative risk (RR) of 0.54 for both death (95% confidence interval [CI], 0.17 to 1.72) and unfavorable outcome (95% CI, 0.29 to 1.01).<sup>31</sup> In adults with TBI, there currently are two active trials in process, RESCUEicp and DECRA, that aim to provide randomized, prospective evidence supporting the role of surgical decompression in TBI.

Cerebrospinal fluid (CSF) diversion is widely used in patients with intracranial hypertension as part of first-tier or standard management, but it has not been methodically investigated.<sup>32</sup>

The dose response of CSF drainage through the extraventricular approach confirms that small reductions in CSF volume robustly influence ICP; however, there are no published series specifically addressing outcomes using this approach to CSF drainage.<sup>33</sup> *Practically, it seems many neurosurgeons embrace the evidence behind CSF diversion but prefer to use the ventricular approach.* 

#### Recommendations

In adults, we cannot currently recommend early decompression as first-line therapy; however, the procedure appears safe, and GRADE C evidence suggests it may prove effective after other less invasive measures (e.g., head elevation, light sedation, and hyperosmolar therapy with mannitol or a hypertonic sodium salt) have failed. GRADE C evidence supports CSF diversion for control of intracranial hypertension in TBI. However, the safest and most effective approach has not yet been defined. There is widely acknowledged historical concern that the lumbar approach will facilitate downward herniation and death.

#### PROPHYLACTIC HYPOTHERMIA AND THERAPEUTIC NORMOTHERMIA

#### Background

Brain injury is worsened by increased temperature. There are multiple mechanisms, including potentiation of inflammatory cascades and elevated metabolic rate, that worsen the gap of metabolic debt. Studies of ischemic stroke and outcome show that admission temperature correlates with mortality.<sup>34,35</sup> Elevated body temperature contributes to length of stay in a multitude of diagnoses requiring neurocritical care.<sup>36</sup> Many neurointensivists take it as a given that fever should not be allowed, enforcing the "conservative measure" of "strict normothermia" using acetaminophen at least and sometimes progressing to fans, ice packs, and even surface cooling and antirigor therapies as intense as neuromuscular blockade. Hypothermia is thought to have value in TBI as both an ICP reducing therapy<sup>37–39</sup> and as a specific neuroprotectant.

#### Evidence

There has not been a randomized trial of therapeutic normothermia versus permissive temperature or normothermia using conservative measures such as acetaminophen alone in TBI. However, there is nonrandomized evidence that endovascular therapeutic normothermia reduces ICP.<sup>40</sup> Studies have been conflicting regarding the efficacy of prophylactic hypothermia in TBI. A randomized, prospective multicenter trial<sup>41</sup> failed to show improvement with hypothermia in TBI patients. This study was followed by an analysis of possible reasons for the negative outcome despite uniform evidence of neuroprotection in preclinical studies. The analysis indicated that outcomes were better in highvolume centers and that there was significant heterogeneity between medical centers in specific therapeutic protocols that were implemented.<sup>42</sup> Several meta-analyses concluded that evidence was insufficient to recommend the use of prophylactic hypothermia in TBI.<sup>43–47</sup> However, a recent meta-analysis by the Brain Trauma Foundation<sup>34</sup> was designed to include studies to minimize heterogeneity. Thirteen trials were judged to meet the inclusion criteria. Six were considered level II and seven level III studies. The meta-analysis only included the level II studies. Although a mortality effect favoring hypothermia was not quite significant (RR, 0.76; 95% CI, 0.55 to 1.05), this analysis did indicate a statistically significant 46% increased chance of a good outcome in the hypothermic patients (RR, 1.46; 95% CI, 1.12 to 1.92). Further analysis indicated that a minimum duration of 48 hours of induced hypothermia was needed to see a protective effect and that this treatment was associated with an increased risk for pneumonia. The BTF and American Association of Neurological Surgeons thus issued a level III recommendation for cautious and selective use of moderate hypothermia for TBI. More recently, a case series comparing prophylactic hypothermia at 33°C (n = 31) versus 35°C (n = 38) in TBI cases with GCS score of 5 or less found equivalent ICP control at the milder hypothermia target with fewer side effects such as hypokalemia, pneumonia, ventricular tachycardias, pulmonary embolus, renal failure, and tendency to lower mortality (27% versus 48%; P = .0801).<sup>37</sup>

#### Recommendations

In severe TBI, there is GRADE C evidence for selective and cautious application of prophylactic moderate hypothermia to 32° to 35°C for 48 hours. The higher temperature may provide equivalent ICP control with fewer adverse effects. Rewarming should be done slowly to minimize the possibility of a rebound increase in ICP. Therapeutic normothermia using endovascular cooling is supported by GRADE D evidence.

#### INDICATIONS FOR INTRACRANIAL PRESSURE MONITORING

This is reviewed in Chapter 57.

# INTRACRANIAL PRESSURE MONITORING TECHNOLOGY

This is reviewed in Chapter 57.

#### INTRACRANIAL PRESSURE THRESHOLDS

#### Background

Elevations in ICP can be due to either hyperemic vasodilation in the context of impaired intracranial compliance or oligemia due to edema or non-neural masses.<sup>48,49</sup> The risk incurred with ICP elevation is ischemic damage or herniation.

#### Evidence

There are no prospective randomized studies designed to determine the threshold for initiation of ICP reducing therapy. Several prospective observational studies reviewed in the BTF review suggest that outcome is better when ICP is kept less than 20 to 25 mm Hg and that herniation is more likely above these thresholds. However, in situations without intracranial mass lesions, ICP greater than 20 mm Hg has been reported to be tolerated.<sup>50</sup>

#### Recommendation

Despite an absence of evidence, in most cases, an ICP higher than 20 to 25 mm Hg should be an indication to increase ICP-reducing therapy.

#### CEREBRAL PERFUSION THRESHOLDS

#### Background

CPP is an important element in determining cerebral blood flow (CBF). Given that a main goal in treatment of TBI is the provision of adequate CBF, decisions regarding CPP goals increase in importance.

#### Evidence

Low CPP, produced by either systemic hypotension or intracranial hypertension is associated with poor clinical outcome.<sup>51,52</sup> Numerous studies using physiologic surrogate end points for cerebral ischemia were reviewed in the BTF meta-analysis.<sup>51</sup> Surrogate measures included (1) decreased CPP to produce ICP rise due to vasodilation, (2) decreased PbrO<sub>2</sub>, (3) increased lactate-to-pyruvate ratio on microdialysis, (4) altered transcranial Doppler waveform, and (5) abnormal jugular venous saturation. A synthetic evaluation of these reports suggests physiologic evidence of cerebral ischemia arises with CPP of 50 to 60 mm Hg or less.<sup>51</sup>

Initial studies evaluating the impact of therapeutically elevated CPP indicated that there might be an improved outcome with this approach.<sup>53,54</sup> This was attractive physiologically. Rosner and coworkers postulated that this approach would promote lower cerebral blood volume due to reflex vasoconstriction in regions of intact autoregulation and thus decrease ICP.<sup>55,56</sup> Subsequent studies, however, have been unable to reproduce these findings.<sup>57</sup> Moreover, studies comparing therapy based on CPP with ICP-based interventions reported a higher incidence of acute respiratory distress syndrome (ARDS), catecholamine

use, and refractory intracranial hypertension with CPPtargeted therapy.<sup>58,59</sup> Given the heterogeneity of the TBI patient population, one explanation may be that CPPtargeted approaches will need to be tailored to each patient's specific pathophysiology.

#### Recommendation

Based on GRADE C microdialysis data, a CPP of less than 50 mm Hg is associated with cerebral ischemic markers and is to be avoided. Data suggest that a CPP of 50 to 70 mm Hg is adequate but that higher CPP may be tolerated when autoregulation is intact. GRADE A RCT evidence shows that therapeutic hypertension to achieve a CPP of 70 mm Hg or more increases the risk for ARDS fivefold without a concurrent improvement in neurologic outcome versus an ICP-targeted strategy. Adjunctive physiologic monitors of brain oxygenation, metabolism, and blood flow may be helpful in individualized CPP decisions.

# BRAIN OXYGEN MONITORING AND THRESHOLDS

#### Background

The primary goal of postinjury management of TBI is to prevent or attenuate deleterious secondary processes. One element of this is evaluation and maintenance of adequate CBF.<sup>60</sup> However, there are no adequate continuous monitors of CBF at this time. Therefore, monitors of continuous cerebral oxygenation have been used as indirect indicators of blood flow adequacy relative to metabolism. This may be accomplished through a sensor in the jugular bulb or an electrode placed directly into brain tissue. From a theoretical perspective, both monitors have conceptual flaws. Monitoring depends on an element of global homogeneity. If this is not so, a substantial decrement in flow in one part of the brain but not in others may be missed.  $PbrO_2$  (partial pressure of  $O_2$  in the brain) suffers from excess focality such that changes occurring in the vicinity of the probe may not be reflective of the entire brain.

#### Evidence

In the BTF meta-analysis, numerous studies of jugular bulb oxygen monitoring in TBI were reviewed. An association with worse outcome is suggested by episodes of SjvO<sub>2</sub> (the jugular venous saturation of oxygen from the jugular bulb) of less than 50%. This may be due to ischemia. Episodes of SjvO<sub>2</sub> higher than 75% also were associated with poor outcomes. This suggests the presence of hyperemia due to dysautoregulation or infarction. These studies suggest that SjvO<sub>2</sub> be kept between 50% and 75%. However, there are no randomized prospective studies that test this hypothesis. Cruz and Cruz<sup>61</sup> reported that improved outcome when TBI patients were managed with adjunctive SjvO<sub>2</sub> monitoring as opposed to CPP-based management. However, the study was not randomized or blinded.

The BTF meta-analysis of brain tissue  $O_2$  monitoring in TBI indicates that low  $Pbro_2$  (<15 mm Hg) is associated with poor outcome. Moreover, depth and duration of

brain hypoxia also appear to be important factors. Using historical controls, Stiefel and colleagues<sup>62</sup> compared the impact of a change in local practice to use PbrO<sub>2</sub> to guide therapy and reported a significant improvement in outcome. This report was neither prospective nor randomized, and the historical controls had a higher mortality than would otherwise have been expected.

#### Recommendations

GRADE C evidence supports use of SjvO<sub>2</sub> and Pbro<sub>2</sub> monitoring as supplements to ICP monitoring in TBI. SjvO<sub>2</sub> of less than 50% and Pbro<sub>2</sub> of less than 10 to 15 mm Hg should be avoided. However, clinicians are cautioned regarding the conceptual limitations and the lack of prospective randomized studies documenting an impact of the use of these modalities on outcome after severe TBI. Toxicity from the therapy recommended to achieve these goals (e.g., prolonged 100% O<sub>2</sub>) needs to be weighed against the lack of higher GRADE evidence supporting their use.

## ANESTHETICS, ANALGESICS, AND SEDATIVES

#### Background

Sedatives and analgesics have an important role in the management of TBI. Pain and agitation are thought to contribute to ICP elevations and increased metabolic rate. Moreover, high-dose barbiturates, benzodiazepines, and propofol decrease metabolic rate in intact brain areas. This is associated with a matched decrease in blood flow that decreases blood volume and thus ICP. Increasing doses of these drugs in normal brain decreases CBF to as much as 50% of normal. At that point, electroencephalogram activity becomes maximally suppressed.<sup>63–65</sup>

#### Evidence

There is no prospective randomized data supporting treatment of pain and agitation as a means to prevent elevated ICP. However, patients with TBI frequently have pain and agitation, and many clinicians believe that it is both unconstructive and unethical to allow unnecessary suffering. In addition, heightened arousal may affect cerebral metabolic demand. There is a single prospective randomized study comparing propofol to morphine for sedation in TBI patients. Propofol was associated with a trend toward lower ICP that did not reach statistical significance. Post hoc analysis of patients who received high-dose propofol suggested a better neurologic outcome despite the lack of a difference in ICP. This was interpreted to suggest a primary neuroprotective action.

The BTF meta-analysis<sup>63</sup> examined two RCTs of prophylactic barbiturate treatment in TBI. This revealed no favorable benefit on neurologic outcome but was associated with potentially problematic hypotension. Eisenberg's five-center RCT<sup>66</sup> of barbiturates for refractory intracranial hypertension revealed that these drugs decreased ICP and, in patients where ICP was controlled, improved survival and led to better neurologic outcome. Hypotension was an ongoing problem associated with barbiturate use.

#### Recommendations

Propofol is recommended for sedation in severe TBI over morphine with GRADE C evidence, but its use should be limited to 48 hours. Administration of higher doses for longer than 48 hours may be associated with improved outcome but carries the risk for the uncommon but potentially lethal propofol infusion syndrome. GRADE A evidence suggests that barbiturates should *not* be given prophylactically for TBI. Barbiturate use is supported in cases of severe refractory intracranial hypertension with GRADE C evidence. Therapeutic hypothermia and decompressive hemicraniectomy are also options in this situation, but there are no comparative data between these three modalities, so one cannot easily recommend which modality ought to be employed earlier in the therapeutic pyramid.

#### NUTRITION

#### Background

Acute illnesses such as in TBI induce a profound catabolic state of stress. This state may be persistent and is associated with significant wasting of protein.<sup>67–69</sup>

#### Evidence

Two studies were used in the BTF meta-analysis. One reported an association between poor nutrition and worse outcome, whereas a second found no such relationship. A recent prospective survey examined mortality among 797 severe TBI patients treated at 22 trauma centers. Patients not fed within 5 and 7 days after TBI had a twofold and fourfold increased mortality rate, respectively. Every 10-kcal/kg decrease in caloric intake was associated with a 30% to 40% increase in mortality. The amount of nutrition during the first 5 days inversely correlated with mortality.<sup>70</sup>

#### Recommendations

Full nutritional support should be implemented at least by day 5 after injury in patients without evidence of previous malnutrition GRADE B.

#### ANTISEIZURE PROPHYLAXIS

#### Background

Posttraumatic seizure (PTS) is classified as early (<7 days after TBI) or late (>7 days after TBI). The incidence of PTS varies from 4% to 25% early and 9% to 42% late in untreated TBI patients.<sup>71</sup> Early PTS can worsen early secondary injury through hypermetabolism, increased ICP, and systemic complications such as aspiration pneumonia and hypertension. It has been proposed that early PTS begets late PTS through neuronal kindling. Late PTS is problematic because of its association with sudden cardiac death, social

and quality-of-life issues, and predisposition to accidents. Unfortunately, antiepileptic therapy produces a set of adverse effects such as rash, Stevens-Johnson syndrome, cognitive deficits, and others that create a need for clinicians to strike a balance between risks and benefits in decisions related to post-TBI seizure prophylactic therapy.

#### Evidence

The BTF meta-analysis<sup>71</sup> reviewed 11 studies and analyzed 5 RCTs. Phenytoin for 7 days, carbamazepine, and valproate reduced the incidence of early PTS. Phenytoin, valproate, and phenobarbital had no effect on the incidence of late PTS. Efficacy required that therapeutic blood levels be achieved. Adverse effects occurred at a low rate in the phenytoin-treated patients. The Cochrane meta-analysis<sup>72</sup> of 11 RCTs and the American Academy of Neurology meta-analysis<sup>73</sup> of 8 RCTs arrived at similar conclusions. No RCTs are available on the efficacy of levetiracetam in TBI, although one prospective, nonrandomized trial of 32 TBI patients receiving 7 days of levetiracetam versus 42 TBI patients receiving phenytoin revealed equivalent seizure control. However, the incidence of abnormal electroencephalogram ("seizure tendency") was higher in the levetiracetam group.<sup>74</sup>

#### Recommendations

Phenytoin is indicated in the first 7 days after TBI for seizure prophylaxis GRADE A. In the absence of PTS, treatment should be stopped after 7 days and only resumed if PTS arises.

#### **HYPERVENTILATION**

#### Background

Hyperventilation decreases ICP by decreasing CBF.<sup>75,76</sup> This occurs without a matched decrease in metabolic rate. Data indicating a beneficial effect from such a decrease in ICP are tempered by concerns that the decrease in CBF could be deleterious after TBI.<sup>77</sup> Hyperventilation does not produce brain damage in the absence of TBI.

#### Evidence

The BTF meta-analysis reviewed three studies. These reported dangerously low CBF arising shortly after TBL<sup>76</sup> Muizelaar and associates<sup>78</sup> performed a prospective randomized study of prolonged hyperventilation in TBI (target  $P_{CO_2}$  of 25 mm Hg). This revealed worse outcome at 3 and 6 months in the hyperventilated patients. The BTF metaanalysis assigns this as a level II study, not making it level I because of some concerns about the power of the study. The Cochrane meta-analysis<sup>75</sup> was unwilling to make any recommendations because of the relatively small sample size.

#### Recommendations

Prolonged prophylactic hyperventilation to Paco<sub>2</sub> of 25 to 30 mm Hg should be avoided in TBI patients (GRADE

B). It may be justified if accompanied by a monitor of CBF adequacy. It also may be justified as a temporary intervention in emergency and temporary sudden increases in ICP such as with life-threatening herniation syndromes.

#### STEROIDS

#### Background

Glucocorticoids have been used for decades to reduce brain edema with brain tumors.<sup>79</sup> Based on these observations, their use was a standard for many years in TBI. Recent studies show no impact of glucocorticoid therapy on brain edema, ICP, or outcomes in TBI.

#### Evidence

Eight RCTs were reviewed in the BTF meta-analysis.<sup>79</sup> The class I study by Roberts and colleagues<sup>80</sup> of 10,008 patients was halted by the data safety monitoring committee due to evidence of a deleterious effect.

#### Recommendations

Glucocorticoids should not be used with TBI (GRADE A).

#### AUTHORS' RECOMMENDATIONS

- Avoid hypotension (systolic pressure < 90 mm Hg) and hypoxemia (Pao<sub>2</sub> < 60 mm Hg or Spo<sub>2</sub> < 90%) after TBI.</li>
- Intracranial hypertension is a major problem after TBI.
- Hyperthermia worsens both ICP and brain injury and should be prevented using conservative measures at a minimum. There are no randomized data to support normothermia or therapeutic hypothermia.
- Decreasing ICP by keeping the head elevated and midline is easy to achieve and has a rational basis but has not been explored through a randomized trial.
- Hyperosmolar therapy is of use following TBI. It is unclear which hyperosmolar agent is best.
- Hyperventilation may lower ICP acutely, but it has not been shown to be effective chronically.
- Decompression is used more commonly than in the past. However, there are no RCTs of decompression that demonstrate a benefit. Decompression may prove effective if conservative medical measures such as hyperosmolar therapy prove inadequate to control ICP.
- CSF drainage is commonly used to treat intracranial hypertension. There are no RCTs to support its use. The benefit of controlled CSF drainage through external ventricular or lumbar approaches may outweigh the risk for downward herniation, although there is widespread belief that the lumbar approach is too dangerous.
- Light sedation prevents agitation and may help prevent elevated ICP. Deep sedation cannot be recommended as a firstline therapy in ICP control but may be considered as part of the treatment of refractory ICP after more conservative therapies such as hyperosmolar therapy have failed.
- Early nutrition is important to reduce mortality after TBI.
- Anticonvulsant use can reduce the incidence of seizures in the first week after TBI. These agents have not been shown to

prevent posttraumatic epilepsy. Antiseizure medications are indicated immediately after TBI but not after the first week after TBI unless posttraumatic epilepsy is present.

- Steroids should not be used with TBI.
- Monitoring of Pbro<sub>2</sub> and SjvO<sub>2</sub> may help to avoid brain hypoxia.

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# How Should Aneurysmal Subarachnoid Hemorrhage Be Managed?

Linda C. Wendell, Joshua M. Levine

Aneurysmal subarachnoid hemorrhage (SAH), a type of hemorrhagic stroke due to rupture of an intracranial aneurysm, affects about 30,000 Americans annually and has a mortality rate of nearly 45%.<sup>1</sup> At least 15% of people with SAH die before reaching the hospital. Of those who survive, a substantial proportion are left with significant disability.<sup>2</sup> Prompt diagnosis, treatment, and anticipation of complications may improve outcome. This chapter reviews major clinical management points and discusses the relevant literature.

#### **EMERGENCY SETTING**

In the emergency setting, once the diagnosis of SAH has been established, initial goals are to stabilize the patient's airway, breathing, and circulation. Early referral to a large-volume center with experienced vascular neurosurgeons, neuroendovascular specialists, and dedicated neurointensivists should be considered. Four studies have demonstrated that hospital volume of SAH patients and procedural experience correlate with improved mortality.<sup>3–6</sup>

#### SUBARACHNOID HEMORRHAGE-RELATED COMPLICATIONS

#### Rebleeding

Aneurysmal rebleeding is one of the most serious initial threats to the patient. The incidence may be as high as 30%,<sup>7</sup> with the greatest risk (roughly 4%) during the first 24 hours.<sup>8</sup> Medical measures are employed to reduce the risk of rebleeding until the culprit aneurysm is excluded from the circulation through surgical or endovascular means.

#### Medical Measures

Bed rest does not alter the incidence of rebleeding,<sup>9</sup> but it has become a standard measure. Blood pressure control is widely recommended to reduce the risk for aneurysmal rebleeding. The benefit of blood pressure reduction must be weighed against the risk for precipitating cerebral ischemia.<sup>10</sup> Although there are no prospective studies that demonstrate the efficacy of antihypertensive therapy, retrospective data suggest an association between hypertension and aneurysmal rebleeding.<sup>11,12</sup> Ohkuma and associates found a statistically significant increase in the incidence of prehospitalization rebleeding in patients whose systolic blood pressure was greater than 160 mm Hg.<sup>12</sup> Because rebleeding may be related to aneurysm expansion, which is largely dictated by changes in transmural pressure, surges in blood pressure may be more important than absolute levels of blood pressure.<sup>12</sup> It is therefore reasonable to treat extreme hypertension and to minimize blood pressure lability.

Antifibrinolytic agents such as tranexamic acid and epsilon aminocaproic acid have been well studied. Ten prospective randomized studies have been performed (Table 59-1). Nine of these (1399 patients) were included in the most recent Cochrane review. In sum, death and poor outcome (death, vegetative state, or severe disability) were not influenced by treatment.<sup>13–23</sup> It appears that, while antifibrinolytic medications reduce the risk of rebleeding, their benefit is offset by an increased risk of cerebral infarction.<sup>14,21,22</sup> A more recent study suggests that early treatment with a short course of antifibrinolytic medication, when combined with measures to prevent cerebral ischemia, may be beneficial.<sup>13</sup> Further study is needed to define the optimal use of antifibrinolytic medications; although these drugs may be beneficial in select patients, at present they should not be used routinely.

#### Surgical and Endovascular Measures

There are two primary methods for excluding aneurysms from the circulation: (1) surgical, in which a craniotomy is performed and a clip is placed across the neck of the aneurysm, and (2) endovascular, in which detachable coils are placed into the aneurysm using catheter-based techniques. The International Subarachnoid Aneurysm Trial (ISAT) is the only large prospective trial comparing these two methods.<sup>24</sup> In this trial, 2143 of 9559 patient were deemed good candidates for either therapy and were randomized to surgical or endovascular aneurysm treatment. Although endovascular treatment was associated with higher recurrent SAH rates (2.9% per year versus 0.9% per year), at 1 year, there was no difference in mortality. Endovascular therapy was associated with less disability

#### Table 59-1 Summary of Randomized Controlled Trials Evaluating Antifibrinolytic Therapy in Subarachnoid Hemorrhage

Study	No. of Subjects (Intervention/No Intervention)	Study Design*	Intervention	Control	Outcomes
Girvin, 1973 <sup>15</sup>	66 (39/27)		Epsilon aminocaproic acid	Standard treatment	No effect on rebleeding, ischemia, or mortality
van Rossum et al, 1977 <sup>16</sup>	51 (26/25)	DB, P	Tranexamic acid	Placebo	No effect on rebleeding or mortality
Chandra, 1978 <sup>17</sup>	39 (20/19)	DB, P	Tranexamic acid	Placebo	No effect on rebleeding or mortality
Maurice-Williams, 1978 <sup>18</sup>	79 (38/41)		Tranexamic acid	Standard treatment	No effect on rebleeding or mortality
Kaste & Ramsay, 1979 <sup>19</sup>	64 (32/32)	DB, P	Tranexamic acid	Placebo	No effect on rebleeding or mortality
Fodstad et al, 1981 <sup>20</sup>	59 (30/29)		Tranexamic acid	Standard treatment	No effect on rebleeding, cerebral ischemia, or mortality
Vermeulen et al, 1984 <sup>21</sup>	479 (241/238)	DB, P	Tranexamic acid	Placebo	Decreased rebleeding; increased cerebral ischemia; no effect on outcome or mortality
Tsementzis et al, 1990 <sup>22</sup>	100 (50/50)	DB, P	Tranexamic acid	Placebo	Increased cerebral ischemia; no effect on rebleeding, outcome, or mortality
Roos et al, 2000 <sup>23</sup>	452 (229/223)	DB, P	Tranexamic acid	Placebo	Decreased rebleeding; no effect on ischemia, outcome, or mortality
Hillman et al, 2002 <sup>13</sup>	505 (254/251)		Tranexamic acid	Standard treatment	Decreased rebleeding; no effect on cerebral ischemia, outcome, or mortality

\*DB, double-blind; P, placebo.

(15.6% versus 21.6%) and less combined morbidity and mortality (23.5% versus 30.9%; P = .0001). Because it is not clear how the decision was made to include patients in the randomization, it may be difficult to generalize the results of this study. Further, long-term outcome data are lacking. Whether to clip or to coil an aneurysm is a complex decision that depends on patient factors (age, comorbidities), aneurysm factors (size, shape, location), and availability of local resources and expertise. Ideally, experienced neurosurgeons and interventional neuroradiologists make the decision collaboratively.<sup>24</sup>

In recent years, there has been a trend toward early aneurysm treatment. Multiple retrospective and prospective studies have established an association between a longer interval to treatment and increased risk for pretreatment hemorrhage. The International Cooperative Study on the Timing of Aneurysm Surgery explored early versus late surgical intervention based on the neurosurgeons' intention-to-treat.<sup>25</sup> Patients whose surgery was planned for within the first 3 days had an overall mortality rate equal to the patients whose surgery was planned for between days 11 and 32. However, patients in the early surgical group had a significantly better clinical recovery than those whose surgery was delayed (P < .01). The patients with the highest mortality were those whose surgery was planned for postictus days 7 to 10, a time when risk for vasospasm is greatest. Based on this study, early surgery is recommended.

#### Hydrocephalus

Acute hydrocephalus (enlargement of the ventricles) occurs in 15% to 30% of SAH patients.<sup>26–30</sup> The presence of hydrocephalus correlates with worse radiographic and clinical grades and with an unfavorable prognosis.<sup>26–29</sup> Clinical characteristics of hydrocephalus range from no symptoms to signs of intracranial hypertension, such as impairment of upward gaze, sixth nerve palsy, and head-ache. If severe, hydrocephalus may impair level of consciousness and should be treated immediately with a ventriculostomy. Cerebrospinal fluid (CSF) drainage usually leads to an improvement in symptoms.<sup>30–32</sup> Overdrainage of CSF should be avoided as it may increase the risk of rebleeding.<sup>27,30</sup> Data regarding treatment of hydrocephalus in SAH are largely retrospective; optimal management of patients with mild symptoms is unknown.

#### Seizures

The evidence regarding incidence, prophylaxis, and treatment of seizures is mostly retrospective. The reported incidence of seizures after SAH varies from 8% to 35%.<sup>33–37</sup> In one retrospective cohort study, most seizures after SAH occurred before hospitalization, and the incidence of in-hospital seizures was 4.1%. These seizures occurred despite prophylaxis with an antiepileptic drug (AED) and occurred at least 1 week after aneurysmal rupture.33 Risk factors associated with the development of seizures include ruptured middle cerebral artery (MCA) aneurysm, intracerebral hemorrhage, thicker cisternal clot, rebleeding, ischemic infarct, and a history of hypertension.<sup>33-36</sup> Two studies demonstrated no difference in outcome between patients who developed seizures and those who did not.33,37 A third study, however, found that seizures at the time of hemorrhage were associated with poor outcome.<sup>38</sup>

The incidence of generalized convulsive status epilepticus (GCSE) is 0.2%, but the incidence of nonconvulsive status epilepticus (NSE) is much higher.<sup>39,40</sup> A prospective study found that 31% of stuporous or comatose SAH patients had NSE when monitored with continuous electroencephalography. The mean onset of NSE was 18 days after hemorrhage.<sup>40</sup> Both GCSE and NSE are associated with worse outcome.<sup>39,40</sup>

The benefit of prophylactic AEDs has not been definitively established. It is reasonable to use AEDs before aneurysm treatment due to risk for seizure-related rebleeding (because of a surge in blood pressure). However, there is no evidence to support the long-term use of AEDs in patients without a history of seizure. In fact, cumulative phenytoin exposure is associated with a worse cognitive outcome at 3 months.<sup>41</sup>

#### Vasospasm

Vasospasm (narrowing of the large-caliber arteries at the base of the brain) usually begins at postbleed day 3, peaks at days 6 to 8, and resolves over 2 to 4 weeks.<sup>42</sup> Symptomatic vasospasm typically manifests with an indolent decrease in level of consciousness or focal neurologic deficits that vary depending on the affected arterial distribution.<sup>42</sup> Thickness of cisternal clot has been associated with the development of vasospasm.<sup>43</sup> Almost one third of patients who survive the initial SAH develop vasospasm,<sup>25</sup> and about half of these die from vasospasm.<sup>44</sup>

#### Detection

In addition to serial neurologic examinations, several methods exist to detect vasospasm. The gold standard for vasospasm detection is conventional (invasive) cerebral angiography. Risks associated with invasive angiography include hematoma, infection, peripheral thromboembolic events, and transient or permanent neurologic deficits. The rate of neurologic complications in SAH patients is 1.8%.<sup>45</sup> Noninvasive angiography with computed tomography (CT) or magnetic resonance imaging (MRI) is less sensitive for detecting vasospasm.<sup>46–48</sup> Small prospective studies indicate that CT angiography (CTA) had a sensitivity of 86% to 91.6%<sup>46,47</sup> CTA is most sensitive for vasospasm of proximal arterial segments and for severe vasospasm and has a high negative predictive value (95%). CTA is limited by artifact from metallic aneurysm clips and coils.<sup>46,47</sup> Magnetic resonance angiography (MRA) is also prone to artifact from clips and coils and from patient movement in the scanner. MRA has a sensitivity for vasospasm detection of 45.6% compared with conventional angiography.<sup>48</sup>

Transcranial Doppler ultrasonography (TCD) detects increased cerebral blood flow velocities (CBFVs) associated with vasospasm. TCD is noninvasive, may be performed daily at the bedside, and is less expensive than many other monitoring tests. However, the overall sensitivity of TCD is 58.6%.<sup>49</sup> TCD is most useful in detecting vasospasm in the middle cerebral artery (MCA) and basilar artery.<sup>49</sup> Induced hypertension and hyperemia also increase CBFVs.<sup>50,51</sup> The Lindegaard ratio (hemispheric index), the ratio between the blood flow velocities in the MCA and the ipsilateral extracranial internal carotid artery (ICA), may be used to distinguish increased CBFVs due to vasospasm from other causes. Indices between 3 and 6 correlate with mild and moderate vasospasm, whereas indices greater than 6 suggest severe vasospasm.<sup>51</sup> A rise in CBFV of greater than 50 cm/second per day also indicates vasospasm. Importantly, elevated TCD velocities do not correlate with the development of delayed ischemic neurologic deficits (DINDs).<sup>52</sup> No study has shown that TCD monitoring affects outcome after SAH.

Continuous electroencephalography (cEEG) is a newer technique for vasospasm detection. A decrease in the ratio of  $\alpha$  brain-wave frequencies (9 to 12 Hz) to  $\delta$  brain-wave frequencies (0 to 4 Hz) correlates strongly with the development of symptomatic vasospasm or DINDs.<sup>53</sup> Continuous EEG may detect vasospasm at least 2 days before TCD. Additionally, cEEG is useful in detecting nonconvulsive seizures. Future studies are needed to better define the role of cEEG for vasospasm detection and to determine its impact on outcome.

#### Prevention and Treatment

Table 59-2 summarizes the randomized trials that have been performed on therapies to prevent vasospasm and DINDs. Hypovolemia is associated with vasospasm and DINDs and should be avoided.<sup>54</sup> Two randomized controlled trials evaluated the effect of prophylactic hypervolemia on cerebral blood flow (CBF) and the incidence of vasospasm.<sup>55,56</sup> Neither study found a significant improvement in CBF, incidence of symptomatic vasospasm, or functional outcome in patients receiving hypervolemic therapy.<sup>55,56</sup> Patients receiving hypervolemic therapy had more complications, including bleeding, congestive heart failure, and infection.<sup>56</sup> Based on these studies, prophylactic hypervolemia is not recommended, and patients should be maintained in a euvolemic state.

Balloon angioplasty may be considered in patients with angiographic evidence of vasospasm. It reverses vasospasm, augments CBF, and improves neurologic deficits but does not affect long-term outcome.<sup>57</sup> Rupture or occlusion of the vessel, disruption of aneurysm clips,

# Table 59-2 Summary of Randomized Controlled Trials Evaluating the Prevention of Vasospasm and Delayed Ischemic Neurologic Deficits in Subarachnoid Hemorrhage

Study	No. of Subjects (Intervention/No Intervention)	Study Design*	Intervention	Control	Outcomes
Lennihan et al, 2000 <sup>55</sup>	82 (41/41)		Hypervolemic therapy	Normovolemic therapy	No difference in symptomatic vasospasm
Egge et al, 2001 <sup>56</sup>	32 (16/16)		Hypervolemic hypertensive hemodilution therapy	Normovolemic therapy	No difference in symptomatic or TCD vasospasm
van den Bergh et al, 2005 <sup>58</sup>	283 (139/144)	DB, P	Magnesium IV	Placebo	Decreased incidence of DINDs; improved clinical outcome at 3 mo
Veyna et al, 2002 <sup>59</sup>	40 (20/20)	Р	Magnesium IV	Placebo	Trend toward improved clinical outcome
Wong et al, 2006 <sup>60</sup>	60 (30/30)	DB	Magnesium IV	Saline	Trend toward decrease in symptomatic vasospasm; decreased transcranial Doppler vasospasm timeframe; no difference in clinical outcome
Schmid-Elsaesser et al, 2006 <sup>61</sup>	104 (53/51)		Magnesium IV	Nimodipine IV	Incidence of vasospasm and clinical outcome comparable
Muroi et al, 2008 <sup>62</sup>	58 (31/27)	Р	Magnesium IV	Placebo	No difference in DINDs; improved clinical outcome at 3 mo
Allen et al, 1983 <sup>64</sup>	116 (56/60)	DB, P	Nimodipine PO	Placebo	Decreased incidence of DINDs
Philippon et al, 1986 <sup>65</sup>	70 (31/39)	DB, P	Nimodipine PO	Placebo	No difference in vasospasm; decreased incidence of DINDs; improved mortality
Neil-Dwyer et al, 1987 <sup>66</sup>	75 (38/37)	DB, P	Nimodipine PO	Placebo	Improved clinical outcome at 3 mo
Petruk et al, 1988 <sup>67</sup>	154 (72/82)	DB, P	Nimodipine PO	Placebo	Decreased incidence of DINDs; improved clinical outcome at 3 mo
Pickard et al, 1989 <sup>68</sup>	554 (278/276)	DB, P	Nimodipine PO	Placebo	Decreased incidence of DINDs; improved clinical outcome at 3 mo
Haley et al, 1993 <sup>69</sup>	906 (449/457)	DB, P	Nicardipine IV	Placebo	Decreased incidence of vasospasm; no difference in clinical outcome
Haley et al, 1994 <sup>70</sup>	365 (184/181)	DB	High-dose nicardipine IV	Low-dose nicardipine IV	Incidence of vasospasm and clinical outcome comparable
Tseng et al, 2005 <sup>71</sup>	80 (40/40)	DB, P	Pravastatin	Placebo	Decreased incidence of vasospasm and DINDs; improved mortality
Tseng et al, 2007 <sup>72</sup>	80 (40/40)	DB, P	Pravastatin	Placebo	Improved clinical outcome at 6 mo
Lynch et al, 2005 <sup>73</sup>	39 (19/20)	DB, P	Simvastatin	Placebo	Decreased incidence of vasospasm
Chou et al, 2008 <sup>74</sup>	39 (19/20)	DB, P	Simvastatin	Placebo	No difference in vasospasm or DINDs; trend toward decreased mortality

\*DB, double-blind; DINDs, delayed ischemic neurologic deficits; P, placebo.

and thrombus formation are recognized complications. Catheter-based intra-arterial delivery of vasodilators, including papaverine, verapamil, nicardipine, nimodipine, and milrinone, also have been used to treat vasospasm. Randomized controlled trials to establish the efficacy of these agents are lacking.

Hypomagnesemia is associated with vasospasm and should be corrected. Five prospective randomized trials suggest an association between intravenous (IV) magnesium therapy and improved clinical outcomes.<sup>58–62</sup> The largest of these demonstrated that continuous magnesium infusions were associated with a lower incidence of DINDs and better functional outcome.<sup>58</sup> At this time, a phase III randomized controlled trial is under way to determine whether magnesium administration improves outcome in aneurysmal SAH.<sup>63</sup>

Calcium channel blockers and statins may improve outcome after SAH. Five double-blind, placebocontrolled trials of oral nimodipine demonstrated improved functional outcomes despite no impact on the incidence or severity of vasospasm.64-68 Patients with SAH should receive nimodipine, 60 mg by mouth or enterally every 4 hours for 21 days. Two randomized controlled trials of IV nicardipine demonstrated no impact on 3-month outcome despite a reduction in the incidence of symptomatic vasospasm.<sup>69,70</sup> Three pilot studies investigated the use of statins in aneurysmal SAH. In one study, treatment with pravastatin for 14 days decreased the incidence of vasospasm and DINDs and shortened the duration of vasospasm and dysautoregulation.<sup>71</sup> Additionally, mortality due to vasospasm and clinical outcomes at 6 months were improved.<sup>72</sup> A second study demonstrated that treatment with simvastatin for 14 days decreased the incidence of vasospasm as measured by MCA CBFV.73 A third study failed to show a difference in incidence of vasospasm and DINDs with simvastatin versus placebo, but did show a trend toward reduced mortality in the simvastatin group.<sup>74</sup> A phase III randomized controlled trial, Simvastatin in Aneurysmal Subarachnoid Hemorrhage (STASH), is currently under way.

#### Hyponatremia

About one third of SAH patients develop hyponatremia.<sup>54,75</sup> Hyponatremia is associated with an increased incidence of DINDs and is more common in patients with anterior communicating artery aneurysms, higher grade of SAH, and hydrocephalus.<sup>54</sup> Although hyponatremia may be due to the syndrome of inappropriate secretion of antidiuretic hormone (SIADH), treatment with fluid restriction is detrimental and leads to increased mortality from DINDs.<sup>54</sup> Alternatively, hyponatremia may be due to cerebral salt wasting, a form of hypovolemic hyponatremia that is treated with volume replacement.<sup>76</sup> Irrespective of the cause of hyponatremia, oral or intravenous sodium chloride is usually sufficient to correct mild hyponatremia. In patients with symptomatic vasospasm or severe hyponatremia, hypertonic saline may be given.<sup>77</sup> Small prospective randomized trials found that fludrocortisone may reduce natriuresis and prevent hyponatremia.<sup>78</sup> In

patients with SIADH, a prospective trial found that conivaptan, an oral vasopressin receptor agonist, effectively corrects hyponatremia.<sup>79</sup>

#### **Cardiac Dysfunction**

#### Electrocardiographic Abnormalities

Ninety percent of patients with SAH experience cardiac arrhythmias, including supraventricular and ventricular premature complexes, supraventricular and ventricular tachycardias, and sinoatrial and atrioventricular block. Life-threatening arrhythmias—usually torsades de pointes or ventricular flutter and fibrillation-are seen in 3% to 4% of patients. They occur most commonly in the first 48 hours and are associated with QT prolongation and with hypokalemia. The clinical and radiographic findings of SAH do not correlate with the presence of arrhythmias.<sup>80</sup> Patients with QT prolongation are more likely to have increased serum cardiac troponin-I.81 Six to 12% of patients have ST-segment elevations or, more commonly, depressions.<sup>81</sup> These abnormalities are associated with neurogenic stunned myocardium (see later) and are not usually due to coronary artery disease or to coronary vasospasm.<sup>82</sup>

#### Cardiomyopathy

SAH patients are susceptible to a reversible cardiomyopathy known as neurogenic stunned myocardium. One purported mechanism is activation of the sympathetic nervous system with consequent catecholamine toxicity. Fifteen percent of patients develop global left ventricular dysfunction, and another 13% to 18% develop regional wall motion abnormalities (RWMAs). The RWMAs do not respect coronary arterial vascular distributions but may occur in the distribution of myocardial sympathetic nerve terminals.<sup>83,84</sup> Predictors of neurogenic stunned myocardium include poor clinical grade, temporal proximity to aneurysm rupture, female sex, larger body surface area, larger left ventricular mass index, elevated serum cardiac troponin-I, tachycardia, lower systolic blood pressure, higher doses of phenylephrine, and previous cocaine or amphetamine use.<sup>84,85</sup> RWMAs most commonly affect the mid-regions of the anteroseptal, anterior, inferoseptal, and anterolateral left ventricular walls (apical-sparing pattern) or the left ventricular base (inverted Takotsubo pattern). Occasionally, the apex is disproportionately involved (Takotsubo pattern). Patients may present with a range of symptoms from mild heart failure to cardiogenic shock. Treatment is supportive and prognosis is excellent.<sup>84</sup>

#### CONCLUSION

The goal of critical care management of patients with SAH is to limit ongoing neurologic injury. Prompt diagnosis and treatment of SAH are crucial. Anticipating complications from rebleeding, hydrocephalus, seizures, and vasospasm is imperative. Further prospective randomized trials are needed to establish the efficacy of new and existing therapies.

#### AUTHORS' RECOMMENDATIONS

- Rebleeding is the most serious initial threat to the patient. Aneurysms should be promptly clipped or coiled. Blood pressure should be controlled until the aneurysm is secured.
- Prophylactic AEDs are reasonable in the acute setting, but there is no evidence supporting their long-term use.
- Vasospasm generally occurs between days 3 and 14. The gold standard for vasospasm detection is conventional cerebral angiography; however, TCDs can be used on a daily basis to monitor for vasospasm. cEEG monitoring is a new technology that may also be considered.
- Treatment of vasospasm includes maintenance of normovolemia and induced hypertension. Balloon angioplasty and pharmacologic vasodilators are used if angiographic evidence of vasospasm is present.
- Oral nimodipine improves outcome in SAH and should be given to all patients unless contraindicated. Further studies will determine whether magnesium and statins also improve outcome after SAH.
- Hyponatremia and cardiac dysfunction are common medical complications of SAH.

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# 60

# How should I Manage Acute Ischemic Stroke in the Intensive Care Unit?

James S. McKinney, Steven R. Messé

Stroke is the third leading cause of death and the leading cause of long-term disability in the United States.<sup>1</sup> Strokes account for more than half of hospital admissions for neurologic disease, and about 85% of strokes are ischemic. Currently, the only medication approved by the U.S. Food and Drug Administration for the treatment of acute ischemic stroke is intravenous recombinant tissue plasminogen activator (rt-PA). The NINDS rt-PA Stroke Study proved that this medication is effective when given within 3 hours of symptom onset.<sup>2</sup> A second large randomized trial reported a more modest benefit for patients treated from 3 to 4.5 hours from symptom onset.<sup>3</sup> Unfortunately, most acute stroke patients are not eligible for rt-PA and thus aggressive and meticulous supportive care is essential to ensure optimal neurologic outcomes.

The American Heart Association/American Stroke Association (AHA/ASA) has published guidelines for the early management of ischemic stroke.<sup>4</sup> The primary goals of acute stroke management are to restore blood flow to ischemic areas, to minimize excess cerebral metabolic demand, and to prevent and treat medical and neurologic complications that lead to secondary brain injury. This chapter serves as an evidence-based summary of the in-hospital treatment of stroke and provides an update on recent clinical advances.

#### CEREBROVASCULAR PATHOPHYSIOLOGY

In contrast to myocardial infarction, which has a fairly well-characterized and uniform pathophysiology, ischemic stroke is caused by a heterogeneous group of etiologies that include cardioembolism, large vessel atherothromboembolism, small vessel disease, disorders of coagulation, arterial dissections, inflammatory and infectious vasculopathies, and unknown or cryptogenic causes.<sup>5</sup> Regardless of etiology, the net result is the reduction or cessation of blood flow to the brain leading to cell death.

Under normal physiologic conditions, *cerebral perfusion pressure* (CPP), defined as the difference between systemic mean arterial pressure (MAP) and intracranial pressure (ICP), is determined almost entirely by the MAP because ICP is relatively low. The brain has the ability to adjust the downstream cerebrovascular resistance (CVR) by a process called *autoregulation*. Autoregulation allows for a relatively constant cerebral blood flow (CBF) despite

changes in CPP. Under normal conditions, CBF remains relatively constant (about 50 mL per 100 g tissue per minute) across a wide range of MAP.<sup>6</sup>

During an acute stroke, the brain becomes ischemic. This may lead to cellular dysfunction and death. Surrounding a core of infarcted dead tissue is an area of relative ischemia called the *penumbra*. This ischemic penumbra is at risk for proceeding to infarction if oxygen delivery does not improve. Tissue oxygenation may be improved by increasing flow through an occluded or stenotic blood vessel or by improving blood flow through collateral channels, both of which may be achieved by increasing CPP. Additionally, excess cellular metabolism accelerates the conversion of penumbra to infarct. The goal of early acute stroke therapy is to salvage the penumbra, minimizing the volume of infarct and functional impairment. Aggressive management of acute stroke patients is vital because up to 40% of stroke patients deteriorate within the first 48 hours, a pattern that is associated with worse long-term clinical outcomes.<sup>7</sup>

#### **CRITICAL CARE MANAGEMENT**

#### **Bed Assignment**

Studies have repeatedly shown that admission to a specialized stroke unit can lessen the morbidity and mortality from a stroke. A meta-analysis demonstrated that treatment in a dedicated stroke unit decreased the 1-year mortality (odds ratio [OR], 0.86; 95% confidence interval [CI], 0.76 to 0.98), odds of death or need for long-term care (OR, 0.82; 95% CI, 0.73 to 0.92), and odds of death or dependency (OR, 0.82; 95% CI, 0.73 to 0.92).<sup>8</sup> These benefits were independent of patient age, sex, or stroke severity. Thus, stroke patients should be cared for in a dedicated stroke unit or critical care unit with specialized stroke training.

#### Airway, Ventilation, and Oxygenation

As in any other medical emergency, airway management is paramount in providing effective therapy. Hypoxia can worsen strokes by further starving vulnerable tissue of oxygen. The patient with a depressed level of consciousness and oropharyngeal dysfunction is at greatest risk for airway compromise. In practice, only a minority of ischemic stroke patients require intubation and mechanical ventilation. Not surprisingly, the need for airway management portends a poor prognosis.<sup>9,10</sup> Available evidence does not support providing supplemental oxygen for all stroke patients, although it should be provided if the oxygen saturation falls below 92%.<sup>4,11</sup>

#### Intravenous Fluid

Intravenous fluid administration is an important intervention for acute stroke patients. These individuals often are volume depleted from limited oral intake and insensible fluid loss. Intravascular hypovolemia can aggravate ischemic strokes by decreasing CPP and increasing blood viscosity. An elevated serum osmolality on admission is associated with higher mortality.<sup>12</sup>

Isotonic solutions, such as 0.9% normal saline, are preferred to maintain euvolemia in stroke patients. Hypotonic solutions and dextrose preparations can cause secondary brain injury and aggravate stroke symptoms by increasing cellular edema and causing local acidosis.<sup>13,14</sup> It is not routinely necessary to place a central venous catheter for fluid management.

#### Head-of-Bed Positioning

There are countervailing priorities in managing head-ofbed (HOB) positioning in acute stroke patients. Maintaining the HOB at more than 30 degrees can potentially increase CSF and venous blood drainage, thereby lowering ICP as well as limiting the risk for aspiration. Alternatively, an elevated HOB can decrease CPP and further limit blood flow to the ischemic penumbra. A small study evaluating middle cerebral artery blood flow showed an average increase in mean flow velocity of 20% by laying the HOB flat from 30 degrees.<sup>15</sup> There are no large randomized controlled trials to direct HOB positioning. However, given that ICP issues often do not manifest for 1 to 2 days after an ischemic stroke, and the ischemic penumbra is most dynamic during the first 24 hours, the HOB should be kept flat for at least the first 24 hours after an ischemic stroke if there is no evidence for elevated ICP. After this time, the HOB can be raised slowly while serial neurologic examinations ensure clinical stability.

#### **Antithrombotic Medications**

Antithrombotic therapy for acute stroke is a controversial topic, although useful data are available to guide decision making. A summary of meta-analyses comparing anti-thrombotic agents is presented in Table 60-1.

Historically, unfractionated heparin (UFH) has been a mainstay of stroke therapy. In 1983, the Cerebral Embolism Study Group published a report of 45 patients with cardioembolic stroke that showed a potential benefit of intravenous (IV) heparin over placebo.<sup>16</sup> Based on the finding of this small study, many have recommended IV heparin for acute stroke treatment.

The largest trial to address this issue was the International Stroke Trial (IST). This study randomized patients to either no heparin or one of two doses of UFH, 5000 units or 12,500 units subcutaneously twice daily.<sup>17</sup> Half the patients also received aspirin, as described later. The rate of recurrent stroke was reduced with heparin administration (2.9% versus 3.8%, P = .005), but this was offset by an equal increase in the rate of symptomatic intracerebral hemorrhage (1.2% versus 0.4%, P < .00001). Thus, there was no difference in overall mortality at 6 months (62.9% versus 62.9%, not significant). Patients treated with low-dose UFH fared better than the high-dose group with fewer significant extracranial hemorrhages, intracerebral hemorrhages, and deaths and nonfatal strokes at 14 days.

Multiple trials have evaluated low-molecular-weight heparin (LMWH) and heparinoids in acute stroke patients. None demonstrated a benefit in its primary end point.<sup>18-23</sup>

In contrast to the heparin data, two large trials, IST and the Chinese Acute Stroke Trial (CAST), have shown an unequivocal benefit from early treatment with aspirin. These trials independently showed a decrease in ischemic stroke recurrence (IST 2.8% versus 3.9%, P < .001; CAST 1.6% versus 2.1%, P = .01) with no significant increase in hemorrhagic conversion (IST 0.9% versus 0.8%, not significant; CAST 1.1% versus 0.9%, not significant).<sup>17,24</sup> This treatment effect was independent of age, stroke severity, stroke subtype, or concomitant heparin use. Currently, aspirin, 325 mg given within 24 to 48 hours of symptom onset, is recommended for most stroke patients.<sup>4</sup>

Other oral antiplatelet agents, including clopidogrel, dipyridamole, and ticlopidine, have not been evaluated in the treatment of acute ischemic stroke. It is reasonable to treat aspirin-allergic patients with clopidogrel. Data from acute myocardial ischemia literature support giving clopidogrel as an initial 300 mg bolus followed by 75 mg daily to rapidly achieve maximal platelet inhibition.<sup>25</sup> The glycoprotein IIb/IIIa inhibitors have been shown to be ineffective in treating acute ischemic stroke.<sup>26</sup>

Despite the findings from these large population trials, many clinicians have postulated that there may be subgroups of patients who would benefit from urgent anticoagulation. A meta-analysis of trials specifically looking at cardioembolic stroke found no benefit for urgent anticoagulation over aspirin or placebo in preventing early recurrent ischemic stroke, death, or disability at followup.<sup>27</sup> There is conflicting evidence to support anticoagulating patients with acute large vessel stenosis or occlusion.<sup>23,28</sup> As such, this decision should be made on a case-by-case basis that accounts for the size of the primary infarct. Most experts recommend anticoagulation for treatment of acute extracranial cervicocephalic arterial dissection, although there are no randomized controlled trials to support this therapy over antiplatelet agents.<sup>29</sup>

#### **Blood Pressure Management**

Acute elevations in blood pressure occur in up to 80% of patients with acute ischemic stroke and tend to decline spontaneously over 10 days after the event.<sup>30</sup> These elevations are likely a compensatory response to increase CPP and CBF to the ischemic penumbra but may also be in response to stress, pain, nausea, or elevated ICP. Although marked hypertension can increase the risk for hemorrhagic transformation or worsen cerebral edema, most patients tolerate the elevated blood pressure well.

Study	No. of Trials	No. of Subjects	Intervention	Control	Outcomes
Chen et al, 2000 <sup>75</sup>	2	40,451	ASA 160-300 mg/ day	Placebo	ASA reduced recurrent ischemic stroke (1.6% vs. 2.3%, $P < .000001$ ) and death without further stroke (5.0% vs. 5.4%, $P = .05$ ). A small increase in hemorrhagic transformation was identified (1.0% vs. 0.9%, $P = .07$ ). ASA therapy resulted in a net decrease in overall stroke and in-hospital death of 9 per 1000 patients (8.2% vs. 9.1%, $P = .001$ ).
Berge et al, 2002 <sup>76</sup>	4	16,558	UFH or LMWH	ASA	Anticoagulants offered no benefit over ASA in reducing death or dependency at follow-up (OR, 1.07; 95% CI, 0.98-1.15). There was a significant increase in symptomatic intracranial hemorrhage (OR, 2.35; 95% CI, 1.49-3.46) and death (OR, 1.10; 95% CI, 1.01-1.29).
Counsell & Sandercock, 2002 <sup>77</sup>	5	705	Heparinoid or LMWH	UFH	Insufficient power to give information regarding outcomes, including death, dependency, and intracranial hemorrhage
Gubitz et al, 2004 <sup>78</sup>	22	23,547	UFH—SC 6, IV 2 LMWH 7 Heparinoids 1 Oral anticoagulants 2 Thrombin inhibitors 2	Placebo 14 ASA 1 No treatment 8	Anticoagulant offered no benefit in reducing death or disability at follow-up (OR, 0.99; 95% CI, 0.93- 1.04). Anticoagulant therapy was associated with 9 fewer recurrent ischemic strokes per 1000 patients, but associated with 9 more hemorrhagic strokes per 1000 patients.
Paciaroni et al, 2007 <sup>27</sup>	7	4624	UFH, LMWH, or heparinoids, <48 hr	ASA or placebo	Anticoagulants were associated with a nonsignificant reduction in recurrent ischemic stroke (OR, 0.68; 95% CI, 0.44-1.06), a significant increase in symptomatic intracranial bleeding (OR, 2.89; 95% CI, 1.19-7.01), and similar rate of death or disability at follow-up (OR, 1.01; 95% CI, 0.82-1.24) in patients with cardioembolic stroke.

Table 60-1 Summary of Meta-Analysis on Antithrombotic Therapy for Acute Ischemic Stroke

ASA, aspirin; CI, confidence interval; IV, intravenous; LMWH, low-molecular-weight heparin; OR, odds ratio; SC, subcutaneous; UFH, unfractionated heparin.

Permissive hypertension is generally recommended in stroke patients. During an acute stroke, the cerebrovascular autoregulation described previously fails, and CBF becomes more directly correlated to the CPP.<sup>31</sup> Thus, aggressive blood pressure reduction can increase infarct size by reducing blood flow to the penumbra.<sup>32</sup> There are no high-level data that adequately address this issue, although trials are ongoing.<sup>33</sup> Table 60-2 presents current AHA recommendations for blood pressure management after the decision to treat the patient with thrombolytics is made. If thrombolytics are not given, blood pressure should not be treated unless it is greater than 220/120 mm Hg.<sup>4</sup> If medically necessary, treatment of hypertension should be performed with caution to minimize worsening of ischemic symptoms. Patients who receive thrombolytic therapy should be treated aggressively to maintain blood pressures lower than 180/105 mm Hg for at least 24 hours because this was the goal defined by the NINDS rt-PA study, and higher blood pressures may be associated with hemorrhagic conversion.<sup>3</sup>

Hypotension is relatively uncommon in stroke patients and portends a poor prognosis.<sup>35</sup> Potential etiologies of hypotension include hypovolemia from dehydration or hemorrhage, aortic dissection, or decreased cardiac output from ischemic heart disease or arrhythmias. Postthrombolytic hypotension should raise concern for either extracranial hemorrhage or cardiac tamponade from hemopericardium. Emergent echocardiography is indicated if sources of extracranial hemorrhage have been excluded.

Drug-induced hypertension is a theoretically attractive method to increase CPP and CBF to the ischemic penumbra. Small case series have shown potential clinical utility using vasopressor agents to induce hypertension.<sup>36–38</sup> Potential adverse affects of vasopressors include cardiac ischemia, renal dysfunction, cerebral edema, and hemorrhagic conversion. These may counteract potential benefits. Therefore, larger randomized trials are needed before this practice can be recommended in routine clinical stroke treatment.

#### Temperature

Fever in stroke patients is associated with increased morbidity and mortality.<sup>39,40</sup> Fever worsens injured brain by multiple mechanisms that include increasing metabolic demand and free radical production.<sup>41</sup> There are no randomized trials evaluating the treatment of fever in stroke, Table 60-2 Management of Arterial Hypertension in Acute Ischemic Stroke after the Decision to Use Thrombolytics Is Made

	Monitoring	Blood Pressure	Treatment Options
Patients not treated with thrombolytics	BP q 1-4 hr × 24 hr depending on clinical status*	Systolic: >220 mm Hg Diastolic: >120 mm Hg	Labetalol, 10 mg IV q 1-2 min, may repeat q 10-20 min, max 300 mg/day Labetalol, 10 mg IV followed by infusion at 2-8 mg/min Nicardipine infusion, 5-15 mg/hr
Patients treated with thrombolytics or mechanical thrombectomy	BP q 15 min during infusion and 2 hr after, then q 30 min $\times$ 6 hr, then q 1 hr $\times$ 24 hr*	Systolic: 180-230 mm Hg Diastolic: 105-120 mm Hg	Labetalol, 10 mg IV q 1-2 min, may repeat q 10-20 min, max 300 mg/day Labetalol, 10 mg IV followed by infusion at 2-8 mg/min
		Systolic: >230 mm Hg Diastolic: >120 mm Hg	Labetalol, 10 mg IV q 1-2 min, may repeat q 10-20 min, max 300 mg/day Labetalol, 10 mg IV followed by infusion at 2-8 mg/min Nicardipine infusion, 5-15 mg/hr

\*Consider continuous arterial pressure monitoring.

BP, blood pressure, IV, intravenous.

Adapted from Adams HP Jr, del Zoppo G, Alberts MJ, et al. Guidelines for the early management of adults with ischemic stroke: A guideline from the American Heart Association/American Stroke Association Stroke Council. *Circulation*. 2007;115:e478-534, Table 10.

but aggressive therapy and a search for the underlying cause are advised. Some centers routinely prescribe antipyretic medications for fever prophylaxis. A few small trials have shown that empirical acetaminophen or ibuprofen can promote normothermia, but it is unclear whether this leads to a demonstrable effect on outcome.<sup>42–44</sup> Studies on prophylactic antibiotics for acute stroke patients have shown mixed results.<sup>45,46</sup> Additional data are needed before prophylactic antibiotics should become part of routine clinical care.

Induced hypothermia has been shown to be neuroprotective after cardiac arrest and is recommended in this patient population.<sup>47,48</sup> However, no clear clinical benefit has been demonstrated in the few small clinical trials evaluating therapeutic hypothermia in stroke, and larger trials are ongoing.<sup>49–51</sup>

#### **Glycemic Control**

Hypoglycemia is a common mimic of acute stroke and can produce focal neurologic impairment. During the initial evaluation of a patient with acute neurologic dysfunction, serum blood sugar levels should be checked emergently, and hypoglycemia should be corrected.

Hyperglycemia is common in critically ill patients. It is present in up to half of acute stroke patients and appears to worsen short-term and long-term outcomes.<sup>52–54</sup> However, the optimal glycemic goal is unknown. Persistent hyperglycemia (>200 mg/dL) within the first 24 hours after a stroke has been correlated with expansion of stroke volume and poor outcomes.<sup>55</sup> However, a recent metaanalysis of glucose control in critically ill patients that included three acute stroke trials found no difference in mortality between very tight glucose control (<110 mg/ dL) and moderately tight glucose control (<150 mg/dL) with an excess of hypoglycemic episodes in those aggressively treated.<sup>56</sup> Based on this most recent analysis, it appears that moderately controlled hyperglycemia (<150 mg/dL) may be adequate in acute stroke patients. Multiple additional studies are evaluating this issue.

#### Venous Thromboembolism

Venous thromboembolism (VTE) is a common preventable medical complication that contributes significantly to the in-hospital morbidity and mortality of stroke patients. The rate of symptomatic deep venous thrombosis (DVT) is about 2% in acute stroke patients.<sup>20</sup> The incidence of pulmonary embolism (PE) is about 1% but accounts for 10% to 25% of early deaths in stroke patients.<sup>57,58</sup>

Methods for DVT prevention include ambulation, anticoagulant drugs, and intermittent pneumatic compression (IPC) devices. Early mobilization and ambulation, if possible, are recommended.<sup>4</sup> Aspirin has been shown to have a modest effect in reducing DVT and PE, but this should not be the sole method of prophylaxis.<sup>59</sup>

The mainstay of VTE prophylaxis in patients hospitalized for ischemic strokes are anticoagulants. Low-dose LMWH and UFH have been shown to be effective and safe.<sup>60,61</sup> A recent meta-analysis of studies comparing prophylactic doses of LMWH and UFH found that use of LMWH after ischemic stroke was associated with a reduction in VTE without increased bleeding complications.<sup>62</sup> IPC may have an additional benefit when combined with anticoagulants in preventing VTE in stroke patients.<sup>63</sup>

### NEUROLOGIC DETERIORATION IN ACUTE STROKE

#### **Recurrent Ischemic Stroke**

The incidence and prevention of symptomatic recurrent ischemic stroke were discussed previously.

#### Hemorrhagic Transformation

In patients not treated with thrombolytics, the risk for spontaneous symptomatic hemorrhagic transformation of ischemic stroke is about 0.5%.<sup>17,64,65</sup> Treatment of spontaneous hemorrhagic transformation is primarily supportive. Some patients may benefit from neurosurgical intervention.

Thrombolytic therapy increases the risk for hemorrhagic transformation. The risk for symptomatic hemorrhage is reported to be about 6% for intravenous rt-PA and 10% for intra-arterial prourokinase.<sup>64,66</sup> Advanced age, high National Institutes of Health (NIH) Stroke Score (NIHSS), elevated serum glucose, and early edema or mass effect have been shown to be predictive of hemorrhage in patients treated with intravenous rt-PA.<sup>67,68</sup>

In cases of neurologic deterioration after thrombolysis, the infusion should be stopped if not yet completed and emergent neuroimaging obtained. If hemorrhagic transformation is seen on imaging, blood should be sent for coagulation studies and a complete blood count, whereas cryoprecipitate and platelet transfusions should be given to reverse the coagulopathy. Packed red blood cells may be transfused if needed for systemic hemorrhage. Neurosurgical consultation may be helpful in selected cases. Small asymptomatic petechiae discovered on follow-up imaging studies are less concerning than hematomas and may represent successful recanalization of the occluded vessel.

#### Cerebral Edema and Elevated Intracranial Pressure

Cerebral infarction leads to cytotoxic edema and tissue swelling. After an ischemic stroke, the period of maximal swelling ranges from 2 to 5 days.<sup>69</sup> With large strokes, this can lead to elevated ICP and herniation. Standard treatment of malignant edema and elevated ICP include elevating the HOB, mild hyperventilation, osmotic diuresis, and cerebrospinal fluid drainage through ventriculostomy. However, these treatments may also reduce cerebral perfusion. No clinical trials exist evaluating these measures in ischemic stroke.

A pooled analysis of three small randomized trials evaluating the effects of prophylactic decompressive hemicraniectomy for malignant middle cerebral artery infarcts in patients younger than 60 years treated within 48 hours of symptom onset has been reported.<sup>70</sup> This study demonstrated that decompressive hemicraniectomy reduced mortality (number needed to treat [NNT], 2) and improved functional outcomes (NNT, 4) without significantly increasing the risk for severe disability.

Patients with large cerebellar infarcts may also require neurosurgical intervention. Suboccipital craniectomy may be performed in patients with large cerebellar strokes with signs of brainstem compression and obstructive hydrocephalus.<sup>71,72</sup>

#### Seizures

Seizures may occur in the acute setting after an ischemic stroke. In theory, they may worsen outcome by predisposing to aspiration, blood pressure fluctuations, increases in ICP, or neuronal injury due to increased metabolic demand. A cohort study found the rate of seizures after stroke to be 4.8% within 2 days and 8.6% overall.<sup>73</sup> Status epilepticus is relatively uncommon in stroke patients with seizures.<sup>74</sup> No data are available for the prophylactic use of antiepileptic drugs (AEDs) for seizure prophylaxis in ischemic stroke patients. Therefore, this practice is not recommended.<sup>4</sup> However, if a seizure occurs, benzodiazepines, in particular lorazepam, are appropriate to terminate a prolonged seizure, and AEDs are recommended for the treatment of seizures secondary to stroke. Treatment of status epilepticus should be managed aggressively as in other circumstances.

#### **AUTHORS' RECOMMENDATIONS**

The treatment of acute ischemic stroke continues from the emergency room through the patient's hospitalization. The goals of acute stroke management are to preserve brain tissue by improving blood flow and to prevent medical and neurologic complications in order to maximize functional recovery. There are many controversial subjects in the management of stroke patients. Consensus practice guidelines have been published by the AHA/ASA regarding early management of ischemic stroke.<sup>4</sup> Based on these guidelines and a review of the current literature, we can make these recommendations.

- Acute stroke patients should be cared for in a unit with specialized expertise in the management of stroke.
- Hypoxia and hypovolemia should be corrected, and the HOB should remain flat for up to 24 hours to maximize delivery of oxygen to ischemic tissue.
- Most stroke patients should be treated with aspirin, 325 mg daily within 24 to 48 hours of stroke symptoms, to reduce the risk for recurrent ischemic event. Clopidogrel may be an acceptable alternative in aspirin-allergic patients.
- Permissive hypertension is acceptable to increase blood flow to ischemic regions of the brain. Conservative treatment of blood pressure higher than 220/120 mm Hg, or higher than 180/105 mm Hg in patients treated with thrombolytics, is recommended.
- Normothermia and euglycemia should be promoted to decrease secondary brain injury.
- Low-dose LMWH or UFH should be used to prevent venous thromboembolic complications.
- Decompressive hemicraniectomy is beneficial in select patients with malignant middle cerebral artery infarcts. Suboccipital craniectomy improves outcomes in patients with large cerebellar strokes causing brainstem compression or hydrocephalus.
- Seizures should be treated with antiepileptic medications. There is no role for prophylactic anticonvulsants in ischemic stroke.

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# Is There a Polymyopathy or Polyneuropathy of Critical Illness? What Is It and How Is It Diagnosed and Managed? How Does It Affect Outcome?

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#### **HISTORICAL REVIEW**

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The demands that critical illness and sepsis place on all systems of the body have long been recognized. However, before the advent of the modern intensive care unit (ICU), patients often died long before such neuromuscular manifestations of critical illness became apparent. With improved care of the critically ill, ICU-acquired muscle weakness has been documented, and its critical importance in both outcome and rehabilitation is increasingly appreciated.

#### DEFINITIONS

Definitions and, therefore, reported incidence of critical illness polyneuropathy and myopathy vary significantly based on case mix, diagnostic methods, and timing of the neurologic examination. Significant controversy surrounds the incidence, mechanisms, and risk factors for such disorders as well as the relative value of electrophysiologic (EP) studies and muscle biopsy. Therefore, a clear system of classification for these disorders is lacking in existing literature.

Bolton and colleagues described the clinical, EP, and morphologic characteristics of a *critical illness polyneuropathy* (CIP), an acute axonal neuropathy responsible for weakness.<sup>1</sup> *Critical illness myopathy* (CIM) was soon proposed as another causative mechanism of weakness.<sup>2</sup> The term *ICU-acquired weakness* also has been used to describe the common scenario wherein clinically overt weakness develops in 25% to 33% of patients who are mechanically ventilated for 7 days or more.<sup>3</sup> Other terminology in the literature to describe weakness in the ICU includes *neuromuscular disorders, acute quadriplegic myopathy, critical illness neuromuscular abnormalities,* and *ICUacquired paresis.* Although early studies emphasized the predominance of CIP in ICU-acquired muscle disorders, more recent work suggests that most patients with CIP also have evidence of non-neuropathic myopathy (Table 61-1).<sup>4</sup> Thus, considerable overlap between the diagnostic criteria for CIP and CIM has been recognized. The term *critical ill*ness polyneuromyopathy (CIPNM) was coined by Bednarik in 2003 to reflect this propensity for combined disorders.<sup>5</sup> Despite the confusion surrounding the exact definitions, most authorities recognize CIP and CIM as two separate and predominant syndromes that often coexist. CIP is defined as an acute axonal neuropathy that develops during treatment of severely ill patients and remits spontaneously once the critical condition is under control. CIM collectively refers to three clinical entities that may be differentiated by biopsy: a diffuse non-necrotizing cachectic myopathy (more properly known as CIM), a selective loss of myosin filaments (known as thick-filament myopathy), and acute necrotizing myopathy of intensive care.<sup>6</sup> Although this chapter discusses CIM and CIP as distinct entities, the clinician must be mindful of the substantial overlap among the disorders.

#### SIGNIFICANCE OF INTENSIVE CARE UNIT WEAKNESS

Definitions and incidence are not the only contentious aspects of these disease states. Significant controversy also surrounds their mechanisms and risk factors, the relative value of EP studies and muscle biopsy, and the influence of these disorders on outcomes. ICU-acquired weakness has been shown to increase duration of mechanical ventilation as well as morbidity and mortality.<sup>7,8</sup> It can predispose critically ill patients to secondary complications such as pneumonia, deep venous thrombosis, and pulmonary embolism. Beyond their influence on morbidity and mortality, CIP and CIM can increase hospital costs significantly. In an economic evaluation of patients requiring prolonged mechanical ventilation, incremental costs due

Table 61-1 Generalized Neuromuscular Conditions Associated with Critical Illness*						
Condition	Incidence	<b>Clinical Features</b>	Electrophsiologic Findings	Serum Creatine Kinase	Muscle Biopsy	Prognosis
Polyneuropathy Critical illness polyneuropathy	Common	Flaccid limbs; respiratory weakness	Axonal degeneration of motor and sensory fibers	Nearly normal	Denervation atrophy	Variable
Neuromuscular transm Transient neuromuscular blockade	ission defect Common with neuromuscular blocking agents	Flaccid limbs; respiratory weakness	Abnormal repetitive nerve stimulation studies	Normal	Normal	Good
Critical illness myopath Thick-filament myosin loss	y Common with steroids, neuromuscular blocking agents, and sepsis	Flaccid limbs; respiratory weakness	Abnormal spontaneous activity	Mildly elevated	Loss of thick (myosin) filaments	Good
Rhabdomyolysis	Rare	Flaccid limbs; weakness	Near normal	Markedly elevated	Normal or mild necrosis (myoglobinuria)	Good
Necrotizing myopathy of intensive care	Rare	Flaccid weakness; myoglobinuria	Severe myopathy	Markedly elevated myoglobinuria	Marked necrosis	Poor
Disuse (cachetic) myopathy	Common (?)	Muscle wasting	Normal	Normal	Normal or type II fiber atrophy	Good
Combined polyneuropathy and myopathy	Common	Flaccid limbs; respiratory weakness	Indicate combined polyneuropathy and myopathy	Variable	Denervation atrophy and myopathy	Variable

From Schweickert WD, Hall J. ICU-acquired weakness. Chest. 2007;131:1541-1549.

to muscle weakness-related prolonged mechanical ventilation exceeded \$100,000 among the nonsurvivors.<sup>9</sup>

Unrecognized ICU weakness also can negatively influence prognosis. It has been demonstrated that, in the absence of an alternate explanation, clinicians can misdiagnose CIP as a central nervous system (CNS) disease and predict a fatal outcome in comatose patients who develop acute paralysis despite the fact that neurologic signs and radiologic imaging fail to indicate worsening brain damage.<sup>10</sup> Thus, recognition of CIP or CIM as causative factors in new-onset muscle weakness, without another explanation, can be important in excluding unreasonably pessimistic prognoses. Although any of these diagnoses may occur in conjunction with worsening CNS disease, clinicians diagnosing reversible CIP or CIM as the primary cause of worsening weakness will more likely advocate continued supportive measures with potential for a greater chance of recovery, eschewing overly bleak prognoses.

#### PREVALENCE

ICU-acquired weakness is quite common. At least 25% to 33% of patients receiving more than 7 days of mechanical ventilation develop clinically overt weakness.<sup>3</sup> Prospective neurophysiologic testing shows varying degrees of neuropathy or myopathy in more than half of patients in the ICU after 7 days or more.<sup>11</sup> Of all defined entities, CIP and CIM are the most common causes of neuromuscular weakness in the ICU.<sup>12</sup> Although neuropathy and myopathy may not be clinically evident in the early stages of critical illness, CIP develops in 50% to 70% of patients with systemic inflammatory response syndrome (SIRS).<sup>13,14</sup> Although CIPNM has been reported in children, its incidence appears to be less than in adults.<sup>15</sup>

#### **RISK FACTORS**

The development of both CIP and CIM may be associated with hyperglycemia,<sup>3</sup> severity of illness,<sup>12</sup> neuromuscular blocking drugs (NMBDs),<sup>16,17</sup> corticosteroids,<sup>3,17</sup> amino-glycoside antibiotics,<sup>11</sup> catecholamines or vasopressors,<sup>18</sup> advanced age,<sup>12</sup> and parenteral nutrition.<sup>12,19</sup> In a study of 95 medical and surgical patients, De Jonghe and associates found that female gender, number of days of multiple organ dysfunction, duration of mechanical ventilation, and use of corticosteroids were independent predictors of CIPNM.<sup>3</sup> However, Bolton<sup>20</sup> found that antibiotics, NMBDs, and nutritional deficiencies do not appear to be etiologic factors.

CIM develops in one third of patients suffering status asthmaticus and 7% of liver transplant recipients.<sup>21,22</sup> CIM also has been reported in patients after heart transplantation.<sup>23</sup> Common to all three of these populations is critical illness and associated systemic inflammation with increased cytokine expression as well as the likelihood that their treatment course would have included either NMBDs, corticosteroids, or both. The medical literature has, for more than 20 years, described the development of weakness following use of NMBDs to facilitate mechanical ventilation or for other reasons (i.e., to prevent rises in intrathoracic or intracranial pressures). Initial reports implicated aminosteroid NMBDs, although benzylisoquinolines have also been associated with CIPNM.<sup>24</sup> However, some recent studies have failed to show an association. It is notable that all NMBDs cause a chemical denervation that presents as an upregulation of acetylcholine receptors.<sup>25</sup> Denervation can lead to profound effects on muscle. Laboratory studies indicate that the steroidal neuromuscular blockers do not have a steroidal effect on the steroidal nuclear receptor.<sup>26</sup> Some experts suggest that the risk for myopathy after the use of NMBDs or corticosteroids increases after 24 to 48 hours of administration. They therefore advocate limiting the use of these agents to as short a period as possible. Levine and associates showed that diaphragmatic inactivity for as little as 18 to 69 hours could result in marked atrophy of diaphragm myofibers.<sup>27</sup> Simple bed rest, even in the absence of inflammation, can lead to decreased insulin sensitivity and inhibited protein synthesis,<sup>28</sup> suggesting that some of the muscle mass loss associated with critical illness may be due to immobilization.

#### PATHOPHYSIOLOGY

Although the pathogenesis of CIP remains unclear, many authors believe that the humoral and cellular inflammatory mediators of SIRS cause disturbances in the microcirculation of peripheral nerves and that CIP thus simply reflects another failing organ system.<sup>29</sup> The development of CIP often is preceded by a septic encephalopathy, and the severity of CIP has been linked to the severity of the Glasgow Coma Scale scores.<sup>30</sup> Additionally, a toxin that kills motor neurons in vitro has been isolated from the sera of CIP patients.<sup>31</sup> However, nerve biopsies in patients with CIP have not revealed significant microangiopathy, edema, thrombus formation, or infarction of nerve fascicles.<sup>32</sup> Further, levels of tumor necrosis factor and interleukin-6, well-known cytokines and markers of inflammation, are not elevated in patients with CIP.<sup>33</sup> This may be related to the fact that these cytokines are released locally by the infiltrating macrophages and exert paracrine effects even in the absence of elevated circulating levels.34

SIRS also appears to be an important predisposing factor for the development of CIM because cytokine release can mediate proteolysis and decreased anabolic insulin signaling.<sup>35</sup> Insulin is a pivotal anabolic hormone involved not only in glucose homeostasis but also in protein synthesis and breakdown.<sup>36</sup> Exogenous steroids and stress-related release of endogenous steroids may trigger protein degradation. This in turn can be potentiated by structural or functional denervation from trauma, surgery, CIP, NMBDs, or even immobilization.<sup>25,28,37</sup> Denervation increases the density of steroid receptors, and this can augment steroid toxicity.38 CIM also may be associated with an endogenous low-molecular-weight myotoxic factor.<sup>39</sup> Multiple other processes may be involved in the pathogenesis of CIM. These include oxidative stress from nitric oxide dysregulation, upregulation of calpain, increased muscle apoptosis, activation of the proteosome

ubiquitin-degradative system, and upregulation of the transforming growth factor- $\beta$ /mitogen-activated protein kinase pathway.<sup>39–42</sup>

#### DIAGNOSIS

A variety of neuropathies may occur in critically ill patients, either in isolation or in combination with CIP or CIM. These may occur as a result of compression from prolonged bed rest, hemorrhage, direct trauma, or ischemia.<sup>20</sup> A systematic approach to the diagnosis of neuromuscular weakness in patients with critical illness is essential (Fig. 61-1). For simplicity, ICU patients with acute neuromuscular weakness can be divided into three groups: (1) patients with preexisting neuromuscular disorders that led to ICU admission, (2) those with new-onset or previously undiagnosed neuromuscular disorders that progress during ICU stay, and (3) those with neuromuscular illness.

Suspicion of CIP or CIM should be aroused when a patient has prolonged ventilator dependence in the absence of cardiac, pulmonary, abdominal, or chest wall abnormalities. In addition, profound weakness despite a



**Figure 61-1.** Diagnostic algorithm for assessing neuromuscular complications in critical illness. CNS, central nervous system; EP, electrophysiologic; ICU-AW, intensive care unit–acquired weakness. (*From Schweickert WD, Hall J. ICU-acquired weakness.* Chest. 2007; 131:1541-1549.)

#### Table 61-2 Diagnostic Criteria for Critical Illness Polyneuropathy\*

- 1. Patient who is critically ill (sepsis and multiple-organ failure, systemic inflammatory response syndrome)
- 2. Difficulty weaning patient from ventilator after neuromuscular causes such as heart and lung disease have been excluded
- 3. Possible limb weakness
- 4. Electrophysiologic evidence of axonal motor and sensory polyneuropathy

\*These diagnostic criteria are now well established, but in certain circumstances, other acute axonal polyneuropathies, such as those due to thiamine deficiency, porphyria, etc., should be excluded.

From Bolton C. Neuromuscular manifestations of critical illness. Muscle Nerve. 2005;32:140-163.

normal sensorium that is suggestive of quadriplegia should cue the clinician toward consideration of a diagnosis of CIP or CIM. Diagnosis should be based on a detailed history (including current medications) and comprehensive physical examination. Systematic investigation of the brain, spinal cord, peripheral nerves, neuromuscular junctions, and muscles should be conducted based on the history and physical examination (see Fig. 61-1). If CNS lesions are suspected, imaging studies should be obtained as indicated. Laboratory studies (e.g., creatinine kinase), advanced EP testing, and, when necessary, histological examination of muscle may help to further clarify the diagnosis.

Early diagnosis is important for a number of reasons. Diagnostic criteria for differentiation between CIM and CIP are indicated in Tables 61-2 and 61-3. Knowing that CIP or CIM, rather than CNS, deterioration may be to blame for new-onset weakness may prevent clinicians from assigning an unreasonably pessimistic prognosis and titrating therapy on the basis of this expectation. Early diagnosis also may be useful in gauging the rate of recovery, setting an expectation for the length of mechanical ventilation or physical rehabilitation, and evaluating response to treatment.

#### Table 61-3 Diagnostic Criteria for Critical Illness Myopathy

- 1. SNAP amplitudes > 90% of the lower limit of normal
- 2. Needle EMG with short-duration, low-amplitude MUPs with early or normal full recruitment, with or without fibrillation potentials
- 3. Absence of a decremental response on repetitive nerve stimulation
- 4. Muscle histopathologic findings of myopathy with myosin loss
- 5. CMAP amplitudes < 80% of the lower limit of normal in two or more nerves without conduction block
- 6. Elevated serum creatine kinase
- 7. Demonstration of muscle inexcitability

\*For a definite diagnosis of critical illness myopathy, patients should have all of the first five features.

CMAP, compound muscle action potentials; EMG, electromyogram; MUP, motor unit potentials; SNAP, sensory nerve action potential.

From Bolton C. Neuromuscular manifestations of critical illness. Muscle Nerve. 2005;32: 140-163.
# **CLINICAL FEATURES**

As mentioned previously, CIP and CIM should be suspected in cases of unexplained difficulty in weaning a patient from mechanical ventilation. CIP generally presents as a symmetrical, flaccid, and predominantly distal quadriparesis (see Table 61-2). Both motor and sensory neuropathies may coexist, but pure forms of each also can occur.<sup>43</sup> Neurologic examination may reveal loss of distal pain, temperature, and vibratory sensation.<sup>44</sup> Cranial nerves are generally spared. This is reflected in bilateral function of facial muscles but no limb movement in response to pain. Cranial nerve involvement requires investigation of other diagnoses.<sup>29</sup> Deep tendon reflexes may be retained even in severe cases. It must be borne in mind that multiple factors in the ICU can interfere with an adequate neurologic examination. These include sedation, reluctance to respond to stimuli due to pain during movement, sleep deprivation, and less than optimal patient cooperation due to fatigue or delirium. Serial examination is required to assess progression and resolution of the disease process. Various standardized scoring systems, such as the Medical Research Council (MRC) score, can be used to promote inter-rater reliability (Table 61-4).45

CIM affects critically ill patients *after* the onset of critical illness (see Table 61-3). Weakness and myopathy that predate a prolonged ICU course should prompt investigation of other causes. CIM often occurs in association with CIP, demonstrating the significant overlap of the two entities. Clinically, CIM is a diffuse, flaccid weakness involving all limb muscles and neck flexors. Facial muscles and the diaphragm are often affected, and ophthalmoplegia may be present.<sup>46</sup> Sensation is spared but often is difficult to evaluate because of the patient's inability to respond to stimuli. Deep tendon reflexes may or may not be diminished, but a finding of normal reflexes does not rule out CIM. Myalgias are rare.<sup>20</sup>

Current ICU practices of reducing levels of sedation have made adequate clinical evaluation of strength more

#### Table 61-4 Medical Research Council (MRC) Scale for Assessment of Muscle Strength

#### FUNCTIONS ASSESSED

Upper extremity: wrist flexion, forearm flexion, shoulder abduction

Lower extremity: ankle dorsiflexion, knee extension, hip flexion

#### SCORE FOR EACH MOVEMENT

- 0: No visible contraction
- 1: Visible muscle contraction, but no limb movement
- 2: Active movement, but not against gravity
- 3: Active movement against gravity
- 4: Active movement against gravity and resistance
- 5: Active movement against full resistance
- Maximum score: 60 (four limbs, maximum of 15 points per limb) (normal)

Minimum score: 0 (quadriplegia)

feasible.<sup>47</sup> As objective methods to measure muscle strength by physical examination continue to improve, the need for extensive EP testing and histologic investigation may decrease.<sup>45</sup>

#### ELECTROPHYSIOLOGIC FEATURES

Because of the difficulties involved in obtaining a complete neurologic examination in ICU patients, some authors consider EP studies to be the gold standard for diagnosis of CIP.48 A comprehensive EP study should focus on both motor and sensory nerve conduction and needle electromyography (EMG) in upper and lower limbs. Investigation of the phrenic nerve and respiratory muscles can lend weight to CIP as a cause of continued ventilator dependence.<sup>20</sup> CIP findings generally indicate a sensorimotor axonopathy and include amplitude reduction of compound muscle action potentials (CMAPs) and sensory nerve action potentials (SNAPs) with normal nerve conduction velocities.<sup>20</sup> If these findings are accompanied by a prolonged CMAP duration, a concomitant myopathy should be considered.<sup>14</sup> Although findings may vary based on the timing of the examination within the course of disease, abnormalities usually are detectable as soon as 48 hours into critical illness.<sup>14</sup> Serial studies may be necessary to aid in both diagnosis and monitoring of progression.<sup>20</sup> Finally, EP studies also may be useful in ruling out CIP because these may reveal other neuromuscular disorders such as Guillain-Barré syndrome or prolonged neuromuscular paralysis due to NMBD. EP studies may also help diagnose junctional disorders such as myasthenia gravis and myasthenic syndrome.

As with CIP, nerve conduction findings in CIM can include low CMAP amplitudes, often accompanied by CMAP prolongation. SNAPs should be normal. EMG often shows abnormal spontaneous activity as fibrillation potentials and positive sharp waves. Direct muscle stimulation can aid in the differentiation of pure CIM and CIP.<sup>49</sup> In CIP, direct muscle stimulation can be elicited, but stimulation of the nerve supplying the muscle does not yield a response. Conversely, in severe CIM, direct muscle stimulation reveals the inexcitability of muscle membranes.<sup>49</sup> However, this technique is often of limited value owing to the commonly overlapping characteristics of CIM and CIP as well as the absence of correlation with muscle biopsy.<sup>50</sup>

#### Controversy in Electrophysiologic Studies

Abnormalities in the EP and histology are common in critically ill patients. This makes differentiation of findings that will influence clinical outcomes difficult.<sup>3</sup> Further, sepsis and multiple organ failure may diminish muscle strength even in the absence of any detectable EP abnormality.<sup>51</sup> In patients with SIRS, CIP, or CIM, the various conduction studies and EMGs of the peripheral and phrenic nerves and the diaphragm often are without predictive value regarding the severity of the CIPNM, duration of mechanical ventilation, or prognosis.<sup>44</sup> Neurophysiologic abnormalities appear to be independent of septic physiology, NMBD or steroid history, Acute

From Schweickert WD, Hall J. ICU-acquired weakness. Chest. 2007;131:1541-1549.

Physiology and Chronic Health Evaluation (APACHE) II score, or organ failure score.<sup>43</sup> Finally, recovery of muscle strength may precede EP improvement. Therefore, some authors argue that EP information contributes little in the overall management of CIP and CIM.<sup>52</sup>

Performance of a comprehensive EP evaluation is timeconsuming, often requiring 45 to 90 minutes. However, Latronico and associates recently demonstrated the efficacy of a simplified EP examination that assesses CMAP in two peripheral nerves (sural and peroneal).<sup>53</sup> They showed that a unilateral reduction of CMAP greater than 2 standard deviations yielded good diagnostic sensitivity (100%) and specificity (67%) when compared with the comprehensive EP study.<sup>53</sup>

#### MORPHOLOGIC FEATURES

Biopsy and autopsy examinations of the central and peripheral nervous systems in patients with CIP reveal varying results. In one study of nine patients who died of their critical illness, diffuse axonal degeneration of both motor and sensory fibers led to significant denervation atrophy of limb and respiratory muscles.<sup>32</sup> However, three similar investigations failed to identify any structural nerve pathology despite clinical and EP evidence of neuropathy.<sup>10,20,54</sup> In explanation, Bolton has proposed that functional change precedes structural abnormalities.<sup>55</sup>

Although a presumptive diagnosis of CIM can be reached through clinical and EP characteristics, muscle biopsy also has been advocated to aid in the diagnosis of CIM. Histologic findings may include any combination of atrophy (predominantly of type II fibers), necrosis and regeneration of muscle fibers, and selective loss of myosin filaments.45 Several subcategories of CIM have been described based on the variety of histologic pathology and the mechanism involved.<sup>56</sup> A core-needle biopsy procedure that uses gel electrophoresis to quantify the ratio of myosin to actin has been used to eliminate the morbidity of an open biopsy.<sup>57</sup> A thick-filament myopathy was first described in association with the use of NMBDs and steroids, whereas a necrotizing myopathy related to sepsis and cytokine release reflects a failure of the microcirculation to adequately supply muscle fibers.<sup>58</sup> Biopsy may not yield definitive pathology, and therefore clinical judgment should be exhausted before pursuing this invasive procedure.

Markedly elevated creatine kinase levels are suggestive of a necrotizing myopathy, whereas a smaller elevation may present in other types of CIM.<sup>58</sup> Creatine kinase levels may also be of use in differentiating CIM from CIP, wherein CK levels increase minimally if at all.

## PREVENTION AND TREATMENT

To date, there is no specific therapy for CIP or CIM. A number of treatments have undergone trials but have failed to show benefit. Small studies have failed to show benefit from intravenous immunoglobulin, plasma exchange, anti-tumor necrosis factor antibodies, interleukin-1 receptor antagonists, or *N*-acetylcysteine.<sup>59,60</sup> Consequently, early

recognition, avoidance of risk factors, and aggressive treatment of sepsis cannot be overemphasized.

Prolonged use of NMBDs should be avoided whenever possible. The administration of NMBDs can produce a chemical denervation.<sup>25</sup> The risk for myopathy after use of NMBDs or corticosteroids increases after 24 to 48 hours of administration. Therefore, limiting the use of these drugs to as short a period as possible is advocated. Two studies have failed to find any relationship between CIP or CIM and the total dose of any sedative medications commonly used in the ICU. This supports the assertion that deep sedation may be safer than prolonged neuromuscular paralysis.<sup>3</sup> Intensive insulin therapy may have a role in reducing the incidence of CIP and CIM.<sup>61</sup> Prolonged immobility may exacerbate CIP or CIM. Sedation protocols that minimize dosages as much as possible may therefore be of use in preventing CIM severity. Passive physiotherapy may also be protective.<sup>3</sup> Likewise, electrolyte abnormalities that can cause muscle damage (hyperkalemia, hypokalemia, and hypophosphatemia) should be treated aggressively.

#### OUTCOMES

#### Short-Term Outcomes

Respiratory failure and morbidity and mortality are significant short-term outcomes that may be affected by CIP and CIM.

#### **Respiratory Failure**

CIP and CIM can result in acute respiratory failure and unplanned ICU readmission.<sup>62</sup> Weaning from mechanical ventilation is estimated to require 2 to 7 times longer in patients with CIP than in controls.<sup>63</sup>

#### Mortality

CIP has been reported as an independent predictor of both ICU and in-hospital mortality.<sup>11,12</sup> However, although studies demonstrate an association between poor short-term outcome and CIP or CIM, poor outcome also may stem from the type and severity of underlying illness independent of neuromuscular pathophysiology.<sup>64</sup>

#### Long-Term Outcomes

In a composite review of 36 studies involving 263 patients evaluating the impact of CIPMN on the outcome of critically ill patients, Latronico and associates found that 68% of patients completely regained the ability to breathe spontaneously and walk independently.<sup>63</sup> Severe quadriparesis, quadriplegia, or paraplegia continued to affect 28%. Milder disabilities such as reduced or absent deep tendon reflexes, stocking-and-glove sensory loss, muscle atrophy, painful hyperesthesia, and limitations in activities of daily living were common.<sup>63</sup> Indeed, van Mook and coworkers estimated only a 50% chance of complete recovery.<sup>65</sup>

A prospective study of patients with CIPNM showed that roughly one third died in the acute phase of disease, whereas one third were ambulatory within 4 months. The remaining third required 4 to 12 months to recover or remained ventilator dependent.<sup>66</sup> Although the median hospital stay in patients with CIP is roughly 3 months, long-term outcomes can be good. Outcomes following severe CIM can be especially poor with the necrotizing variant.<sup>11</sup> In survivors of prolonged critical illness, clinical and neurophysiologic evidence of neuropathy may persist for up to 5 years from hospital discharge.<sup>67</sup> Fortunately, such prolonged evidence of myopathy is uncommon.<sup>67</sup>

## CONCLUSION

CIP and CIM are common problems in the ICU and can contribute to high morbidity and mortality. Although both entities can exist in isolation, considerable overlap of findings is the norm. Clinicians should be cognizant of risk factors and vigilant for early signs of disease. Diagnosis relies on history, clinical examination, and EP studies but may be challenging because of factors such as inability of the patient to cooperate and the high incidence of unrelated EP and histologic abnormalities. Treatment hinges on prevention and physiologic support, and an iterative, multidisciplinary approach involving clinicians and basic scientists is essential to further define the pathogenic mechanisms of CIP and CIM. As our knowledge of the conditions increases, clinicians will be able to shift from reactive, symptomatic treatments to proactive strategies focused on causative mechanisms.

#### AUTHORS' RECOMMENDATIONS

- Muscle weakness associated with critical illness is a definite entity and has been described with different names. Strict division between critical illness polyneuropathy and critical illness myopathy increasingly is being abandoned and titled as *critical illness polyneuromyopathy* (CIPNM), a term that reflects the multilevel and multifactional pathologic state.
- Myopathy in the absence of neuropathy usually occurs in the absence of inflammation, particularly after the use of muscle relaxants or steroids.
- Muscle weakness associated with critical illness influences not only hospital and rehabilitation costs but also, more importantly, morbidity and mortality.
- No definitive EP, imaging, histologic, or clinical testing can differentiate the etiologic factors resulting in CIPNM.
- Risk factors for CIPNM include systemic inflammation or sepsis, prolonged use of muscle relaxants, and steroids.
   Prolonged immobilization even in the absence of inflammation can lead to muscle weakness.
- At this time, there is no specific treatment available for CIPNM. All current treatments are preventative or symptomatic. Intensive insulin therapy may be of some benefit.

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# Is Hypothermia Useful in Managing Critically III Patients? Which Ones? Under What Conditions?

Tomas Drabek, Patrick M. Kochanek

Hypothermia at the dawn of the 21st century represents a unique approach that has been tested for many clinical conditions. Although it may seem simplistic compared with other current sophisticated life-preserving methods, it has proved to be a most powerful tool to improve outcome from some of the most severe insults found in the critically ill. The concept of therapeutic hypothermia has a rich history, but we have yet to fully explore its potential, fine-tune its indications, or optimize its application.

The interest in hypothermia dates back to Hippocrates. He suggested that topical cooling might prevent bleeding. During the Napoleonic wars, Napoleon's surgeon observed that wounded soldiers placed farther from fire died later than those closer to fire. In the 1930s, Fay cooled the extremities of patients presenting with tumors and, in 1940, described better-than-expected results when patients with severe traumatic brain injury (TBI) were exposed to hypothermia for 4 to 7 days. The use of hypothermia in modern history dates back to the 1950s when elective moderate hypothermia (28° to 32°C) was induced during general anesthesia for brain and heart protection. At the same time, the effects of hypothermia on oxygen metabolism were described. As early as the 1960s, Safar suggested applying hypothermia to patients resuscitated from cardiac arrest (CA).

The following decades were characterized by periodic ebb and flow in enthusiasm for hypothermia. The initial concept that "deeper and longer is better" was offset in early trials by problems with bleeding and septic complications. The seminal work of Busto and coworkers showed in an animal model that mild hypothermia was effective in cerebral resuscitation.<sup>1</sup>

Several mechanisms that mediate the protective effects of hypothermia have been identified. However, the overall response probably results from a combination of multiple mechanisms that vary with the level and duration of hypothermia. Thus, the level of hypothermia to be used in different settings may vary widely; deep hypothermia (15° to 22°C) is used in cardiac surgery to enable circulatory arrest, whereas mild hypothermia (32° to 34°C) is used to improve outcome after CA and other ischemiareperfusion events. Hypothermia can be induced simply, using surface cooling, or through sophisticated techniques with specially designed catheters and blankets. The almost universal ability to induce hypothermia makes it a widely applicable, highly attractive approach.

Despite its long history, the widespread clinical application of hypothermia is a relatively new phenomenon. Recent results from two clinical trials demonstrated the benefit of therapeutic hypothermia after CA.<sup>2,3</sup> This renewed interest in cooling has spurred the initiation of a new series of clinical trials exploring other potential scenarios in which one would hypothesize that hypothermia would be beneficial. In this chapter, we focus on mild to moderate hypothermia that does not require the use of cardiopulmonary bypass (CPB) and can be accomplished in an intensive care unit (ICU).

#### TEMPERATURE MONITORING

The normal body temperature in healthy individuals (measured in the oral cavity) is  $36.8^{\circ} \pm 0.4^{\circ}$ C, with normal diurnal variations of 0.5°C. Rectal temperatures are usually 0.4°C higher than oral readings.<sup>4</sup> Lower esophageal temperature closely reflects the core temperature as well as rectal temperature and bladder temperature. The temperature measured by pulmonary artery catheters most closely correlates with brain temperature during rapid cooling.<sup>5</sup> Clinically, tympanic temperature, which measures radiating heat from the tympanic membrane, is often used as a surrogate for deep brain temperature. Based on the method of cooling, the difference in temperature between various monitoring sites could be significant. In addition, there is no generally accepted, clearly defined range for various levels of hypothermia. In clinical practice, temperatures of 33° to 36°C are usually referred to as *mild hypothermia*, 28° to 32°C as *moderate* hypothermia, and below 28°C as deep hypothermia.<sup>6</sup>

# **COOLING METHODS**

Traditionally, external cooling with ice packs applied over great vessels or ice-water–soaked cloth blankets has been used to treat hyperthermia and, eventually, induce hypothermia. Gastric, peritoneal, or pulmonary lavage was used

to rewarm drowning victims, and this approach could be used in reverse for cooling. Recently, cooling with a rapid intravenous (IV) infusion of ice-cold solutions gained popularity for its ease, general availability, and considerable lack of adverse effects, even in CA victims. Bernard and associates used large volumes (30 mL/kg) of ice-cold (4°C) IV fluid in CA victims and was able to decrease the core temperature from 35.5° to 33.8°C within 30 minutes.<sup>2</sup> Using a similar approach, Kim and colleagues achieved a 1.5°C temperature decrease over 30 minutes.<sup>7</sup> Most importantly, they did not observe any clinically important changes in vital signs, electrolytes, arterial blood gases, or coagulation parameters. Although IV fluids can initiate cooling effectively, they are not effective for maintaining hypothermia.<sup>8</sup> Cooling blankets with circulating water offer fairly rapid cooling but require attaching a bulky control console to the patient. Similar limitations apply to intravascular cooling catheters. However, both contemporary surface cooling devices and intravascular cooling catheters are able to maintain hypothermia precisely. Kliegel and colleagues successfully combined the rapid induction of hypothermia with IV fluids and subsequent cooling with an intravascular catheter.<sup>9</sup> Submersion in ice-water represents the fastest cooling method (0.11° to 0.25°C/minute). This approach may be useful in heatstroke victims but is unlikely to be feasible in the intensive care unit. An effort to eliminate the potential complications associated with whole-body hypothermia led to the development of devices to induce selective brain hypothermia. Cooling helmets have been used in multiple trials in both pediatric and adult populations.<sup>10–12</sup> Other techniques that might provide more rapid cooling are being explored in various animal models. These include nasopharyngeal cooling, neck cooling, and direct cooling of blood in the carotid arteries. Cooling using extracorporeal circulation is extremely effective, but its use is logistically limited.

Unfortunately, no drug currently available will induce hypothermia in humans or large animals. Blackstone and associates used inhaled hydrogen sulfide to induce deep hypothermia in spontaneously breathing mice.<sup>13</sup> However, this phenomenon remained an isolated observation that was not reproduced in higher species. Although hibernation-induction triggers have been used to induce hypothermia in natural hibernators, the same effect could not be reproduced in non-hibernators.

Future trials will determine the ideal method, timing, and duration of cooling. In addition, the rate of rewarming appears to significantly affect the benefits of hypothermia.

## COMPLICATIONS ASSOCIATED WITH THERAPEUTIC HYPOTHERMIA

Hypothermia initiates multiple physiologic changes in the circulatory, respiratory, and coagulation systems. It also has profound metabolic effects. These changes are temperature dependent. Mild hypothermia most often induces sinus tachycardia. More dangerous cardiovascular complications usually are seen at temperatures below 30°C. These include atrial fibrillation, bradycardia, and terminal ventricular fibrillation (VF) at about 25°C. The mild hypothermia currently used in clinical practice is hemodynamically well tolerated, with about a 25% decrease in cardiac output and an increase in systemic vascular resistance and central venous pressure. In healthy subjects, mild hypothermia increased myocardial perfusion.<sup>14</sup> Hypothermia also induces the release of endogenous catecholamines with a four- to seven-fold increase in norepinephrine levels, even with minimal temperature changes (0.7° to 1.2°C).<sup>15</sup> This adrenergic response is associated with an increase in blood pressure, vascular tone, and oxygen consumption that could be detrimental in patients with marginal cardiac reserve.

The bleeding diathesis associated with hypothermia is a result of platelet depletion or dysfunction and clotting factor depletion. The magnitude of changes is often difficult to assess because clinical laboratories adjust the temperatures of all samples to a standard 37°C. Reed and coworkers cooled plasma containing clotting factors equivalent to 100% of normal to 35°, 33°, and 31°C.<sup>16</sup> Partial thromboplastin time (PTT) in these samples was prolonged as if factor IX had been depleted to 39%, 16%, and 2.5% of normal, respectively. Factor activity is also severely impaired below 30°C; for example, at 25°C, clotting activity ranges from 0% (factor VIII and factor IX) to 5% (factor II and factor VII).<sup>16</sup> This suggests that factors are dysfunctional, not depleted, because the changes were observed despite 100% or greater factor concentrations measured in the studied samples. Thromboelastography (TEG) may be a useful tool in the setting of therapeutic hypothermia.<sup>17</sup> The TEG from hypothermic swine (32°C) showed prolonged initial clotting time (R-time) and decreased clotting rapidity ( $\alpha$ -angle). These changes suggest a deficit in thrombin availability or delay in thrombin generation or activation but not a decrease in clot strength or an increase in clot lysis.<sup>18</sup> Other TEG-based studies suggest that clot firmness is decreased in temperatures lower than 30°C.<sup>19</sup> Bleeding time, one indicator of platelet function, was prolonged 2.5-fold in a sample from a cold  $(32^{\circ}C)$  versus a warm  $(37^{\circ}C)$  extremity in baboons.<sup>20</sup> In a similar experiment in human volunteers, clotting times were 3 times longer at 22°C than at 37°C.<sup>21</sup> Concurrent acidosis and hypothermia further impaired coagulation.<sup>22</sup> Those effects should be taken into consideration when resuscitating trauma victims with ongoing bleeding. Systemic and local normothermia is essential for coagulation. However, trials indicate that neither mild nor moderate therapeutic hypothermia is associated with bleeding complications in patients with severe TBI.23,24

Hypothermia may lead to leukopenia and an increased risk for infection. Several studies in patients after CA, TBI, or acute stroke showed an increased risk for pneumonia, especially when the duration of hypothermia was prolonged (>48 to 72 hours).<sup>25–27</sup> Shorter hypothermic periods (<24 hours) appear to be safer.<sup>2,3,24</sup> Obviously, the tradeoff of increased infection rate may be worthwhile if greater neuroprotection can be achieved.

Electrolyte disorders, although common in therapeutic hypothermia, usually are minor and can be treated easily in a critical care setting. The most commonly observed abnormalities are hypernatremia, hypokalemia, hypomagnesemia, hypophosphatemia, and hypocalcemia.<sup>28,29</sup> Magnesium supplementation may be especially important

given its known protective role in neuronal and myocardial injury.<sup>28,30–32</sup>

Hypothermia-induced decreases in insulin sensitivity may lead to hyperglycemia. This could enhance susceptibility to infection and also might exacerbate secondary brain injury.<sup>33–35</sup> Tight glycemic control may be warranted, although the recent work by Vespa and associates suggests caution and use of insulin at higher glucose levels of probably more than 150 mg/dL.<sup>36</sup>

Drug metabolism is profoundly altered by hypothermia. Some drugs are affected more than others. Mild to moderate hypothermia decreases systemic clearance of cytochrome P-450–metabolized drugs by about 7% to 22% per 1°C below 37°C.<sup>36</sup> Hypothermia decreases the potency and efficacy of certain drugs.<sup>37</sup>

#### **MECHANISM OF ACTION OF HYPOTHERMIA**

The original concept of hypothermic protection was based on the fact that cerebral metabolic rate is decreased by 5% to 7% for each 1°C decrease in body temperature.<sup>38</sup> However, this observation does not explain the ability of even small temperature changes to affect physiology and provide neuroprotection. Protection by hypothermia in experimental central nervous system (CNS) injury might involve a myriad of mechanisms: maintenance of physiologic adenosine triphosphate (ATP) concentrations, suppression of glutamate release, attenuation of oxidative or nitrative stress, blunting of the inflammatory response, prevention of energy failure, limitation of cytoskeletal damage, increased levels of neurotrophins, prevention of anoxic depolarization, regulation of gene expression, attenuation of apoptosis or limitation of blood-brain barrier injury, and vasogenic edema. In TBI or ischemic stroke, therapeutic hypothermia reduces intracranial pressure (ICP).<sup>39,40</sup> However, direct neuroprotection has been more difficult to demonstrate outside of the laboratory.

Various combinations of those mechanisms could be responsible for the different outcome in the wide variety of CNS injuries, with hypothermia being beneficial in only selected settings.

#### HYPOTHERMIA IN CARDIAC ARREST

The earliest experience with hypothermia involved "accidental" hypothermia. In these instances, it was noted that victims of drowning in cold water survive a much longer period of CA than would be expected if the accident occurs at ambient temperature. To our knowledge, the initial case series of therapeutic hypothermia applied to victims of CA of various origin (respiratory failure, trauma) was published 1958. Surprisingly, the target temperatures and duration of cooling (30° to 34°C for 24 to 72 hours) closely resembled current recommendations (32° to 34°C for 12 to 24 hours). In 1959, Benson and colleagues reported the first case series of in-hospital CA patients.<sup>41</sup> Their data revealed favorable neurologic recovery in 50% of hypothermic patients versus 14% of normothermic patients. Despite these early promising results, the clinical use of hypothermia was abandoned until the late 1990s.

The reason is not clear. However, it is possible that the complications associated with deeper levels of hypothermia ( $<30^{\circ}$ C) and prolonged use, as observed in animal studies, played a role.<sup>42,43</sup> Laboratory studies in the 1980s explored the potential of mild hypothermia to protect while limiting complications. Busto and associates found that small increments in intraischemic temperatures ( $33^{\circ}$ ,  $34^{\circ}$ ,  $36^{\circ}$ , and  $39^{\circ}$ C) translated into large differences in neuronal loss in a rat model.<sup>44</sup> Safar's group followed that work, showing benefit in experimental CA.<sup>45</sup> These studies provided evidence that even mild hypothermia could significantly improve outcome in CA.

Timing of hypothermia induction also is critical. Initiating hypothermia during the insult yields the best outcome but is rarely clinically feasible. Delayed hypothermia is beneficial in the early postinsult period, but the effect declines over time.<sup>46</sup> Based on studies by Colbourne and coworkers in gerbils, minimal delay and longer duration are of utmost importance to fully benefit from hypothermia.<sup>47–49</sup>

Several randomized human trials assessed the efficacy of hypothermia after CA. Hachimi-Idrissi and colleagues studied 30 patients after CA.<sup>50</sup> Victims were randomized to either hypothermia induced with a cooling helmet or to standard treatment. Target temperature was 34°C, duration was 4 hours, and the patients were allowed to rewarm spontaneously over 8 hours. This feasibility study showed favorable neurologic recovery in 2 of 16 patients in the hypothermia group compared with none in the normothermia group. No increase in complications was noted.

Two studies published in 2002 clearly established the value of hypothermia in CA. Bernard and colleagues in Australia studied 77 patients after CA from VF.<sup>2</sup> The patients assigned to hypothermia were cooled to 33°C over 12 hours with ice packs. Twenty-one of 43 patients (49%) in the hypothermic group survived with good neurologic outcome, whereas this was noted in only 9 of 34 patients who were not cooled (26%, P = .046). The odds ratio for a good outcome with hypothermia was 5.25 (95% confidence interval [CI], 1.47 to 18.76; P = .011). In the European multicenter Hypothermia after Cardiac Arrest (HACA) trial, patients resuscitated after CA from VF or ventricular tachycardia were randomly assigned to hypothermia (32° to 34°C for 24 hours, cooling with cold air) or to normothermia.<sup>3</sup> In the hypothermia group, 75 of 136 patients (55%) showed favorable neurologic outcome, compared with 54 of 137 in the normothermic group (39%) (risk ratio, 1.68; 95% CI, 1.29 to 2.07; number needed to treat, 6).<sup>3</sup> The fact that the results from those two studies were similar was even more compelling. Surprisingly, hypothermia was effective despite a relative delay in initiation and slow onset. Tiainen and associates studied cognitive and neurophysiologic outcome in a cohort of 70 patients randomly assigned to hypothermia (33°C for 24 hours) or normothermia.<sup>51</sup> Three months after CA, 28 of 36 patients in the hypothermic group versus 22 of 34 in the normothermic group were alive (P = .226). Although the primary end point of this study was not outcome, the high survival rate in both groups might explain the failure of hypothermia to improve outcome. The authors concluded that the use of therapeutic hypothermia was not associated with cognitive decline or neurophysiologic deficits.

As therapeutic hypothermia began to be used routinely, several registries for follow-up were established. Arrich and associates evaluated the data from 650 patients from 19 centers entered into the European Resuscitation Council Hypothermia after CA Registry.<sup>52</sup> Of all patients, 462 (79%) received therapeutic hypothermia, 347 (59%) were cooled with an endovascular device, and 114 (19%) received other cooling methods such as ice packs, cooling blankets, or cold fluids. The rate of adverse events was lower (hemorrhage 3%, arrhythmia 6%) and the cooling rate was faster than in published clinical trials. Therapeutic hypothermia is thus feasible and can be used safely and effectively outside a randomized clinical trial.

Oksanen reviewed the data from CA survivors admitted to Finnish ICUs between 2004 and 2005.<sup>53</sup> Almost all ICUs used hypothermia (19 of 20), but it appeared to be implemented only in selected groups of patients (4% in 2004, 28% in 2005). Despite the underuse of hypothermia, the survival rate at 6 months was 55%.

As a result of these studies, the International Liaison Committee on Resuscitation recommends that, "Unconscious adult patients with spontaneous circulation after out-of-hospital CA should be cooled to 32°C to 34°C for 12 to 24 hours when the initial rhythm was VF. Cooling to 32°C to 34°C for 12 to 24 hours may be considered for unconscious adult patients with spontaneous circulation after out-of-hospital CA from any other rhythm or CA in hospital."<sup>54</sup>

Despite this endorsement, hypothermia in the United States is underused. It is estimated that if U.S. physicians were to use therapeutic hypothermia in all eligible patients, 2298 additional patients per year would achieve a good neurologic outcome.<sup>55</sup> It remains for future trials to determine whether the benefits conferred by hypothermia can be extended to victims of in-hospital CA or non-VF CA, or to children.

#### THERAPEUTIC HYPOTHERMIA IN ISCHEMIC STROKE

Experimental animal studies addressing focal brain ischemia have shown up to 90% lesion reduction with hypothermia.<sup>56,57</sup> This has sparked an interest in using this method in patients with ischemic stroke. Importantly, it was found that brain temperatures in stroke patients appear to exceed core temperature by at least 1°C (1.0° to 2.1°C).<sup>58,59</sup> A study that involved 3790 patients demonstrated that preventing hyperthermia in stroke patients improved outcome.<sup>60</sup> However, a pharmacologic-based strategy to induce hypothermia using acetaminophen resulted in a body temperature decrease of only 0.22°C.<sup>42</sup> Therefore, this approach is not clinically useful. Schwab and colleagues performed two noncontrolled trials in acute ischemic stroke patients to evaluate the effect of hypothermia (33°C for 24 to 72 hours). In the first study, hypothermia was initiated in 25 patients 14 hours after first symptoms (range, 4 to 24 hours).<sup>40</sup> Target temperature was achieved after 3 to 6 hours. Passive rewarming was achieved over 18 hours (range, 17 to 24 hours). ICP decreased in all patients during hypothermia, but significant increases in ICP were observed during rewarming.

Pneumonia was observed in 40% of patients. In the second study, 50 patients were subjected to hypothermia in a manner similar to the previous study.<sup>27</sup> ICP decreased from  $20 \pm 14$  mm Hg to  $12 \pm 5$  mm Hg during hypothermia. Shorter rewarming periods (<16 hours) were associated with a marked ICP increase and higher mortality when compared with longer rewarming periods. Mortality in this study was 38%, which compares favorably with outcomes of other studies with similar patient populations without hypothermia, showing mortality rates of 78% to 79%.<sup>61,62</sup>

Kammersgaard and colleagues used hypothermia ( $35.5^{\circ}$ C for 6 to 17 hours) in 17 awake patients and compared the outcome data with matched subjects from the Copenhagen registry.<sup>63</sup> Neurologic impairment as assessed by the Scandinavian Stroke Scale at 6 months was similar ( $42 \pm 14$  versus  $48 \pm 11$ , respectively; P = .21).

De Georgia and associates conducted a feasibility trial of 40 patients randomized to intravascular cooling (33°C for 24 hours) or control therapy after ischemic stroke.<sup>64</sup> Clinical outcomes and lesion size at 1 month were similar in both groups. No adverse side effects were observed.

Hemicraniectomy represents the most invasive approach to treat ischemic stroke. Georgiadis and associates randomized 36 patients to either hemicraniectomy or hypothermia.<sup>65</sup> Mortality was 12% in hemicraniectomy versus 47% in hypothermia. The latter also was associated with a higher complication rate. Els and colleagues compared hypothermia with hemicraniectomy (HH, n = 12) to hemicraniectomy alone (HA, n = 13).<sup>66</sup> These data demonstrate a trend toward better outcome in the HH group at 6 months (P < .08).

Thus, there currently are no robust data to support the use of induced hypothermia in patients with ischemic stroke. Given that small trials suggest benefit, additional trials are indicated.

#### HYPOTHERMIA FOR SPINAL CORD INJURY

A limited number of studies have addressed the use of hypothermia after traumatic spinal cord injury (SCI). The results from the animal studies are mixed. However, the models are quite varied. No studies using whole-body hypothermia for SCI have been published. Regional cooling of spinal cord might be a viable alternative. This approach, reviewed by Kwon and coworkers, was assessed in small case series in the 1970s and 1980s.<sup>67</sup> Despite some encouraging results, the authors of all respective studies acknowledge the limitations (e.g., small number of patients, differences in clinical assessment of deficits, and lack of controls) and the need for larger controlled studies. In cardiovascular surgery, both regional and systemic hypothermia were used to prevent ischemic SCI during thoracoabdominal aortic aneurysm repair (TAA).<sup>68</sup> Svensson and associates retrospectively evaluated data from 132 patients after TAA repair with CPB and found that active moderate (29° to 32°C) or profound (<20°C) hypothermia, but not passive mild hypothermia, protected equally against neurologic deficits (34.5°C).<sup>69</sup> Similarly, Kouchoukos and colleagues reported substantial protection against paralysis and end-organ failure in 211 patients undergoing TAA repair with CPBinduced systemic hypothermia (15° to 19°C) without other interventions.<sup>70</sup> Von Segesser and coworkers prospectively analyzed 100 patients scheduled for TAA repair with CPB.<sup>71</sup> Total clamp time and CPB duration were longer in the hypothermic patients. Although they observed no difference in paraplegia between normothermic and hypothermic (29°C) patients (8% in both groups), there was a trend toward improved mortality (15% versus 4%; P = .06; odds ratio, 4.1).

Regional cooling with an ice-cold epidural saline infusion has been used to achieve cerebrospinal fluid (CSF) temperature of 25° to 27°C while maintaining systemic normothermia.<sup>72</sup> In a review of 445 patients summarizing 20 years of experience, epidural cooling significantly reduced the risk for SCI in patients with types I to III TAA (13.7% versus 29%; P = .01).<sup>73</sup> Similar results were reported by Tabayashi and associates, who combined epidural cooling with CSF drainage to decrease postoperative SCI.<sup>74</sup>

Currently, there is a paucity of evidence to suggest that hypothermia should be applied after traumatic SCI. Preventive induction of regional hypothermia for major vascular procedures with or without additional measures, including systemic hypothermia, appears promising but was not validated in a large prospective randomized study.

#### HYPOTHERMIA FOR TRAUMATIC BRAIN INJURY

Current diagnostic and therapeutic approaches to patients with TBI vary widely between institutions. Treatments have been aimed at maintenance of cerebral blood flow, surgical intervention, and prevention of edema. Unlike CA patients, the onset of neuronal death in TBI occurs early in the course of the syndrome.<sup>75</sup> Many experimental studies in animals have shown that hypothermia is of value after TBI. Up to 30 randomized controlled trials addressing the use of hypothermia after TBI have been conducted. Methodology and results are conflicting. The depth and duration of hypothermia applied have varied widely, as have the use of other therapeutic modalities (e.g., CSF drainage, osmotic therapy, sedation, or paralysis). Better results were achieved in centers with expertise in applied hypothermia. Five published meta-analyses indicate a trend toward improved neurologic outcome and mortality when hypothermia was used, but definitive statistical significance is lacking.

Hypothermia is effective in reducing increased ICP. Early start of cooling, adequate duration, and very slow rewarming are crucial to maintain the beneficial effect. Patients hypothermic on admission should possibly be maintained hypothermic or very slowly rewarmed. However, despite superior ICP control, favorable neurologic outcome could not be achieved in all patients.<sup>76</sup>

Most recently, in an international multicenter trial, Hutchison and colleagues randomized 225 children with TBI to hypothermia (32.5°C for 24 hours) or normothermia.<sup>77</sup> At 6 months, 31% versus 22% of patients had unfavorable outcome (defined as severe disability, a persistent vegetative state, or death) in the hypothermic versus normothermic group, respectively (P = .14). Mortality was higher in the hypothermic versus normothermic group (21% versus 12%; P = .06). In this study, hypothermia therapy did not improve the neurologic outcome, with a strong trend to increased mortality. The relatively delayed start of hypothermia and short duration could be contributing factors, with rewarming occurring during the anticipated period of peak edema.

In conclusion, hypothermia should be considered in patients with TBI and increased ICP. Early initiation, duration for greater than 48 hours, and slow rewarming with tight monitoring of ICP appear to be of paramount importance.

#### HYPOTHERMIA FOR MYOCARDIAL INFARCTION

Many patients recovering from CA develop myocardial ischemia that requires further intervention. Given the effect of hypothermia on neurologic recovery, it is intriguing to hypothesize that hypothermia could limit myocardial damage. However, there is a paucity of evidence that specifically addresses the effect of hypothermia on myocardial injury within or beyond the setting of CA. The results of animal studies focused on reduction of infarct size with hypothermia are inconclusive. However, use of hypothermia appears feasible. In a multicenter but small study, Dixon and associates randomized 42 patients with acute myocardial infarction to primary percutaneous coronary intervention (PCI) with or without endovascular cooling (33°C for 3 hours); there was not a statistically significant difference in the median infarct size.<sup>78</sup> The feasibility of endovascular cooling in awake patients undergoing PCI was confirmed in a nonrandomized study (LOWTEMP trial).<sup>79</sup> Wolfrum and coworkers found that, compared with historical controls, the initiation of hypothermia did not delay other interventions.<sup>80</sup> In a nonrandomized study, Hovdenes and colleagues reported that PCI could be performed on CA patients who developed acute myocardial infarction, including some who required an intra-aortic balloon pump.<sup>81</sup>

In summary, the data suggest that hypothermia is feasible in hemodynamically unstable CA patients who require hemodynamic support and that the initiation of a hypothermia protocol does not delay further interventions. However, therapeutic hypothermia cannot be endorsed in acute myocardial infarction patients without CA.

## HYPOTHERMIA FOR HYPOXIC-ISCHEMIC ENCEPHALOPATHY

Hypoxic-ischemic encephalopathy (HIE) from asphyxial insults is associated with high mortality and long-term neurodevelopmental disability in survivors. This is especially true in infants and children. The injury is two staged. A certain amount of damage results from acute, primary neuronal death. This often is followed by a second, delayed period of neuronal loss. This secondary injury provides a therapeutic window in which further damage might be prevented. Logically, hypothermia might be of value during this time.

Selective head cooling has been tested primarily in infants. However, body core temperature must be decreased to achieve cooling of deep brain structures.<sup>82</sup>

The data from eight randomized controlled trials comprising 638 near-term infants were summarized in a recent Cochrane review. Therapeutic hypothermia was shown to be beneficial to term newborns with HIE. Death or major disability, mortality, and neurodevelopmental disability were all reduced without increasing disability in survivors. The relative risk reduction was 24%, with number needed to treat of 7 in moderate or severe HIE. Cooled infants developed significant thrombocytopenia and required inotropes for hypotension.<sup>83</sup> Thus, hypothermia appears to be beneficial in the treatment of HIE in infants. Additional studies are needed in children and adults with asphyxial insults.

# CONCLUSION

Therapeutic hypothermia in the ICU represents a promising multifaceted therapy for several medical conditions. Although extremely powerful, it requires careful titration of its depth, duration, and rewarming. To date, hypothermia is a generally accepted treatment for out-ofhospital CA in adults and for HIE in newborns. Studies may well confirm its value in other settings. The current technology to induce and maintain hypothermia allows for precise temperature control. Future studies should focus on optimizing hypothermic treatment to the full benefit of patients (Table 62-1).

#### **AUTHORS' RECOMMENDATIONS**

- Mild therapeutic hypothermia, applied after restoration of spontaneous circulation, is steadily gaining acceptance as a neuroprotective intervention in the treatment of adults who remain neurologically unresponsive after cardiac arrest.
- Mild therapeutic hypothermia is also gaining acceptance in the treatment of term newborns suffering hypoxic-ischemic insults in the perinatal period.
- Based on studies in experimental models, mild therapeutic hypothermia may have other potential uses as a neuroprotectant in neurointensive care, such as in stroke, TBI, SCI, and other conditions. However, further studies are needed to determine whether this potential benefit is translatable to the human condition.

Table 62-1 Summa	Table 62-1 Summary of Randomized Controlled Trials*							
Study	No. of Subjects (Intervention/ No Intervention)	Intervention	Control	Outcomes				
TRAUMATIC BRAIN IN	JURY IN CHILDREN							
Adelson et al, 2005 <sup>76</sup>	37/38	Hypothermia	Normothermia	Nonsignificant decrease in mortality with hypothermia; decrease in ICP; rebound increase in ICP with rewarming; no difference in outcome				
Hutchison et al, 2008 <sup>77</sup>	108/117	Hypothermia	Normothermia	Trend to unfavorable outcome (RR, 1.41 [0.89–2.22]; P = .14) and mortality (RR, 1.40 [0.90–2.27]; $P = .06$ ) with hypothermia				
INJURY								
Gentilello, 1997 <sup>84</sup>	29/28	Rapid rewarming	Standard rewarming	Less fluid requirement and time to achieve normothermia in the rapid rewarming group				
ISCHEMIC STROKE								
De Georgia et al, 2004 <sup>64</sup>	18/22	Hypothermia	Normothermia	No difference in lesion growth on MRI				
SPINAL CORD INJURY	Y							
von Segesser et al, 2001 <sup>71</sup>	48/52	Hypothermia	Normothermia	Strong trend for reduction in mortality with hypothermia (2/48  vs.  8/52; P = .06); freedom from negative events improved with hypothermia (OR, 2.0 [0.3-4.4]; P = .04)				

\*Use with no meta-analyses available.

ICP, intracranial pressure; MRI, magnetic resonance imaging; OR, odds ratio; RR, relative risk.

- The mechanisms underlying the beneficial effects of therapeutic hypothermia appear to be multifactorial and are only beginning to be understood in the clinical setting.
- Optimization of cooling methods, duration and depth of hypothermia, approach to rewarming, and minimization and management of side effects are needed to maximize the therapeutic potential of resuscitative mild hypothermia.

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# 3 How Does Critical Illness Change Metabolism?

# Mark E. Nunnally

The evolution of a discreet injury into a syndrome that spans neurologic, endocrine, and metabolic systems, sometimes leading to radical changes in end-organ function, is one of the fundamental characteristics of the critically ill patient. Many metabolic changes in this syndrome have been described, but the meaning of these changes remains subject to interpretation. Without interpretation, the observations remain isolated facts unable to guide clinical management. Evidence-based management of critical illness, therefore, must rely on theoretical interpretation.

The relationship between tissue injury and total-body metabolic changes has been well evaluated. Cuthbertson was among the first to describe and explain the stress response, a pattern of metabolic changes in injured patients.<sup>1</sup> In his framework, the physiology of critical illness was an adaptive response. Metabolic changes from "normal" were necessary to heal serious injury. This concept informs the scientific inquiry into which processes are biologically helpful or harmful and which should be supplemented or suppressed. Such scientific debate extends to nutrition, care of endocrine systems, and intervention in immunologic signaling. In each case, there is usually a dearth of clear evidence, a glut of theory, and an absence of consensus. Nevertheless, good data do exist. This chapter considers the predictable pattern in response to injury, the role of interventions that depend on this pattern, and the diagnostic utility of comparing a patient's clinical data to the stress response pattern.

#### PATHOPHYSIOLOGY AND MECHANISM OF ACTION

Hypermetabolism is the trademark of critical illness, a phenomenon originally described as "ebb and flow,"<sup>2</sup> in which a period of hypoperfusion to maintain survival is followed by a healing period. As description in critical care evolved, these phases became shock and postresuscitation hypermetabolism, respectively. To these two phases was added a third phase. This anabolic phase follows resolution of the stress response and persists for weeks to months (Fig. 63-1). Changes affect the entire body, change activity in each organ system, and are reflected in secondary failures of these systems. Available evidence supports the theory that this adaptive response makes tissue healing possible.

## Neurologic

Brain tissue uses a wide variety of metabolic fuel. During stress, glucose and lactate metabolism increases, but so does that of amino acids. The encephalopathy of critical illness is believed to be related to the presence of elevated levels of aromatic amino acids and their metabolites.<sup>3–5</sup> In some cases, global cerebral function is impaired, as evidenced by alterations ranging from delirium to overt coma.

#### Cardiovascular

Stress increases the need for oxygen in the periphery. Cardiac output increases, and peripheral vascular tone decreases, augmenting blood flow to peripheral tissues, possibly at the expense of loss of flow to other vascular beds, to facilitate delivery. That oxygen consumption is highest in tissues with the highest levels of leukocytes suggests that delivery is increased to feed cells that repair tissue and control infection.<sup>6,7</sup> Capillary beds leak because of the loss of tight junctions. The balance between fluid extravasation and reabsorption consequently favors the formation of edema because plasma proteins accumulate outside vessels walls, pulling fluid and electrolytes with them.

The result of these changes is circulatory hyperdynamism and edema, with increased peripheral delivery of oxygen and nutrients. In some patients, myocardial damage ensues. This may lead to a failure to supplement oxygen delivery that is associated with a high mortality in critical illness lung injury.<sup>8</sup> Attempts to mediate this response through supplementation of oxygen delivery<sup>9,10</sup> have been met with mixed and often detrimental results. With recovery, edema resolves, although reduced oncotic pressure in plasma may make the period of anabolism longer.

#### Fluids, Electrolytes, and Nutrition

Tissue edema and intravascular resuscitation increase body water, and patients characteristically gain weight. The distribution of water during the stress response was explored by Moore and colleagues.<sup>11</sup> The extracellular and vascular compartments expand,<sup>11–14</sup> but intracellular water is lost. This suggests that water can actively shift from the intracellular space to the extracellular



**Figure 63-1.** Stress response curve, as described by Cuthbertson.<sup>1,2</sup> A period of shock may or may not precede the hyperdynamic phase, during which nutrient and oxygen delivery is increased to peripheral tissues. For details on organ-specific alterations, see text.

space and back again. This effect has implications for electrolyte balance.

Hypernatremia from insensible water loss or diuretic use or hyponatremia from water retention with vascular expansion is possible. Hypokalemia, hypomagnesemia, and hyperphosphatemia are frequent findings as the response abates because of shifts of water back into the intracellular space (where potassium and magnesium are dominant cations and phosphate and proteins the major anions). Hypophosphatemia also can result from exhaustion of phosphate during hypermetabolism or as a part of the refeeding syndrome.<sup>15,16</sup>

As oxygen delivery increases, so does energy production. Carbohydrate metabolism increases in tissues such as immune cells.<sup>6,7</sup> Glucose consumption decreases in many other tissues, resulting in a syndrome of glucose intolerance. Whole-body glucose delivery increases as a consequence of decreased peripheral uptake<sup>17,18</sup> and increased production. Gluconeogenesis in the liver is augmented, converting amino acids and glycerol to glucose even during hyperglycemia.<sup>19,20</sup> Amino acids, freed from peripheral protein stores, feed this process. It is likely that the driving force for increased glucose production and decreased utilization results from the demand imposed by leukocytes in areas of injury. This also explains the drive to hyperglycemia and edema formation. Injured areas are relatively avascular, and the delivery of substrate requires a loss of barriers to diffusion and a concentration gradient. Protein catabolism outpaces protein production, and liver protein synthesis globally decreases and is shifted toward the production of acute-phase proteins and enzymes involved in gluconeogenesis. Peripheral activities accelerate protein breakdown. Lipid metabolism increases in the stress response, but not as much as triglyceride hydrolysis and re-esterification.<sup>21,22</sup> This results in elevated serum triglycerides. Many fat stores undergo mobilization and subsequent recomposition.

All these changes produce the commonly observed metabolic syndrome of critical illness. Patients gain weight, mostly water, during the stress response. The water burden is eventually mobilized and lost as patients recover. During the entire process, body protein stores are consumed, resulting in a substantial loss of lean body mass and circulating proteins such as albumin. Fatty tissue also is consumed, but consumption is much less than that of protein. With recovery, a prolonged anabolic phase slowly repletes protein stores, especially in muscle.

#### Pulmonary

The sensitivity of pulmonary gas exchange to systemic perturbations reflects how often pulmonary insufficiency accompanies the stress response. Increases in oxygen consumption and carbon dioxide production put greater demand on the pulmonary system. Tachypnea and type I (oxygenation) and type II (ventilation) failure occur. Changes in capillary permeability and perivascular fluid flux force fluids and proteins into alveoli. Inflammatory infiltration exacerbates extravasation in certain patients. At the same time, altered immune function and risk for aspiration increase the likelihood of pulmonary infection. These changes can culminate in pulmonary failure, including the adult respiratory distress syndrome (ARDS).

#### Gastrointestinal

Protein turnover manifests in the gastrointestinal system by increased organ edema and atrophy of villi.<sup>23</sup> Gastric or large bowel ileus frequently signals worsening stress. These changes can confound attempts to provide enteric nutrition and potentially lead to bowel obstruction. Hepatic metabolic changes were described previously; excretion of bilirubin and other metabolites also is impaired.

#### Renal

Renal blood flow is a large proportion of cardiac output in healthy individuals. With peripheral vasodilation, perfusion can be "stolen" from the kidneys. Multiple renal insults that decrease perfusion and circulating mediators may produce a syndrome of oliguria and impaired tubular function. Metabolically active tubular cells suspend function and become quiescent until the stress has long resolved. The extreme example of this condition is acute kidney injury. With recovery, renal function often returns.<sup>24</sup> Because of fluid and electrolyte shifts as a consequence of the stress response, changes in kidney function are particularly problematic.

#### Immunologic

The stress response involves complex immunologic and neurologic signaling. Plasma cytokine concentrations vary throughout the response, as does immune function. Cell-mediated immunity is classically suppressed during inflammation.<sup>25</sup> The implications of immunologic changes are incompletely understood, but it is generally accepted that susceptibility to infection increases as systemic inflammatory signals are elevated.

#### Endocrine

The endocrine axis appears to be integral in signaling changes that accompany the stress response. This aspect of metabolism in critical illness has led to the most interesting and controversial clinical data. Hypermetabolism results from upregulation of catabolic signals and suppression of anabolic hormone signaling. Cortisol, catecholamines, and glucagon drive part of stress hyperglycemia.<sup>18</sup> Relative cortisol deficiency, described in some patients,<sup>26</sup> might worsen vasodilatory shock and stall recovery. Altered peripheral response to insulin is probably also the result of immunologic signaling to peripheral tissues such as muscle and fat.<sup>27-30</sup> Quantity and pulsatility of growth hormone secretion diminish,<sup>31</sup> whereas prolactin secretion is elevated.<sup>32</sup> Vasopressin secretion from the posterior pituitary increases in response to shock but can become depleted, possibly as a form of neuroendocrine exhaustion.<sup>33</sup> The thyroid axis is disturbed, not by changes in thyroid-stimulating hormone as much as by altered peripheral conversion to rT<sub>3</sub> instead of T<sub>3</sub>.<sup>34,35</sup> The implications of increases in  $rT_3$  are not well understood.

The results of changes in endocrine signaling include stress hyperglycemia, the euthyroid sick syndrome, disorders of sleep cycles, and altered immunologic function. In broad terms, the stress response results in pituitary hypersecretion and altered peripheral sensitivity that may give way to exhaustion.

#### AVAILABLE DATA

The complexities and cyclic nature of the stress response make its direct study difficult. However, several clinical trials of signal modulation and metabolism suggest ways in which the syndrome is mediated and how attempts to interfere with it might help or harm.

Herndon and colleagues<sup>36</sup> studied the use of  $\beta$ -blockade in burned children to reduce the loss of muscle mass. They found that large doses of propranolol (average, 6.3 mg/kg per day) produced a 6% absolute difference in lean body mass after 2 weeks of hospitalization. This trial examined the role of catecholamines in stress hypermetabolism and showed that blockade of rampant protein metabolism might improve outcomes in certain settings. Numerous investigators have studied adrenal hormone replacement to improve the patient's condition in septic shock, but the metabolic and immunologic consequences of this therapy are difficult to disentangle. Large doses of cortisol worsened mortality.<sup>37</sup> One study reported that selective administration of lower doses in patients in whom cortisol levels did not increase after an ACTH stimulation test increased survival.<sup>26</sup> Other investigators<sup>38</sup> found no survival benefit. Some have questioned the value of diagnostic tests for adrenal insufficiency because protein binding is so variable among critically ill patients.<sup>39</sup> Current evidence does not show much benefit from therapeutic administration of steroid to patients during the stress response. Chapter 73 gives a more comprehensive discussion.

Nutritional support to prevent excessive protein loss, hyperglycemia, or hyperlipidemia and to improve organ and immune function also has been studied. Nutritional topics are treated in Chapters 64–68.

Supplementation with anabolic hormones is an enticing intervention to improve outcomes in a patient population with rampant catabolism and loss of lean muscle mass. Studies of androgen are few and have mixed results.<sup>40</sup> In one study, growth hormone supplementation resulted in increased mortality.<sup>41</sup> Misdirected attempts to alter stress metabolism can have adverse consequences.

Insulin therapy is one of the most studied interventions for modulation of stress metabolism. In a surgical population, survival improved and organ dysfunction decreased with insulin therapy designed to reduce serum glucose levels to near normal.<sup>42</sup> A subsequent study of patients in a medical intensive care unit by the same investigators  $^{43}$  and studies by other authors  $^{44-46}$  have failed to replicate these results. The original study was criticized for the large proportion of cardiac surgery patients, the restriction of benefit to patients who stayed in the ICU longer, and the aggressive nutrition given to the patients.<sup>47</sup> Stress metabolism changes during the course of critical illness. It is conceivable that the goals of insulin therapy should vary with patients' position on the stress curve such that catabolism is not overly suppressed early and anabolism is supported late. This recommendation remains largely unstudied.

## **INTERPRETATION OF DATA**

The available data present a small perspective on the diagnostic and therapeutic implications of stress metabolism. The pattern of metabolic and physiologic changes with tissue damage has been observed among patients suffering a variety of injuries. Although variable, the pattern includes increased oxygen delivery, catabolism, and evolving organ dysfunction. The astute clinician should be able to diagnose new injuries, such as a secondary infection; make timely interventions; and anticipate the need for resuscitation or diuresis and whether to escalate or taper support therapies. Direct hormonal interventions, such as cortisol or insulin therapy, might have different results depending on the patient's course in the stress response. Signals that hypermetabolism is decreasing might herald source control of inflammatory stress or tissue injury. New onset of a triad of encephalopathy, glucose intolerance, and ileus in a patient who had been recovering from surgery should provoke a search for new tissue damage, especially that resulting from infection. Conversely, hypokalemia, negative spontaneous fluid balance, and resolving hyperglycemia should prompt de-escalation of supportive therapy and invasive monitoring.

A certain subset of patients appears to transition from traditional stress to a protracted period of organ failure, endocrine exhaustion, and ongoing catabolism. This condition is described as *chronic critical illness*. These patients represent a new challenge for which successful therapeutics have yet to be validated.<sup>48–50</sup> They will be the focus of many future investigations by critical care physicians.

The stress response concept is a valuable framework for organizing care for the critically ill patient. Recognizing worsening or resolving inflammatory signals should guide care. Anticipating and assessing deviations from a recognized pattern establish a sound rationale for patient management.

#### CONCLUSION

Metabolism increases with critical illness. The pattern of increase and decline is commonly referred to as the *stress response*. The response follows a predictable pattern and affects every organ system. Increased oxygen and nutrient delivery underlies the observed physiologic changes. The stress response pattern is a useful tool to guide clinical therapy.

#### AUTHOR'S RECOMMENDATIONS

- Critical illness increases global metabolism.
- This process can be thought of as an adaptive response to facilitate tissue healing.
- Critically ill patients undergo a predictable pattern of metabolic and physiologic changes in the stress response. After injury (with or without initial shock), metabolism accelerates with gradual (days to weeks) recovery followed by a longer (weeks to months) period of anabolic recovery of proteins. The response is manifested in every organ system in the body.
- Astute clinicians can exploit their knowledge of the stress response by predicting the pattern, mapping patient physiology to the expected changes, and making diagnostic and therapeutic decisions based on expected trajectory or unexpected variation from the common stress response pattern.

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# Does Enteral Nutrition (Including Early Enteral) Result in Better Outcomes Than Parenteral Nutrition in Critically III Patients?

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Comparisons of enteral nutrition (EN) and parenteral nutrition (PN) have been made during the past 30 years. Despite the large number of clinical studies directed at this concern, the question of which approach is superior remains unanswered. In part, this reflects the vast heterogeneity in studies. This makes the generation of a sound, useful metaanalysis particularly problematic. Over the course of the debate, practice has changed and new data have been generated. Tighter glycemic control, improved enteral formulations, better infection control practice and more effective feeding protocols have called into question the results of earlier performed clinical trials comparing EN and PN. Even if conclusions can be drawn from meta-analyses of older trials comparing EN and PN, their applicability to today's practices is yet to be determined. And, while the appropriate time to initiate feeding in the critically ill patient and the use of early EN are supported by research, the same can not be said of early PN. Whether the combination of EN and PN improves outcomes in critically ill patients has also become a relevant question.

Nevertheless, until new studies elucidate new data, older trial outcomes and meta-analyses of these trails should be used. This method, along with good clinical judgment and discretion, can be used to determine the best therapeutic course for critically ill patients.

## ENTERAL NUTRITION VERSUS PARENTERAL NUTRITION

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A large number of studies have compared EN and PN. Results of these studies are best depicted in three metaanalyses. Two were conducted solely in critically ill patients, and one was in critically ill and hospitalized patients (Table 64-1).<sup>1–3</sup> It is important to note that most of the studies used to generate these meta-analyses were conducted before implementation of glycemic control in the intensive care unit (ICU) setting. In addition, the studies in these meta-analyses were heterogeneous in design, patient population, and feeding strategy, which limits any definitive conclusions. Gramlich and colleagues examined mortality and infectious complications across 13 studies. The contributing studies were performed between 1980 and 2002 and involved diverse critically ill populations including patients with trauma, cardiac bypass, sepsis, head injury, and malnutrition.<sup>1</sup> No difference in mortality was found between patients receiving EN versus PN (relative risk [RR], 1.08; 95% confidence interval [CI], 0.70 to 1.65; P = .7). Nine of the 13 studies reported infectious complications. When analyzed, EN was associated with fewer infectious complications than PN (RR, 0.64; 95% CI, 0.47 to 0.87; P = .004). There was no difference in the number of ventilator days or length of stay.

Of the 11 studies that reported on nutritional intake, 5 studies associated PN with greater caloric intake. Interestingly, in a subgroup analysis of studies in which the PN groups were fed more calories than the EN groups, EN was associated with a trend toward increased mortality (RR, 1.58; 95% CI, 0.75 to 3.35; P = .2). In another subgroup analysis, no differences in mortality rate were observed in patients receiving PN with higher blood glucose concentrations compared with those who received EN (RR, 0.093; 95% CI, 0.021 to 4.15; P = .90).

In a large meta-analysis, Braunschweig and colleagues compiled outcome results from 20 prospective randomized controlled trials (PRCTs) in 1033 patients (n = 508 EN, n = 525 PN) conducted from 1981 to 1998.<sup>2</sup> These reflected a variety of both critically ill and hospitalized patients receiving either EN or PN. Sixteen of the 20 studies reported that EN was associated with a significantly lower risk for infection (RR, 0.66; 95% CI, 0.56 to 0.79). No difference in mortality was reported (RR, 0.96; 95% CI, 0.55 to 1.65). Time to initiation of feeding was not discussed in this meta-analysis.

A more recent EN versus PN meta-analysis by Simpson and Doig examined outcome results from 11 robust PRCTs in strictly critically ill patients conducted from 1983 to 2002.<sup>3</sup> Nine trials used an intent-to-treat analysis. When data were aggregated, there was an overall significant mortality benefit with PN (odds ratio [OR], 0.51; 95% CI, 0.27 to 0.97; P = .04). Six of the nine trials started

Study	No. of Trials	No. of Subjects	Populations	Intervention	Outcomes
Gramlich et al, 2004 <sup>1</sup>	13	407 EN; 400 PN	Trauma, head injury, sepsis, pancreatitis, surgical, burn, malnutrition	PRCTs of EN versus PN in critically ill adult patients	EN resulted in statistically significant decreased infections; no statistically significant difference in LOS, days on vent, mortality
Braunschweig et al, 2001 <sup>2</sup>	20	508 EN; 525 PN	Pancreatitis, UC, CD, surgery, trauma, MOF, cancer	PRCTs of EN versus PN in adult patients	EN resulted in statistically significant decreased infections; no statistically significant difference in mortality or other complications
Simpson & Doig, 2004 <sup>3</sup>	11	343 EN; 345 PN	Trauma, pancreatitis, sepsis, cancer, surgical and medical critically ill	PRCTs, ITT, EN versus PN in critically ill adult patients	Statistically significant mortality benefit was reported with the use of PN in 9 ITT trials (see <i>a priori</i> <i>subgroup analysi</i> s)
	6	219 EN; 224 PN	Trauma, surgical, cancer	A priori defined subgroup analysis: PRCTs, intent to treat; early EN (24 hr) versus early PN in critically ill adult patients	No statistically significant differences in mortality comparing early EN to PN; however, a statistically significant mortality benefit in favor of the use of PN was seen when comparing delayed EN with PN

Table 64-1 Summary of Meta-Analyses Comparing Enteral Nutrition to Parenteral Nutrition

CD, Crohn disease; EN, enteral nutrition; ITT, intent to treat; LOS, length of stay; MOF, multisystem organ failure; PN, parenteral nutrition; PRCT, prospective randomized controlled trial; UC, ulcerative colitis; vent, ventilator.

EN within 24 hours of admission, meeting the criteria for early EN. When early EN was compared with PN, there was no difference in mortality, and the benefit initially described for PN was lost (OR, 1.07; 95% CI, 0.39 to 2.95; P = .89). When comparing delayed EN and PN, there was a significant mortality benefit in favor of PN (OR, 0.29; 95% CI, 0.12 to 0.70; P, 0.006). Based on these data, it appears that PN may only have a mortality benefit when compared with delayed EN.

The meta-analyses by Simpson and Doig also evaluated infectious complications.<sup>3</sup> Six of the nine trials reported positive culture results and found a significant increase in infectious complications with PN (OR, 1.66; 95% CI, 1.09 to 2.51). Of these six trials, four met criteria for early EN versus PN. Aggregation of these four trials resulted in a nonsignificant trend toward increased infectious complications with PN (OR, 1.47; 95% CI, 0.90 to 2.38; P = .12).

Based on the results of these meta-analyses, there appears to be no difference in mortality between EN and PN but a decrease in infectious complications with EN. However, the quantity and timing of feeding initiation may be of greater importance than the route and may significantly affect outcomes.

## EARLY ENTERAL NUTRITION VERSUS EARLY PARENTERAL NUTRITION

When compared with delayed EN, early EN is associated with increased calorie delivery, decreased hospital length of stay, decreased infectious complications, and a trend toward decreased mortality.<sup>4–8</sup> National and international

guidelines<sup>9-11</sup> support the use of early EN. However, the comparison of early EN to PN is more problematic

Two meta-analyses reviewed the use of early EN to PN (Table 64-2).<sup>12,13</sup> In a meta-analysis of early EN versus PN by Moore and associates, data from eight PRCTs including 230 patients were analyzed.<sup>12</sup> These studies included moderately to severely stressed postoperative patients (blunt and penetrating trauma as well as nontrauma surgery). Early EN was defined as the initiation of nutrition therapy within 8 to 72 hours of surgery. The data were analyzed using two separate approaches. The first excluded dropouts and thus involved 194 patients (92 EN and 102 PN). The second was based on intent-to-treat and assessed 230 patients (118 EN and 112 PN).

In the first analysis, time to the initiation of nutrition therapy between groups was not statistically different (32.5  $\pm$  1.8 hours in the EN group and 32.8  $\pm$  1.7 hours in the PN group). There was a statistically significant increase in the rate of total septic complications (bacteremia, intra-abdominal abscess, catheter-related sepsis, and pneumonia) associated with patients receiving PN (59% versus 38%; *P* = .007). Blood glucose concentrations were significantly lower in the EN group at baseline and throughout the study period (a difference of 19 mg/dL at baseline, *P* = .02; 28 mg/dL at mid-study, *P* = .03; and 94 mg/dL by end of study, *P* = .001). As expected, gastrointestinal complications were significantly greater in patients receiving EN.

The intent-to-treat analysis revealed a trend in septic and nonseptic postoperative complication rates that favored EN (41% versus 52%; P = .09). Twice as many PN patients developed one or more infections (16% versus Table 64-2 Summary of Meta-Analyses Comparing Early Enteral Nutrition to Early Parenteral Nutrition

Study	No. of Trials	No. of Subjects	Populations	Intervention	Outcomes
Moore et al, 1992 <sup>12</sup>	8	Phase 1: 92 EN; 102 PN	Blunt and penetrating trauma, nontrauma surgery	Phase 1: PRCTs of early EN versus early PN in critically ill, adult patients	Phase 1: early EN resulted in statistically significant decreased septic and total complications; no statistically significant differences were reported with LOS or mortality
		Phase 2: 118 EN; 112 PN		Phase 2: PRCTs, ITT of early EN versus early PN in critically ill, adult patients	Phase 2: early EN resulted in statistically significant decreased septic complications; no statistically significant differences were reported with total complications, LOS, or mortality
Peter et al, 2005 <sup>13</sup>	30	1213 EN; 1217 PN	Trauma, head injury, cancer, GI surgery, transplantation, pancreatitis, IBD, malnutrition	PRCTs of early EN versus early PN	Early EN (<96 hr) resulted in statistically significant decreased hospital and ICU LOS, infective and noninfective complications; no statistically significant differences in mortality

EN, enteral nutrition; IBD, inflammatory bowel disease; ICU, intensive care unit; ITT, intent to treat; LOS, length of stay; PN, parenteral nutrition; PRCT, prospective randomized controlled trial.

35%; P = .01), but there was no difference in the number of infectious complications per patient. Subgroup analysis identified a statistically significant decrease in the number of patients receiving EN with septic complications specifically among all trauma (P = .02) and blunt trauma (P = .02).

In a meta-analysis, Peter and colleagues revisited the comparison of early EN with early PN and included the results of many PRCTs that were published after the work of Moore and associates.<sup>13</sup> Early EN was defined as initiation of nutrition therapy within 96 hours of ICU admission. Clinical outcome data included hospital mortality or complications or hospital length of stay (LOS). Trials were excluded if outcomes reported were physiologic or biochemical end points or if immunonutrition, defined as arginine, nucleotides, omega-3 fatty acids, or glutamine, was initiated. A total of 30 studies were identified and further divided into three categories: medical (10 PRCTs), surgical (11 PRCTs), and trauma (9 PRCTs).

The results of the analysis found no significant differences between groups with respect to mortality. With regard to the other outcomes assessed, hospital and ICU LOS was significantly reduced in patients receiving EN (hospital LOS mean weighted difference [MWD], 1.2 days; 95% CI, 0.38 to 2.03; P = .004; and ICU LOS MWD, 1.4 days; 95% CI, 0.37 to 2.4; P = .008). Complications were divided into four separate categories: infectious complications, noninfectious complications, technical complications, and diarrhea. Analysis of all studies showed a significant increase in both infectious and noninfectious complications in the PN group (risk difference [RD], 7.9%; *P* = .001; and RD, 4.9%; *P* = .04, respectively). Analvsis of technical complications across all groups did not favor EN or PN. However, a subgroup analysis reported a statistically significant increase in technical complications for PN in the medical subgroup (RD, 9.4%; P =.006). As suspected, the incidence of diarrhea across all

ICU groups was higher with EN (RD, 8.7%; P = .001). Overall, the route of nutrition therapy did not affect mortality. However, PN was noted to increase both infectious and noninfectious complications, especially within the medical subgroup. With respect to LOS, both ICU and hospital LOS was decreased in the patients receiving EN.

Although excluded from Peter and colleagues' metaanalysis, it is prudent to report the findings from a multicenter PRCT that compared the use of early enteral immunonutrition with PN. Bertolini and associates compared early enteral immunonutrition with PN in patients with severe sepsis.<sup>14</sup> Nutrition therapy was initiated within 48 hours of ICU admission. EN patients achieved goal rate with 4 days of initiation.<sup>14</sup> Patients were divided into two subgroups: those with severe sepsis and those with nonsevere sepsis. Each group then was divided into those receiving EN and PN. Although 239 patients were enrolled, only 36 were randomized within the severe sepsis group. Investigators reported a trend toward increased ICU mortality in the EN group (44.4% versus 14.3%; P = .072) but found no significant difference in 28-day mortality. It is important to note that the investigators theorized that the trend in increased mortality was associated with EN enhanced with L-arginine. L-Arginine has been found to increase nitrous oxide production and may theoretically exacerbate hypotension in patients with sepsis. Clinical practice guidelines have since recommended against the use of L-arginine-enhanced EN in patients with severe sepsis.<sup>10</sup>

Based on the results of these meta-analyses, early EN is associated with decreased infectious complications. However, differences in mortality between patients receiving early EN and PN have not been observed. Reported improvements in noninfectious complications, ICU LOS, and hospital LOS vary between the meta-analyses and may be dependent on PRCT design and analysis. Delayed EN may eliminate the benefit, perhaps because of an associated calorie deficit.

#### ENTERAL NUTRITION VERSUS ENTERAL NUTRITION PLUS SUPPLEMENTAL PARENTERAL NUTRITION

It has been hypothesized that there are benefits from the use of EN plus supplemental PN. Negative energy balance, or a failure to provide an appropriate number of calories over a period of days, is associated with worse outcome. Based on observational and cohort studies, these include bloodstream infection, morbidity, and mortality.<sup>15–21</sup> Supplementing EN with PN is one way to improve nutritional intake and circumvent the caloric deficit. This approach incorporates the beneficial effects of EN while avoiding underfeeding.

Dhaliwal and associates performed a meta-analysis of five studies comparing EN plus PN to EN plus placebo and found no difference in rates of infectious complications, length of stay, or ventilator days.<sup>22</sup> However, this analysis compared a heterogeneous group of patients receiving variable nutritional intake that was not designed to meet energy goals. Four of the five included studies had a sample size of less than 40 total patients, two examined burn patients, and only two evaluated outcomes other than mortality. These studies also used intravenous soy-based lipid emulsions and failed to implement glucose control, two parameters associated with immune depression.<sup>23–26</sup>

The largest of these trials was a prospective study published in 2000 by Bauer and colleagues, which was an intent-to-treat analysis of 120 ICU patients.<sup>27</sup> Enteral therapy in this study consisted of bolus feeding with a standard, noncommercial, polymeric 1 kcal/mL diet. PN was provided as a compounded 3-in-1 solution. This study found no difference in mortality at either 90 days or 2 years and no difference in ICU LOS. However, the treatment group (EN + PN) experienced a significantly shorter hospital LOS and increased prealbumin and retinolbinding protein (nutritional markers) at day 7.<sup>22,27</sup>

It is important to note that since the study by Bauer and colleagues, there have been significant changes in nutrition support practice in critically ill patients. These limit applicability. Overfeeding with PN once was a common practice but is now thought to contribute to septic morbidity. Similarly, because of a risk for aspiration and intolerance, enteral formulas most often are initiated as continuous, rather than bolus, feedings. Additionally, glucose control is more stringent in ICUs than when prior studies were performed.

One study examined infectious complications and hospital mortality when EN and supplemental PN were administered to patients in shock after blunt trauma. Sena and associates examined 567 patients who received a median of 4 days of PN therapy retrospectively as part of a larger study on inflammation and the host response to injury.<sup>28</sup> A significantly greater risk for nosocomial infection (bloodstream and urinary tract infection) was found with early PN versus no early PN (RR, 2.1 [1.6 to 2.6]; P < .001), but no overall increase in risk for mortality was noted. However, the group receiving supplemental PN had more severe injuries, shock, blood transfusions, and higher Acute Physiology and Chronic Health Evaluation (APACHE) II scores. This may have contributed to these findings. In addition, 66% of PN patients received little or no EN in the first week of the study. On average, PN patients received more than 30 kcal/kg per day during days 7 through 14. This could be considered overfeeding.<sup>9–11,28</sup>

Many questions remain unanswered. More large-scale PRCTs are needed that incorporate current standards of care to determine the impact of supplemental PN on morbidity and mortality.

## CONCLUSION

The use of early EN versus PN has been reported to decrease infectious complications but not mortality. EN is the preferred route of specialized nutrition therapy and should be considered first line. However, changes in practice limit the strength of previous studies. Whether the combination of EN plus supplemental PN is advantageous remains unanswered.

#### AUTHORS' RECOMMENDATIONS

- EN is associated with fewer infectious complications, greater feasibility, and lower cost than PN and thus should be the preferred route if possible.
- Early EN (24 to 48 hours) in the ICU patient decreases morbidity relative to delayed EN and should be considered first-line therapy.
- PN usually results in greater early caloric intake than EN, but there is little evidence to correlate caloric deficit with clinical outcomes.
- More conclusive evidence using current standards of care is needed regarding supplemental PN.

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# 55 Is It Enh

# Is It Important to Deliver Enhanced Levels of Arginine to Critically III Patients?

Sunil Karhadkar, Adrian Barbul

#### **ARGININE METABOLISM**

Arginine (ARG; 2-amino-5-guanidovaleric acid) is an aliphatic four-carbon dibasic amino acid with a strong guanidinium group that was first isolated in 1886 from lupin seedlings.<sup>1</sup> It was not until the discovery of the urea cycle by Krebs and Henseleit in 1932 that the importance of ARG in intermediary metabolism was clarified. In the past two decades, ARG has been shown to be the unique precursor for nitric oxide (NO), an evanescent molecule with many biologic effects.

Every day, 15 to 20 g of ARG is produced endogenously. One third is derived from dietary ingestion, making ARG a conditionally dispensable amino acid. The intestinal absorption of ARG occurs through a transport system shared with lysine, ornithine, and cysteine. These ingested amino acids are converted to citrulline for absorption. Windmueller and Spaeth,<sup>2</sup> in a rodent model, demonstrated that the small intestine is the predominant source of circulating citrulline for endogenous ARG synthesis. Most endogenous ARG synthesis in adults involves the intestinal-renal axis. This also is known as the interorgan pathway. In this process, renal tubular cells extract circulating citrulline released into the blood from enterocytes.<sup>3,4</sup> Argininosuccinate synthase and argininosuccinate lyase in the cytosol of the renal tubular cells sequentially metabolize citrulline to L-arginine. This endogenous synthesis of ARG from citrulline is not affected by dietary intake of ARG.<sup>5</sup> Consequently, impairment of small bowel or renal function can reduce endogenous ARG synthesis, thereby increasing the dietary requirement.<sup>6</sup> Synthesis of ARG from citrulline also occurs at a low level in many other cells,<sup>7</sup> and cellular capacity for ARG synthesis can be markedly increased under circumstances that induce enzymes that synthesize NO.

The fate of circulating ARG is determined by nutritional status and age. In the fed state, ARG is channeled toward protein biosynthesis, and ARG–aminoacyl transfer RNA (tRNA) is an important intermediary in this process. Other fates include conversion to urea, creatine, ornithine, agmatine, citrulline, and NO. The regulation of this process and selection of the predominant degradative pathway lie with several critical enzymes: nitric oxide synthase (NOS), arginine-glycine amidinotransferase, arginase, arginine decarboxylase, and arginyl-tRNA synthetase.

It is clear that in situations of stress as in disease, trauma, and sepsis, endogenous synthesis of ARG may become insufficient to meet the heightened demands that increased protein turnover requires. Additionally, inducible NOS(iNOS) and other enzymes preferentially catabolize ARG at the expense of its bioavailability for protein synthetic function. In such situations, ARG can become indispensable for optimal growth and maintenance of positive nitrogen balance.

Another key role for ARG is within the urea cycle, the major pathway for ammonia detoxification. Arginase, the enzyme responsible for the catabolism of arginine in the urea cycle, has two distinct isoenzymes, each encoded by separate genes. Type I arginase, a cytosolic enzyme, is highly expressed in the liver as a component of the urea cycle and also is present in wound-derived fibroblasts. Type II arginase is a mitochondrial enzyme expressed at lower levels in the kidneys, brain, small intestine, mammary glands, and macrophages. Any condition that increases demand for ammonia detoxification is likely to increase ARG requirements.

Among other critical actions of ARG are its prosecretory effects. These include the release of somatotropin and prolactin from the hypophysis and promotion of release of insulin.<sup>8,9</sup> In addition, the production of insulin-like growth factor (IGF) and the release of glucagon, somatostatin, pancreatic polypeptides, and catecholamines are enhanced by ARG.<sup>10</sup> Moreover, ARG is the precursor of polyamines (putrescine, spermine, and spermidine). These have key roles in cellular proliferation. Finally, through the formation of glutamate, ARG can yield increased amounts of proline.<sup>11</sup>

ARG also acts as an activator of *N*-acetylglutamate synthase, which synthesizes *N*-acetylglutamate from glutamate and acetyl–coenzyme A (CoA). Because *N*-acetylglutamate is an essential cofactor for carbamoyl-phosphate synthase I (CPS I), a key enzyme in ARG and urea synthesis, ARG may play a regulatory role in its own metabolism.

Lastly, ARG is conjugated with *N*-terminal aspartate or glutamate residues of proteins, thereby targeting them for ubiquitin-dependent proteolysis. This implicates ARG in

the process of scavenging toxic metabolites of tissue breakdown.

# ARGININE AND NUTRITIONAL THERAPY

Many animal and human studies have demonstrated improved wound healing, immune function, and host antitumor responses when supplemental ARG is administered either alone or in addition to a complete diet. Several enteral formulations that contain supplemental doses of ARG, glutamine, omega-3 fatty acids, and RNA<sup>12</sup> were marketed and tested in large numbers of postsurgical and intensive care unit (ICU) patients. This concept of immunonutrition has been widely applied, has been subjected to multiple meta-analyses, and is still surrounded by confusion and controversy.

The scientific rationale for inclusion of ARG as an immunomodulator has been well established. In animal experiments, arginine decreases thymus involution associated with trauma; promotes thymus cellularity, lymphocyte proliferation, natural killer cell activity, and macrophage cytotoxicity; and improves delayed-type hypersensitivity, resistance to bacterial infections, survival to sepsis, and burns and wound healing. In healthy human subjects, arginine supplementation increases blood lymphocyte proliferation in response to mitogens and promotes wound healing.<sup>13</sup> Therefore, ARG supplementation has been the subject of several preclinical trials of immunonutrition. Meta-analyses of these trials showed significant reductions in length of hospital stay but did not demonstrate any reduction in mortality.<sup>14</sup> Controversy persists as to whether ARG content in the immunonutrition formulas was paradoxically deleterious in patients given the amino acid parenterally. However, consensus recommendations from the U.S. summit on immuneenhancing enteral therapy (2001) stated that there is clearly established benefit in elective gastrointestinal surgery and in trauma.

#### **ARGININE AND CRITICAL ILLNESS**

The role of ARG in wound healing was first shown in the 1970s, when it was hypothesized that after injury, the amino acid requirements of the adult organism would revert to those of the growing infant. Animals fed an ARG-deficient diet for 4 to 6 weeks and then subjected to minor trauma demonstrated increased postoperative weight loss, increased mortality, and a notable decrease in wound-breaking strength and wound collagen accumulation compared with animals fed a diet containing ARG. Subsequent experiments revealed that non–ARG-deficient chow-fed rats supplemented with an additional 1% ARG had enhanced wound healings.<sup>15,16</sup> Similar findings were observed in parenterally fed rats given an amino acid mixture containing high doses (7.5 g/L) of ARG.<sup>17</sup>

Two studies in healthy human volunteers examined the effects of ARG supplementation using a welldescribed micromodel. Oral ARG supplementation of 17 to 24 g/day significantly increased hydroxyproline and total protein deposition in the wounds of both young and elderly (>70 years of age) healthy human volunteers. ARG supplementation had no effect on the rate of epithelialization of skin defect, indicating that the predominant effect of arginine is on wound collagen deposition.<sup>13,16,18</sup>

Oral ARG supplementation is well tolerated and has been the focus of recent studies of wound healing and medical outcomes. Despite improvements in markers of collagen biosynthesis in healthy volunteers, clinical evidence of improved wound healing has not been reported often. Patients undergoing resection for oral or laryngeal cancer were randomized to receive either an enteral diet supplement containing only fiber or one containing fiber and ARG. Postoperative infectious complications were similar in the two groups, as were plasma protein levels of albumin, transferrin, and prealbumin. Patients treated with ARG, however, had lower rates of fistula formation and, consequently, shorter hospital lengths of stay. Healing responses to ARG nutritional supplementation in nursing home patients with pressure ulcers have been modest or absent, but the study groups are small.<sup>19</sup>

Several mechanisms have been postulated to explain the positive effect of ARG on wound healing. First, although ARG constitutes a small amount of the collagen molecule (<5%), it is possible that supplemental ARG provides a necessary substrate for collagen synthesis at the wound site. In addition, ARG levels are essentially undetectable within the wound during the later phases of healing when fibroplasia predominates.

Second, ARG is one of the most potent secretagogues of pituitary growth hormone. The beneficial effects of supplemental arginine on wound healing are similar to the effects of growth hormone.<sup>20,21</sup> ARG does not enhance wound healing in hypophysectomized as it does in normal pituitary-bearing animals. In humans, ARG supplementation in doses that have been shown to improve wound healing also increases plasma IGF, the peripheral mediator of growth hormone activity.<sup>13</sup>

Third, supplemental ARG has a unique effect on T-cell function. Arginine stimulates T-cell responses and reduces the inhibitory effect of injury and wounding on T-cell function. T lymphocytes are known to be essential for normal wound healing, as evidence by decreased wound breaking strength in animals treated with mono-clonal antibodies against all T lymphocytes. In addition, T lymphocytes can be detected immunohistochemically in distinctive patterns throughout the various phases of wound healing. Studies have shown that each specific T-cell type has a modulating role in different stages of cutaneous healing.<sup>22</sup>

Finally, ARG could act favorably as a substrate for the generation of NO within the wound. Several studies suggest that NO plays a critical role in wound healing. Inhibitors of NOS significantly impair the healing of cutaneous incisional wounds. ARG is catabolized in wounds through both metabolic pathways—through NOS and arginase. Both pathways deplete the wound environment of extracellular arginine, thus emphasizing its essential nature in wound healing. Supranormal collagen deposition has been observed after transfection of iNOS DNA into wounds.<sup>23,24</sup>

ARG, given in large doses, helps maintain immune homeostasis, particularly with respect to T-cell and

macrophage functions. As in wounds, L-arginine is metabolized in macrophages and lymphocytes by two independent enzymes, NOS and arginase I. These are upregulated in trauma, sepsis, and liver transplantation, among others. The result is a decrease in plasma levels of arginine. This coincides with major decreases in T-cell proliferation. Supplementation with L-arginine has been shown to increase CD4<sup>+</sup> cells, suggesting that arginine may play an important role in reversing the immunosuppression observed during periods of stress.<sup>25</sup>

Several clinical conditions in humans and animals are associated with increased activity of both arginase enzymes, leading to excessive destruction and consequent unavailability of L-arginine. Enhanced arginase activity in the liver has been implicated in the increased tolerance of the liver to organ rejection. Trauma is another condition associated with decreased plasma arginine levels and with greater than 10-fold increase in arginase activity.<sup>26,27</sup> These observations led many investigators to propose the use of arginine-based nutrients to modify the immunologic and inflammatory responses in humans.

A reversal of the alteration in T-cell function associated with trauma or surgery has been demonstrated in patients fed enteral diets rich in arginine. Patients undergoing major abdominal operations for gastrointestinal malignancies had increased in vitro immune responses that correlated with decreased wound infections and decreased length of hospital stay when supplemented with arginine.<sup>28</sup> Additionally, moderately stressed ICU patients given an enteral diet containing large amounts of arginine demonstrated preservation or enhancement of T-lymphocyte blastogenesis.<sup>29</sup> In children with severe burn injuries, maintenance of normal plasma levels of arginine correlates with parameters of enhanced host immune and nutritional status.<sup>30</sup> Whether these effects translate into an improvement in clinical outcomes in critically ill patients remains unclear.

#### **ARGININE METABOLISM IN SEPSIS**

It has been postulated that sepsis and organ dysfunction states are characterized by ARG deficiency.<sup>10</sup> The etiology of ARG deficiency in critically ill patients is multifactorial. Critically ill patients often receive no enteral nutrition in the initial phase of their stay. Impaired intestinal absorption, depletion of citrulline, reduced renal arginine synthesis, and renal dysfunction all contribute to depletion of this amino acid.

Bacterial endotoxin and inflammatory chemokines are potent modulators of the cationic amino acid transporters (CATs) that modulate import of ARG into cells. This interaction involves upregulation of CAT2 and downregulation of CAT1, channeling arginine preferentially to NOS2 with potentiation of the inflammatory response. The amount of ARG used by this increased NO output likely is small because NOS also competes with the degradation enzyme arginase for the same substrate. Enhanced arginase activity in sepsis results in a threefold increase in urea production in septic children.<sup>5</sup> As arginase depletes arginine, there is a substrate-dependent downregulation of  $NOS_2$ . Clearly, the metabolism of arginine in sepsis is not straightforward. The process also may be different at different time points and may be altered by the type of insult.

Complicating this scenario is the increased production of dimethylarginine, an endogenously occurring competitive inhibitor of NOS derived from protein catabolism in sepsis. Levels of asymmetrical dimethylarginine correlate with severity of organ failure, inflammation, and presence of shock in severe sepsis.<sup>31</sup>

Finally, studies in transgenic mice overexpress arginase I, implicating sepsis-induced ARG deficiency in the pathogenesis of multiple-organ dysfunction syndrome.<sup>5</sup>

#### **USE OF ARGININE AS THERAPY IN SEPSIS**

Clinical data on the use of ARG alone in sepsis are lacking. There have been are several experiments in rodents in which the use of parenteral ARG alone or as part of a total parenteral nutrition regimen improved survival and reduced generation of inflammatory cytokines.<sup>32,33</sup> A recent study examined the effect of high doses of ARG in a canine model of septic shock. Parenteral ARG increased mortality, worsened shock, and decreased metabolic acidosis. The authors concluded that ARG therapy should be avoided in critically ill patients with septic shock.<sup>34</sup> ARG infusions have been shown to provoke severe hyperkalemia and fatal dysrhythmias.<sup>23</sup> Therefore, ARG administration in acute, hypodynamic shock should be avoided.<sup>35</sup> It remains unclear, however, whether its use in later phases of sepsis may be beneficial.

#### AUTHORS' RECOMMENDATIONS

- Trauma, sepsis, and physiologic stress are associated with a relative deficiency in bioavailable ARG.
- ARG supplementation improves wound healing and has immunostimulant effects.
- Further research is needed to determine the specific influence of ARG on outcome in the critically ill. This requires controlled populations and must account for the influence of NOS messenger RNA, renal and hepatic dysfunction, and genetic variability.
- Arginine-supplemented diets are cautiously recommended in critically ill patients.

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# 66

# Does Trace Element Deficiency Develop in Critically III Patients? Should It Be Treated?

Mette M. Berger

What do essential trace elements (TEs) have in common, and what characterizes their deficiency? Eleven trace elements, all metals and metalloids, have been shown to be essential in humans (Table 66-1) through demonstration of human or animal deficiency conditions. Three other TEs (nickel, silicon, tin) probably also are essential, even if no clinical deficit has been demonstrated, likely owing to their wide presence in the environment. During the first conference on trace substances in environment and health in 1967 in Columbia, Missouri,<sup>1</sup> essential TEs were defined as inorganic substances constituting less than 0.01% of body mass that were present in fairly constant concentration of less than 50  $\mu$ g/g tissue or fluid. It also was stated that TE absence caused reproducible biochemical, structural, and functional deficiencies. Finally, these alterations could be prevented or corrected by intake of the element. From the above definitions, it is obvious that functional enzymatic alterations appear before the visible clinical signs of deficit. Because body stores are limited (see Table 66-1), biochemical alterations caused by deficiency may develop after as short a time as 4 to 5 days. For example, such a delay is sufficient to overwhelm antioxidant defenses in the absence of the selenium required for glutathione peroxidase (GPx) to be active. The development of the clinical signs by contrast requires weeks, much too long to become visible in most intensive care unit (ICU) patients.

TEs have different roles. The nutritional functions are the best known, with the involvement of the 11 essential TEs in metabolic pathways through their activity as enzyme cofactors of carbohydrate, lipid, and protein metabolism. Their role in immune defense, including both humoral and cellular immunity, is less well recognized but equally important. Recent studies have highlighted the regulatory roles of selenium and zinc in gene transcription and expression. Finally, investigations in the past 15 years have demonstrated the importance of TEs, and particularly of selenium, in antioxidant and associated immune defense.

Consequences of clinical TE deficit are many and serious. Those most relevant in ICU settings involve selenium and zinc, and copper in major burns, and effect oxidative damage to tissues and organs, infections, inappropriate inflammatory response, and delayed wound healing.<sup>2</sup> Antioxidant supplementation trials are based on the rationale that confining free radicals in defined spaces and concentrations will reduce the development of inflammation-associated organ failures. Subclinical deficiency will have different consequences that are dependent on the metabolic state. Neonates, children, pregnant women and patients with major wounds are at higher risk because of increased metabolic requirements.<sup>3</sup>

The number of TEs studied in critically ill patients remains limited. Although iron status and its relation to anemia have been investigated for many years, the recent interest in the antioxidant functions of selenium has resulted in the publication of a fair number of trials. Searching the Medline and PubMed databases between 1975 and the first quarter of 2010 with the key words "trace elements" and "critically ill" or "ICU" provides 171 papers, including 60 reviews and 8 editorials. Roughly one third of these papers are devoted to iron and another third to selenium. Randomized controlled supplementation trials are few for many reasons, including that many factors affect ICU outcome, with optimal nutrition support and TE status being only a part of them; TE balance studies are difficult to carry out because of the many contaminants; and the instability and variability of the patients make interpretation difficult.

# PATHOPHYSIOLOGY OF DEFICIENCY

#### **Causes of Trace Element Deficiency**

Several mechanisms, alone or in combination, are involved. Some, such as exudative losses in burns, are sufficiently important to cause early enzymatic disturbances, followed by clinical signs of deficiency in a few weeks.

1. The patient may belong to a population at risk for deficiency before development of the acute condition. This is particularly true for the European population that is characterized by a generally poor selenium status<sup>4</sup> and to a lesser extent poor iron and zinc status. These patients are particularly sensitive to oxidative damage associated with critical illness.<sup>5</sup> Patients with Table 66-1 Essential Trace Elements: Body Stores, Distribution, and Doses Present in Three European Industrial Products

Element	Quantity	Location	Ranges of Doses in Industrial Intravenous Preparations*
Cu	100 mg	Liver, enzymes	0.48-1.27 mg
Fe	3-5 g	Liver, spleen > hemoglobin, myoglobin, cytochromes	1-1.95 mg
Se	6-20 mg	Liver, kidney > muscle, bone, blood	20-70 µg
Zn	1.4-2.3 g	Bone > genitalia, skin, liver, kidney, muscle, pancreas	3.27-10 mg
Со	<1 mg	Blood	0-1.47 μg
Ι	20-50 mg	60% Thyroid > muscle, ovaries, blood	0.01-0.13 µg
Mn	12-16 mg	Mitochondria (liver, bone, kidney, pancreas, small intestine)	0.2-0.55 mg
Мо	9-16 mg	Mitochondria (same as Mn)	10-25 μg
Cr	4-6 mg	Spleen, heart, kidney	10-15 μg
F	<1 mg	Bone	0.57-1.45 mg
V	100 mcg	Kidney, spleen, liver, bone, testes and lung	none

\*Addamel N or Additrace, Fresenius Kabi AG, Bad Homburg, Germany; Tracutil, B. Braun Melsungen AG, Germany; Decan, Laboratoires Aguettant, Lyon, France.

malnutrition on admission also may suffer TE deficiencies. Examples include cancer patients, pregnant women with hyperemesis, patients with anorexia nervosa, malnutrition or malabsorption.

- 2. The patients may be subjected to persistent oxidative stress due to either their conditions (e.g., acute respiratory distress syndrome, burns, sepsis, inflammation) or treatments (e.g., ventilation with elevated Fio<sub>2</sub>, dialysis, transfusion) that consume endogenous antioxidants and deplete body stores, worsening the body's response.<sup>6</sup>
- 3. Abnormal losses (Table 66-2) may be due to the following factors:
  - *The acute condition*: Surgical blood loss and other types of bleeding, drains, fistulas, and exudates. Patients with major burns (i.e., involving more than 20% of

body surface) are included in this category,<sup>7</sup> as are major trauma victims who have drains.<sup>8</sup> Losses must be very large to cause clinically visible deficits during the ICU stay. An example would be the rapid zinc depletion associated with high-output intestinal fistulas. VAC dressings may also cause significant losses.

• *Treatment*: Three studies have shown that TEs and vitamins are lost in the effluent through the membranes used in continuous renal replacement therapy.<sup>9–11</sup> An in vitro study showed that continuous venovenous hemofiltration clearance of chromium, copper, selenium, manganese, and zinc differs among elements.<sup>12</sup> Selenium and copper might need to be replaced with doses that exceed those provided in supplementation guidelines by as much as 200% to 300%.<sup>10</sup>

Study	Type of Condition	Type of Biologic Fluid and Trace Element
Berger et al, 1992 <sup>43,44</sup>	Major burns (adults)	Cutaneous exudates: large losses of copper (20% of body content in 7 days), selenium (10% of body content), and zinc (10% of body content)
Voruganti et al, 2005 <sup>45</sup>	Major burns (children)	Cutaneous exudates: copper, zinc
Dudrick et al, 1999 <sup>46</sup>	Upper intestinal fistulas	Zinc: variable amounts (3-12 mg) depending on the location of the fistula (maximal at ileal level) and on its output
Higgins et al, 2000 <sup>16</sup>	Critical illness	Urinary losses of copper, iron, and zinc
Story et al, 1999 <sup>9</sup>	Acute renal failure on continuous renal replacement	Ultrafiltrate: significant quantities of vitamin C, chromium, and copper
Berger et al, 1996 <sup>8</sup>	Major trauma	Negative balances of selenium and zinc
Berger et al, 2004 <sup>10</sup>	Acute renal failure on continuous renal replacement	Effluent: thiamine, copper, selenium, and zinc
Klein et al, 2008 <sup>11</sup>	Major trauma with renal failure	Effluent and urinary losses of selenium, manganese, and boron

#### Table 66-2 Studies That Demonstrated Trace Element Losses Susceptible to Causing Deficiency in Critically III Patients

- *Phlebotomy and other causes of bleeding*: Anemia is common in ICU patients, affecting nearly 95% after 3 days.<sup>13</sup> Causes are many, but iron deficiency contributes to long-standing critical care illness. A large proportion of critically ill patients suffer from the typical functional iron deficiency of acute inflammation-related anemia. However, in a Spanish study that had diagnosed inflammation-related anemia in 72% of ICU patients, 21% had an associated real iron deficiency (low transferrin saturation and ferritin).<sup>14</sup>
- 4. Nutritional support–related mechanisms include the following:
  - Critically ill patients frequently are hypermetabolic and have increased macronutrient, vitamin, and TE requirements that are not necessarily met by standard feeding solutions. Most enteral diets are conceived for standard and stable hospital patients. Such individuals are metabolically very different from ICU patients, but deficiencies have been shown to occur during prolonged use even in stable patients.
  - Incomplete artificial feeding, that is, delivering parenteral nutrition without prescribing TE from the start. Most industrial parenteral nutrition bags do not include TEs because of stability problems, and TE therefore must be prescribed separately. Enteral feeding solutions also have been developed for stable non-ICU patients. For example, some case reports indicate that selenium doses in enteral feeds are insufficient.<sup>15</sup>
- 5. Chelation of circulating TEs by EDTA-containing drugs.<sup>16,17</sup> This has been shown to occur with propofol. A prospective randomized controlled trial investigating propofol infusions in 106 critically ill patients showed that critical illness was associated with increased urinary losses of zinc, copper, and iron.<sup>16</sup> The propofol EDTA-treated patients had greater urinary losses of zinc and iron and lower serum zinc concentrations compared with the non-EDTA sedative group. No adverse events indicative of trace metal deficiency were observed in either group.

#### DIAGNOSIS OF DEFICIT

Although TE losses have been demonstrated in some conditions, the ICU stay generally is too short for development of clinically apparent deficiency. The patients

often develop biologic deficits that are difficult to detect. Status determination may be particularly difficult because the concomitant inflammatory response deeply modifies TE distribution in the body. This results in low circulating concentrations of all TEs other than copper and manganese, even in the absence of deficiency. Cytokinemediated mechanisms in SIRS cause a reprioritization of protein synthesis, in particular of metallothionein, and a redistribution of micronutrients<sup>18</sup> from the circulating compartment to tissues and organs involved in immune defense and synthesis.<sup>19,20</sup> This leads to a depletion of the plasma antioxidant capacity. The circulating compartment only reflects flow between tissues and organs.<sup>7</sup> When plasma concentration decreases sharply, they generally reflect deficiency and can be used as indirect markers of status. Direct markers remain few, with the exception of selenium and plasma GPx activity declines in parallel with plasma selenium.<sup>21</sup> Lower plasma selenium concentrations with low GPx activity have been found repeatedly in systemic inflammatory response syndrome (SIRS) and in sepsis.<sup>21,22</sup> They are associated with more extensive tissue damage, the presence of infection or of organ dysfunction or failure, and increased ICU mortality.<sup>6</sup> Selenium supplementation restores the activity of the enzyme<sup>21</sup> and is associated with improved clinical outcome. Therefore, the answer to the question, "Does a plasma TE concentration much below the normal ranges reflect a deficiency in the inflammatory ICU patient?" is "Probably yes," but it depends on how low the plasma concentration is and on the intensity of the inflammatory response (C-reactive protein level). In our clinical research experience, plasma concentrations more than 15% to 20% below the lowest reference range reflect more than inflammatory alterations and should be considered a potential deficit.

# AVAILABLE SYSTEMATIC REVIEWS

The literature contains only two meta-analyses of trace elements in the ICU population. Both were conducted by the same Canadian group (Table 66-3). The first included all micronutrients and focused on selenium,<sup>23</sup> whereas the latest focused on zinc.<sup>24</sup> Most of the trials showed low plasma concentrations of the investigated micronutrients on admission. Levels remained low in the placebo groups but normalized with supplementation. Restoration of normal levels was associated with a better clinical course,

Table 66-3 Sum	imary of N	leta-Analyses on N	licronutrients and Trac	e Elements	in the Intensive Care Unit
Study	No. of Trials	No. of Subjects (Intervention/No Intervention)	Intervention	Control	Outcomes
Heyland et al, 2005 <sup>23</sup>	11	898 (451/447)	Enteral and intravenous micronutrients with selenium	Placebo	Lower mortality with selenium Intravenous antioxidants more efficient than enteral
Heyland et al, 2008 <sup>24</sup>	4	131 (65/66)	Intravenous zinc, alone or in combination	Placebo	Zinc: lower mortality Fewer infections

 Table 66-4 Summary of the Four Latest Randomized Trace Elements Trials in Intensive

 Care Unit Patients (January, 2010)

Study	No. of Subjects (Intervention/No Intervention)	Study Design	Intervention	Outcomes
Mishra et al, 2007 <sup>25</sup>	40 (18/22)	DB, P, ITT Severe sepsis	Selenium 475, 315, 160 μg/ day for 3 days each (total 9 days)	Increased GPx activity Unchanged renal function
Angstwurm et al, 2007 <sup>26</sup>	238 (116/122)	DB, P, ITT Severe sepsis	Selenium 1000 µg/day for 14 days	Lower mortality with selenium ( $P = .049$ ), particularly in the most severe patients ( $P = .018$ ); unchanged organ function
Forceville et al, 2007 <sup>27</sup>	60 (31/29)	DB, P, ITT Septic shock	Selenium 4 mg then 1000 µg/day for 9 days	Median durations of mechanical ventilation were 14 in placebo and 19 days in selenium group; no difference in mortality
Berger et al, 2008 <sup>28</sup>	200 (102/98)	DB, P, ITT Major trauma, complex cardiac surgery, SAH	Selenium 400 μg then 200 μg + zinc, vitamin C, and vitamin E for a total of 5 days	Blunting of inflammatory response (CRP), increased GPx activity, and shorter hospital stay in trauma subgroup; no difference in mortality

CRP, C-reactive protein; DB, double blind; GPx, glutathione peroxidase; ITT, intent-to-treat; P, placebo controlled; SAH, subarachnoid hemorrhage.

including fewer infections, improved organ function, and better outcome. Both meta-analyses concluded that available evidence favored supplementation with the intravenous route over the enteral route for bioavailability reasons.

Four randomized trials have been published since these meta-analyses. These are summarized in Table 66-4. The British trial was underpowered and showed no clear clinical benefit despite correction of GPx activity.<sup>25</sup> The German trial showed a reduction of mortality<sup>26</sup> but no clear-cut impact on organ function. The French trial in septic shock showed no clear benefit of very large selenium doses.<sup>27</sup> The Swiss trial showed that the response depended on the intensity of inflammation; patients who had conditions with an intense SIRS, such as major trauma patients, had a shorter hospital stay.<sup>28</sup>

# INTERPRETATION AND DECISION TO TREAT

Although it is obvious that a clinically apparent deficit should be treated, TE and vitamins should be delivered from the first day whenever parenteral nutrition is indicated. However, there are no data regarding conditions with no clinical sign of deficit. Should biochemical alterations be treated with a goal of preventing development of full-blown clinical deficit? An argument in favor of active selenium supplementation is the continued decline of plasma selenium concentrations over time in the absence of supplementation in SIRS patients.<sup>6</sup> In conditions with large losses, the example of major burns is particularly demonstrative.<sup>29</sup> The prevention of deficiency in cases in which a deficit develops early owing to cutaneous losses is rational, and replacement is supported by randomized trials.<sup>22,30,31</sup> Another condition with rapid depletion is continuous renal replacement therapy. Letting these patients develop the expected TE deficiency while in the ICU will only prolong care because of increased infectious complications and delayed wound healing.

There are confirmatory animal data showing that early deficits benefit from early intervention. In models<sup>32,33</sup> where TE depletion is severe, supplementation is associated with improved markers of oxidative stress in major burn<sup>34</sup> and reduced mortality in trauma.<sup>35</sup>

How should a patient with incipient deficiency be detected? Doing blood TE determinations is not common practice, and results are difficult to interpret because of the omnipresent inflammatory response, particularly during the first week of acute illness, where fluid resuscitation and fluid inflation further complicate the picture. Nevertheless, levels are the only practical tool for diagnosis in clinical settings. After such a determination, a weekly follow-up may be justified in the presence of very abnormal values. Using clinical judgment, it is possible to detect these patients with only a small subsequent amount of laboratory testing.

#### SUPPLEMENTATION: PRACTICAL ISSUES

Administration of TE should follow precise rules, the recent ESPEN guidelines define their daily use with parenteral nutrition.<sup>36,37</sup> Multivitamin and TE preparations from the industry are suitable for most patients requiring parenteral nutrition, and a standard dose should be delivered daily (note that the doses are designed for a patient weighing 70 to 90 kg, so the dose may have to be adapted to extreme weight). Individual patients may require additional supplements of copper, selenium, or zinc, depending on their clinical condition. Providing these TEs as separate solution often is the only option because providing 2, 3, or 5 times the parenteral nutrition solution will result in inappropriately high delivery of manganese. Ideally, TE preparations should provide a low-manganese product for all<sup>38</sup> and a manganese-free product for patients with severe liver disease. However, the latter does not exist commercially. Practically, doses of micronutrients in excess of standard should be infused slowly (over a minimum of 6 hours and optimally 12 hours) to minimized high losses through urine excretion.

Potential side effects must be considered. Micronutrients, and particularly TEs, have dose-response curves, significant interactions, and a potential for toxicity. Supplementation with very large doses of a single TE may be detrimental. In his editorial to a study by Story and colleagues,<sup>9</sup> Bistrian asked whether losses, particularly of vitamin C, should be replaced.<sup>39</sup> He did not clearly answer the question, but he was concerned about the risk for oxalosis from ascorbic acid in chronic renal failure. It has been shown since that the deleterious effects of vitamin C deficiency are more important than the very small risk for oxalosis.<sup>40</sup> Today, we believe that any significant loss that lasts for more than 5 days should be replaced. This new paradigm requires confirmation by randomized trials.

Iron supplements are particularly tricky. Because oral and enteral supplementation is rather ineffective in ICU patients, intravenous iron may be required for correction of real or functional iron deficiency.<sup>13</sup> Iron supplementation is challenging in patients with inflammatory conditions. Indeed, parenteral iron worsens organ damage in animal models because it stimulates inflammation when delivered during sepsis.<sup>41</sup> Concerns have been raised about a possible increased risk for infection when parenteral iron therapy is used in critical care patients,<sup>42</sup> but the risks associated with transfusion also are quite real. Therefore, iron supplementation should be considered in the presence of very low serum iron associated with low ferritin.

A frequent question is whether TE may be delivered by the nasogastric tube; the answer is, "No," because of poor absorption of TEs by this route (except for Se) and by competition for absorption between several TEs.

Optimal doses of TE have not yet been determined. Nevertheless, parenteral nutrition doses remain the reference point in most patients. These are insufficient if an antioxidant effect is sought. Selenium is safe in doses of up to 500  $\mu$ g/day and zinc in doses up to 40 mg/day by the intravenous route. This corresponds to up to 10 times the recommended parenteral nutrition doses.

#### CONCLUSION

TE deficiency states exist in the ICU but often are clinically obscure. They may exist before admission, may develop in some patients at risk (i.e., those with large losses of biologic fluids due to their pathology, such as major burns, intestinal fistulas, or high-output drains) or arise as a result of ICU treatments (continuous renal replacement therapy). Acute depletion of TE stores results in biologic deficiency syndromes that prolong ICU complications (increasing infections, delayed wound healing) and length of stay with only minor visible clinical signs. Although clear-cut deficits should be treated, the substitution of TE known to be lost should be considered in many pathologies. Preventing the development of a deficiency is rational and is associated with shorter hospital stay. Determination of blood concentrations of selenium and zinc (and of copper in burn patients) remains the only way to detect incipient deficiencies and should be considered in conditions at risk after 7 to 10 days in the ICU in absence of substitution.

#### **AUTHOR'S RECOMMENDATIONS**

- Critically ill patients develop acute biologic TE deficiency syndromes in conditions with large biologic fluid losses.
   Obvious clinical deficiency requires weeks to develop and does not become visible because of the generally short length of ICU stay.
- The TEs most likely to be lost are selenium and zinc, as well as copper in major burns. Detection of incipient deficiency is based on considerations of pathologies at risk and demonstration of plasma levels more than 15% to 20% below reference ranges.
- Low plasma concentrations of selenium and zinc are observed in all severe critical care patients, and selenium levels decrease over time in the absence of supplementation. This is associated with depressed antioxidant defenses and impaired organ function.
- Substitution of losses is rational; it should be done in cases of predictable biologic fluid losses exceeding 5 days.

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# 67 Do Immunonutrients Improve Outcome in the Critically III?

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Treatment for critically ill patients changes continuously. This is driven, at least in part, by a better understanding of disease processes, advances in technology, and new pharmaceutical and nutraceutical agents. Nutritional support of the critically ill patient had advanced radically during the past 30 years. This reflects the advent of parenteral nutrition and the development of specialized enteral nutrition formulas.<sup>1</sup> Enteral nutrition remains the preferred form of nutrition support in the critically ill patient when the gastrointestinal tract is functional.<sup>2–7</sup> Several manufacturers include immunemodifying agents in enteral nutrition formulas in attempts to modulate the immune system and improve clinical outcome.

## PATHOPHYSIOLOGY AND MECHANISM OF ACTION

Defining the mechanism of action for *immunonutrition* is difficult because this term loosely describes enteral formulas with one or more of the following additives: arginine, glutamine, nucleotides (RNA), omega-3 fatty acids, and branched-chain amino acids (BCAAs). The literature generally classifies formulas containing any or all of these components as immune-enhancing diets (IEDs).<sup>1,8–11</sup>

# Arginine

Arginine affects the immune system in two ways. First, it is metabolized by inducible nitric oxide synthetase (iNOS). Second, this amino acid is a substrate for arginase 1.<sup>11,12</sup> iNOS converts arginine into nitric oxide, a potent oxidant that aids immune cells in both intracellular and extracellular bacterial killing. Arginase 1 metabolizes arginine into ornithine, a precursor for polyamines and proline, which stimulate cell repair and encourage wound healing.<sup>13–15</sup>

#### Glutamine

The nonessential amino acid glutamine becomes conditionally essential in the face of stress such as inflammation or injury.<sup>16</sup> Glutamine also upregulates the immune system by providing fuel to immune cells and encouraging clonal proliferation. Glutamine directly enhances the function of T lymphocytes, B lymphocytes, lymphokineactivated killer cells, and macrophages.<sup>17–20</sup> Finally, glutamine serves as a primary energy substrate for enterocytes and plays an important role in proliferation of the intestinal mucosa and other cell types.<sup>20–23</sup>

# **Nucleotides (RNA)**

Nucleotides (purines and pyrimidines) stimulate the immune system in several ways.<sup>24</sup> Nucleotides influence the production of a multitude of cell types in the central and peripheral immune system, including peripheral T cells, pluripotent hemopoietic stem cells, and cells in the thymus. They have key roles in cell-mediated immunity by stimulating T cells to produce growth factors such as interleukin-2 (IL-2), IL-3, and granulocyte-macrophage colony-stimulating factor (GM-CSF),<sup>21,22</sup> which are critical in immune response. Nucleotides are also needed for bacterial and fungal killing; therefore, they are essential for the immune system to overcome infection.<sup>25–28</sup>

# **Omega-3 Fatty Acids**

Omega-3 fatty acids, usually supplemented in the form of eicosapentaenoic acid and docosahexaenoic acid, influence the production of inflammatory mediators.<sup>29</sup> Specifically, omega-3 fatty acids downregulate inflammatory eicosanoid production from arachidonic acid. This results in the production of the 2 and 4 series of prostaglandins, which are less inflammatory than the proinflammatory 3 and 5 series stimulated by omega-6 fatty acids. These alterations decrease the production of inflammatory cytokines such as IL-1 and tumor necrosis factor (TNF).<sup>30</sup> Omega-3 fatty acids dampen the inflammatory response in states in which excessive inflammation is detrimental. Omega-3 fatty acids are usually derived from fish oil, borage oil, or canola oil.<sup>31</sup>

# **Branched-Chain Amino Acids**

BCAAs are essential amino acids metabolized almost exclusively by the muscle and provide an important precursor of glutamine.<sup>32</sup> BCAA administration may exert positive effects on amino acid and protein profiles in septic patients.<sup>33</sup>

## DO IMMUNE-ENHANCING DIETS IMPROVE OUTCOMES IN CRITICALLY ILL PATIENTS?

The lack of uniformity of trial design and the outcomes in patients administered IEDs makes this question difficult to answer, even with several meta-analyses available.<sup>8–11</sup> The meta-analyses and the trials they analyze lack homogeneity. In analyzing these trials, the reader should pay attention to four key areas: (1) the trials' definition of immunonutrition, (2) timing of initiation of feeds, (3) amount of formula infused and whether the patients reached their goals in terms of kilocalories and protein, and (4) the patient population studied. All these factors may influence outcomes.

#### Immunonutrition

Some trials use commercially available products, such as Impact, Immun-Aid, Oxepa, and Stresson. Other trials have various combinations and doses of arginine, glutamine, BCAAs, omega-3 fatty acids, and RNA, given as supplementation to standard isonitrogenous enteral feeding products. The definition of immunonutrition often varies from trial to trial, a fact that should warn the reader regarding the generalizability and validity (or lack thereof) of the results.

#### Timing of Initiation of Feeding

The timing of instituting feeding also varied among the trials. Because several trials in critically ill patients suggest that early enteral feeding is associated with lower infectious complications, time to initiation of feeds is an important variable. Also, because timing is important for many interventions in the treatment of critically ill patients (e.g., antibiotics,<sup>34</sup> activated protein C therapy,<sup>35</sup> and goal-directed volume repletion),<sup>36</sup> timing may also be critical for the success (or failure) of immunonutrition.

#### **Doses and Kilocalories**

The amount of enteral formula infused, calculation of goal kilocalories, and whether patients reach their caloric goals are important variables in trials. Again, if we consider the different immunonutrients as drugs, the doses of these nutrients (reported in terms of how much enteral formula is infused) may be important. Calculation of goal calories and whether the patients reached their goals are important for the same reasons.

#### Population

The populations studied also may have a bearing on the success or lack of success of IEDs. Although some trials focus on a generic "critically ill" population, others hone in on a specific subset of critically ill patients (septic, trauma, burn, acute respiratory distress syndrome [ARDS], or surgical patients). It is important to recognize the different groups studied and the effectiveness or lack of effectiveness that IEDs have in each subgroup.

Interpretation, integration, and application of the results from these multiple trials and meta-analyses to an individual patient thus prove difficult. The trials and the meta-analyses have varying types and doses of nutrients as well as different populations of patients and different outcomes. Pharmacologically, decisions regarding the effectiveness of a particular medication require data with standardization of doses, routes, and (most important) the same medication for every patient! For example, medical investigators would never test all known antibiotics against a particular species of bacteria and, then, when only a few antibiotics are determined to be effective against that bacteria, conclude that "all antibiotics are ineffective against the bacteria in question." So, it is important to evaluate what, when, and in what population immunonutrition was effective.

## BENEFICIAL EFFECTS OF IMMUNE-ENHANCING DIETS IN SPECIFIC POPULATIONS OF CRITICALLY ILL PATIENTS

#### Critically III Trauma Patients

The critically ill trauma population is one of the most studied populations showing beneficial effects of IEDs. A summary of trials is available in Table 67-1.<sup>37-41</sup> Four of the five trials showed statistically significant positive patient outcomes, namely, fewer infectious complications and shorter length of hospital stay, when IEDs were used.

When these and other trials were grouped into metaanalyses, both Beale<sup>8</sup> and Montejo<sup>11</sup> agreed that IEDs shorten time on mechanical ventilation in trauma patients. Montejo<sup>11</sup> and Beale<sup>8</sup> and their colleagues concluded that IEDs are beneficial in trauma patients, with evidence of lowered incidence of bacteremia and intra-abdominal infections, although there was insufficient evidence that IEDs lower the incidence of nosocomial pneumonia, wound infection, urinary tract infection, sepsis, ARDS, or multiple-organ dysfunction syndrome (MODS). Montejo and associates<sup>11</sup> concluded that IEDs decrease ICU length of stay in trauma patients.

#### **Critically III Surgical Patients**

See Table 67-2 for a summary of trials in critically ill surgery patients.<sup>42–44</sup> These trials report positive outcomes when IEDs are used, even though mortality was not significantly affected in any trial. When these and other trials were grouped into meta-analyses, Beale<sup>8</sup> and Montejo<sup>11</sup> and their colleagues agreed that IEDs decrease infection rate and decrease hospital length of stay of surgical patients.

#### **Critically III Burn Patients**

In comparison with other populations, the use of IEDs in the critically ill burn population is not well studied. One study focusing on burn patients<sup>45</sup> compares a low-fat enteral formula supplemented with fish oil to a standard diet (35% fat) and concludes that fish oil did not improve

Table 67-1	Table 67-1 IEDs in Critically III Trauma Patients						
Study	Immune- Enhancing Diet	Timing	Kilocalorie Goals	Amount Delivered	Statistically Significant Outcomes		
Brown et al, 1994 <sup>37</sup>	Diet with arginine, α-linoleic acid, and β-carotenes	Within 7 days of injury	35 kcal/kg/day and 1.5 g protein/day	All patients received more than 85% of the caloric goal at day 3	IEDs: fewer infections, better nitrogen balance, and lower CRP		
Kudsk et al, 1996 <sup>38</sup>	Immun-Aid	24 hr after surgery	0.32–0.38 g nitrogen/kg/day	Mean nitrogen intake for both groups was 0.23 g/kg/day	IEDs: fewer infections, shorter hospital length of stay		
Mendez et al, 1997 <sup>39</sup>	Diet supplemented with arginine, trace elements and canola oil	First 3 days of admission	30 kcal/kg/day and 1.5 g protein/kg/day	All patients reached 85% of the caloric goal by day 3	No significant differences in outcomes		
Moore et al, 1994 <sup>40</sup>	Immun-Aid	24 hr after trauma	35 kcal/kg/day in the first 72 hours	NS between groups	IEDs: fewer abdominal abscesses, fewer new multiorgan failure cases		
Weimann et al, 1998 <sup>41</sup>	Impact	48 hr after trauma	35-40 kcal/kg/day	Not reported	IEDs: fewer days of SIRS or multiorgan failure		

CRP, C-reactive protein; IED, immune-enhancing diet; NS, not significant.

#### Table 67-2 IEDs in Critically III Surgical Patients

Study	Immune- Enhancing Diet	Timing	Goals	Delivered	Statistically Significant Outcomes
Daly et al, 1992 <sup>42</sup>	Impact	Within 12 hr after surgery	25 kcal/kg/day	NS between groups	IEDs: fewer infections and wound complications and shorter LOS
Gianotti et al, 1997 <sup>43</sup>	Impact	6 hr after surgery	105 kJ/kg/day	Only 6.3% in each group failed to reach the nutrition goal	IEDs: shorter LOS and better immune profile
Senkal et al, 1997 <sup>44</sup>	Impact	12 hr after surgery	25 kcal/kg/day Inclusion criteria of tolerance of 3000 mL of formula	All patients received at least 3000 mL of formula	IEDs: lower cost and lower number of late complications

IED, immune-enhancing diet; LOS, length of stay; NS, not significant.

clinical outcomes. Peng and coworkers<sup>46</sup> supplemented glutamine in addition to standard enteral formulas and showed that the IED improved wound healing and reduced length of hospital stay. Another trial by Garrel and associates<sup>47</sup> showed decreased infectious complications when burn patients were given formulas supplemented with glutamine. Therefore, glutamine supplementation may provide some clinical benefit in burn patients, but there is no evidence to support other immune-enhancing ingredients in this population.

#### **Overall Critically III Patients**

Within the overall critically ill population, trials vary in their inclusion criteria and target population. Although some investigators study IEDs in all critically ill patients, others narrow their inclusion criteria to include only subsets. For example, some trials focus on septic patients,

some focus on ARDS patients, and some focus on mechanically ventilated patients with severe sepsis and septic shock. A summary of these trials is found in Table 67-3.<sup>48-55</sup> Looking at these trials, it is important to note that the benefits of IEDs are seen in a targeted population when enteral nutrition is initiated early (within 24 hours) in the hospital stay. Overall, IEDs improve oxygenation in mechanically ventilated patients with sepsis or ARDS. In some trials, IEDs offer a mortality benefit, whereas in others, they do not. As for the meta-analyses, they offer conflicting opinions. Beale and associates<sup>8</sup> conclude that IEDs decrease infection rate overall, while Heyland and colleagues9 maintain that IEDs have no effect on rate of infectious complications. All metaanalyses<sup>8–11</sup> agree that the use of IEDs decreases hospital length of stay, although Montejo and associates<sup>11</sup> argue that this only occurs in surgical patients. All these authors<sup>8–11</sup> conclude that IEDs fail to affect mortality.

Table 67-3 IEDs in V	arious Populations of	f Criticall	v III Medical	Patients
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Study	Immune-	Timing	Goals	Delivered	Outcomes
	Enhancing Device				
Atkinson et al, 1998 <sup>48</sup>	Impact	Within 72 hr of admission	>2.5 L of formula	Nonsignificant between groups	IEDs: lower duration of mechanical ventilation and shorter hospital stay
Bower et al, 1995 <sup>49</sup>	Impact	Within 48 hr of event causing ICU admission	Up to 1.25 times REE	Both groups received 75% to 85% of what was ordered	Of patients who received ≥821 mL/day, IEDs showed shorter LOS and fewer infections.
Gadek et al, 1999 <sup>50</sup> (ARDS patients)	Oxepa	Within 24 hr of randomization	75% of BEE × 1.3, Harris-Benedict	All included patients received goal calories for a minimum of 4 ± 1 days from study day 1	IEDs: fewer days of MV and shorter LOS in ICU; lower incidence of new organ failure
Galban et al, 2000 <sup>51</sup> (septic patients)	Impact	Within 36 hr of sepsis	1.3 × Harris- Benedict	Nonsignificant between groups	IEDs: lower mortality rate and lower number of bacteremias and nosocomial infections
Kieft et al, 2005 <sup>52</sup>	Stresson Multi Fibre	Within 48 hr of admission to the ICU	Harris-Benedict × stress factor of clinician's choice	Patients received 62.8% to 72.5% of required	IEDs: no significant benefits
Pacht et al, 2003 <sup>53</sup> (ARDS)	Охера	Within 24 hr of meeting study criteria	50% of Harris- Benedict × 1.33	Nonsignificant between groups	IEDS: improved oxygenation and decrease in inflammatory cytokines and cells in BAL fluid
Pontes-Arrudas et al, 2006 <sup>54</sup> (severe sepsis and septic shock)	Oxepa	Within 6 hr of meeting study criteria	75% of BEE V 1.3, Harris-Benedict within 72 hr	Nonsignificant between groups	IEDs: mortality benefit and better oxygenation; fewer days of MV, fewer ICU days, and fewer new organ dysfunction
Singer et al, 2006 <sup>55</sup> (ARDS)	Pulmocare	Within 24 hr of ICU admission	70% of REE $\times$ 1.2	All patients received enteral nutrition for ≥14 days at a rate not exceeding REE × 1.25	IEDs: improvement in oxygenation, lung compliance; fewer days of MV; no mortality benefit

ARDS, acute respiratory distress syndrome; BAL, bronchoalveolar lavage; BEE, basal energy expenditure; ICU, intensive care unit; IED, immune-enhancing diet; LOS, length of stay; MV, mechanical ventilation; REE, resting energy expenditure.

#### IMMUNE-ENHANCING DIETS AND MORTALITY

Controversy surrounds issues of mortality differences with IEDs. Most trials fail to show a mortality benefit <sup>51,54</sup> have in common that enteral nutrition is initiated early in the ICU course and advanced to goal rate within a predefined time frame, usually 48 hours. All meta-analyses<sup>8–11</sup> agree that IEDs produce no effects on overall patient mortality, but individual trials show conflicting results, especially in septic patients. The study by Galban and colleagues<sup>51</sup> documented a significant reduction in mortality with IEDs, whereas in Bower and associates' study,<sup>49</sup> results approached significance for a higher relative risk for death with immunonutrition. This particular trial noted that the increased mortality occurred in patients classified as "unsuccessful feeders." Montejo and associates,<sup>11</sup> in

their meta-analysis, performed a subgroup analysis of burn, surgical, and trauma patients and found that IEDs failed to affect mortality. All meta-analyses<sup>8–11</sup> concluded that IEDs generate no overall effect on mortality in critically ill patients.

#### Interpretation

Although interpretation of these trials is challenging, they provide uniformity and consistency in some conclusions. Overall, IEDs decrease infectious complications and hospital length of stay, with little or no effect on overall mortality. Results of clinical trials provide better evidence of benefit and effectiveness of IEDs in trauma and surgical patients with less evidence in mixed populations of critically ill patients. The influence of variables such as specifically responsive populations, optimal time for initiation of diet, choice and dose of immunonutrients in the diets,
and harm versus benefit of arginine in septic patients remains poorly defined from the existing data. With regard to the septic population, Bertolini and coworkers<sup>56</sup> state that arginine and omega-3 fatty acids can be associated with opposite effects on the immune system and that "no attempt has been made to target immunonutrients to the different phases ... and to the haemodynamic conditions of patients." They concluded that future studies involving immunonutrients should be based on "robust knowledge of basic mechanisms of action" because their caloric and pharmacologic actions have the "potential to greatly influence physiological functions when administered at pharmacological doses."

#### CONCLUSION

The term *immunonutrients* remains, at best, ill-defined. It includes nutrients such as glutamine, arginine, omega-3 fatty acids, and nucleotides (among others), either alone or in combination. Existing trials that study nutrient effects in the critically ill population lack uniformity in the number, amount, and combination of these nutrients. A critically ill patient population is by no means a homogeneous population and may include medical, surgical, trauma, and burn patients, as well as septic and nonseptic patients. Although several trials and meta-analyses attempt to determine whether IEDs affect outcome in critical illness, results agree in some areas but disagree in others. It is uniformly agreed that IEDs provide benefit overall in decreasing infectious complications and decreasing length of stay, especially in trauma and surgical populations, but it remains unclear whether immunonutrition harms certain patients (e.g., septic patients). Although there is controversy regarding mortality with IEDs in this subpopulation, the results of the metaanalyses suggest no overall effect. Future trials should include the following:

- Standardized number and choice of nutrients
- Standardized doses
- Targeted patient populations

Until trials include these traits, it will remain unclear which patients will benefit from immunonutrition.

#### **AUTHORS' RECOMMENDATIONS**

- Trauma and Post-surgical patients
  - use Immun-Aid or Impact
  - initiate within 24 hours of trauma or surgery
  - advance to goal tube feed rate within 48 hours
- avoid use in septic patients
- ARDS patients
  - use Oxepa or Pulmocare
  - initiate within 6 hours of diagnosis
  - use in septic or non-septic patients
- Burn patients
- glutamine may have benefit

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# 8 Is It Appropriate to Underfeed the Critically III Patient?

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Critically ill patients are often hypermetabolic and can rapidly become nutritionally compromised.<sup>1</sup> Malnutrition is prevalent in these patients and has been associated with increased morbidity and mortality, particularly in the surgical population.<sup>2</sup> Consequently, the goals of nutrition therapy in critically ill patients are to attenuate the metabolic response to stress or injury by providing nutrition consistent with the patient's condition, to prevent or treat nutrient deficiencies, and to avoid complications related to the route of nutrition delivery. Ultimately, attainment of these goals should translate into improved patient outcomes.<sup>3</sup> Despite nutrition therapy being an integral part of standard patient care, evidence surrounding the appropriate assessment of nutritional status and the appropriate substrate, timing, route, and amount of nutritional support in critically ill patients is limited, particularly in medical patients. One important unanswered question that has recently become more prominent in the critical care literature pertains to dose or amount of nutrition. There is a general consensus that excessive underfeeding and overfeeding have deleterious effects and should be avoided, but controversy exists over what the feeding target should be. During the past decade, some authors have proposed the concept of hypocaloric feeding or permissive underfeeding to reduce the metabolic complications associated with the acute stress response.<sup>4,5</sup> In fact, unplanned hypocaloric feeding is common in clinical practice because of disruptions in delivery of nutrition as a result of gastrointestinal intolerance, fasting for procedures, and routine nursing practices.<sup>6</sup> Most critically ill patients do not meet nutritional requirements, and recent studies report that average energy intakes are 49% to 70% of calculated requirements.<sup>7–13</sup> Consequently, we are faced with the question, Is it appropriate to underfeed the critically ill patient?

To answer this question, we used a systematic approach to reviewing the literature on hypocaloric feeding in critical care. To locate relevant articles, four bibliographic databases (Medline, Embase, CINAHL, and the Cochrane Library) were searched. Search terms included "nutritional support" or "enteral nutrition" or "parenteral nutrition" or "energy intake" or "hypocaloric feeding" or "energy debt" and "critical care" or "critical illness" or "intensive care units." These searches spanned from January 1996 to November 2007. In addition, personal files and relevant review articles were searched for additional studies. There were no language restrictions

on included studies. Data reported in abstract form only were excluded. Studies were included in the review process if they met the following criteria: (1) study designprospective or retrospective observational study or randomized or nonrandomized clinical trial or meta-analysis; (2) population—mechanically ventilated, critically ill adult patients; (3) intervention (if applicable)—early aggressive versus early lower-dose enteral nutrition, early versus delayed enteral nutrition, enteral nutrition alone versus enteral nutrition plus supplemental parenteral nutrition; (4) outcomes-at least one of the following: mortality (intensive care unit [ICU], hospital, longterm), length of stay, and infectious and noninfectious complications. Because our goal was to determine the optimal amount of energy to feed the critically ill, we excluded studies that examined protein intake and outcomes. In contrast to the purported benefits of energy restriction, protein restriction is associated with worse clinical outcomes in both animal models and clinical studies.<sup>14,15</sup> We also excluded studies that considered only parenteral nutrition or only obese patients because these studies apply to a minority of critically ill patients, limiting our ability to apply results to general clinical practice. By adopting this systematic approach to appraise the current literature, we are able to draw conclusions about the evidence and generate hypotheses to be tested in future research.

#### OBSERVATIONAL STUDIES ON HYPOCALORIC NUTRITION IN CRITICALLY ILL PATIENTS

During the past decade, several observational studies have examined the association between energy intake and clinically important outcomes in critically ill patients. Two studies examined energy debt as an indicator of nutritional adequacy. Dvir and colleagues conducted an observational study of the impact of daily cumulative energy balance measured by a bedside computerized information system on the outcomes of 50 mechanically ventilated critically ill patients.<sup>16</sup> Mean energy balance was -460 kcal per 24 hours (range, -1025 to +259 kcal per day), and mean cumulative energy balance was -4767 kcal. Negative cumulative energy balance was highly correlated with occurrence of acute respiratory distress syndrome (ARDS; P = .01) and renal failure (P = .0001), need for surgery (P = .008), pressure sores (P = .007), and total complication rate (P = .0001), but was not associated with length of mechanical ventilation, length of ICU or hospital stay, or mortality. The same association was found for maximal negative energy balance.

Villet and associates also explored the association between cumulative energy balance and clinical outcomes in a prospective cohort study of 48 surgical critically ill patients.<sup>17</sup> Patients' weekly *caloric balance* (defined as calories received minus calories targeted) was calculated. After adjustment for Simplified Acute Physiology score (SAPS) II,<sup>18</sup> Sequential Organ Failure Assessment (SOFA) score,<sup>19</sup> body mass index (BMI), and age, cumulative energy deficit was associated with longer ICU length of stay (P = .0001), more days on mechanical ventilation (P = .0002), and more complications (P = .0003). As a sensitivity analysis, they examined cumulative energy debt during the first week of the patients' ICU stay and found that a negative energy balance greater than -10,000 kcal was associated with worse clinical outcomes.

Other observational studies have examined mean energy intake relative to recommended intake as an indicator of adequacy of nutrition. Rubinson and associates conducted a prospective observational cohort study of 138 medical intensive care unit (MICU) patients.<sup>13</sup> Daily energy intake was recorded during the entire MICU stay, and patients were grouped into quartiles based on percentages of energy requirements as recommended by the American College of Chest Physicians (ACCP) in their 1997 guidelines.<sup>3</sup> To ensure that the study population was representative of the patients to whom the ACCP guidelines are directed, only patients who did not take any food by mouth for greater than 96 hours after ICU admission were included. Simple Kaplan-Meier analyses found that patients in the lowest quartile of energy intake (less than about 6 kcal/kg per day) had a higher risk for bloodstream infection than all other patients (P < .05). After multivariable Cox proportional hazards analysis adjusting for severity of illness (SAPS II) at MICU admission, patients who received an average of greater than or equal to 25% of their recommended energy intake had a significant reduction in the risk for bloodstream infection (hazard ratio, 0.27; 95% confidence interval [CI], 0.11 to 0.68).

In a similar study, Krishnan and colleagues performed a prospective cohort study of 187 critically ill patients<sup>10</sup> with an ICU stay of at least 96 hours. Patients were categorized into tertiles according to percentage of ACCP recommended levels of energy intake achieved.<sup>3</sup> The authors found that patients in the highest tertile (receiving >66% of recommended calories) were less likely to be discharged from the hospital alive and to achieve spontaneous ventilation before ICU discharge when compared with patients in the lowest tertile. Patients in the middle tertile (33% to 65%), however, were more likely than patients in the lowest tertile to be discharged from the ICU breathing spontaneously.

We have performed a similar analysis<sup>20</sup> using crosssectional survey data from the follow-up phase of a previous cluster randomized trial of dissemination of Canadian Clinical Practice Guidelines for nutrition support.<sup>21</sup> According to mean daily energy intake from enteral nutrition (EN) as a percentage of calories prescribed, 669 patients from 59 Canadian ICUs were divided into tertiles. We found no association between energy intake and mortality after adjusting for the following potential confounders: age, admission category and diagnosis, gender, BMI, timing of initiation of EN, and presence of ARDS). However, greater energy intake was associated with longer ICU and hospital length of stay. Compared with the lowest tertile, patients in the middle and highest tertiles stayed in the ICU an average of 4.8 days (P = .01) and 8.2 days (P < .001) longer. Patients in the middle and not highest tertiles also stayed in the hospital a mean of 4.5 days (P = .02) and 8.0 days (P < .001) longer.

A recent prospective cohort study of 77 surgical and medical ICU patients employed a regression tree analysis to examine the association between total energy intake and clinical outcomes.<sup>22</sup> This analysis included kilocalories from lipid-based sedatives or dextrose-containing intravenous fluids in addition to calories from nutrition support in their assessment of total energy intake. All patients were underfed, with 50% of surgical and 56% of medical patients meeting goal calories. Results of the regression analysis demonstrated that percent goal calories received was a significant predictor of patient outcome. If the percent goal calories received was greater than 82%, the estimated average length of stay was 24 days, whereas, if the percent goal calories was less than 82%, the average length of stay was 12 days. This relationship of approaching goal calories being associated with an increased length of stay was also consistent for hospital length of stay. Furthermore, the analysis indicated that the threshold at which percent calories received impacts on outcomes is lower for surgical patients. Patients receiving 67% or higher goal calories had a mean ICU length of stay of 23.5 days, whereas those receiving less than 67% goal calories had a mean length of stay of 10.4 days. As in our analysis, these results should be interpreted with caution as greater energy intake was achieved by patients with longer lengths of stay because they had more days in the ICU to meet goal calories. The small sample size used for the regression tree analysis is an additional limitation of the study.

Finally, in a recent nonrandomized trial, 150 mechanically ventilated patients in a medical ICU were assigned to treatment groups on alternating days (rather than by random allocation) to evaluate early aggressive EN compared with delayed EN.<sup>23</sup> Enteral nutrition was delivered through gastric bolus feeding every 4 hours. Patients in the early EN group were scheduled to receive their targeted amount of EN on day 1 after enrollment, whereas patients in the delayed EN group were scheduled to receive 20% of their energy requirements on days 1 to 5, with full-calorie EN starting on day 5. During the first 5 days of mechanical ventilation, patients in the early group received 28% of their estimated energy requirements (average, 474 kcal per day), whereas patients in the delayed group received 7% of their energy requirements (126 kcal per day). Patients in the early-feeding group had a statistically greater incidence of ventilator-associated pneumonia (49.3% versus 30.7%; P = .02), longer ICU length of stay (13.6 versus 9.8 days; P = .043), and longer hospital length of stay (22.9 versus 16.7 days; P = .023). However, there was no difference in hospital mortality between the two groups. Because both these groups were truly underfed and were near or below the 25% goal calorie threshold shown to increase risk for infection in the study by Rubinson and associates,<sup>13</sup> it is difficult to interpret these findings. The use of bolus feedings, which may increase risk for regurgitation and aspiration, further limits the inferences that can be drawn from this study.

Integrating across all these aforementioned studies, it would appear that the optimal dose of EN would be more than 25% but less than 82% of goal calories. However, as acknowledged by many of their authors, these observational studies have an obvious and common bias in the critical care nutrition literature: that sicker patients are more likely to stay longer in the ICU and more likely to be difficult to feed enterally and that longer exposure to the ICU increases the chances of having complications. Thus, observational research cannot reliably answer our question of whether it is appropriate to underfeed the critically ill patient. Many unmeasured factors likely play a role in clinicians' decisions to deliver nutritional support to individual critically ill patients (such as the patient's expected length of stay and perceived nutritional status), and even the most carefully performed observational study might still be limited by residual confounding.

To find the answer, we need to seek evidence from randomized controlled trials (RCTs). Unfortunately, there are no published studies that directly answer this question, but considerable insight can be derived from examination of studies of route of delivery (EN versus parenteral nutrition [PN]), timing (early versus delayed EN initiation), and dose (full versus partial feeding).

#### RANDOMIZED CONTROLLED TRIALS COMPARING ENTERAL NUTRITION AND PARENTERAL NUTRITION

There have been numerous trials comparing EN and PN.<sup>24–36</sup> In these RCTs, patients in the PN groups achieve target energy intake rapidly after initiation, whereas patients in the EN group may take several days to achieve target energy intake, and usually fail to do so, resulting in a substantial energy debt. Four meta-analyses (two in critically ill patients<sup>37,38</sup> and two that also included hospitalized patients<sup>39,40</sup>) have all concluded there is no difference in mortality between patients receiving EN or PN, but fewer complications are associated with EN than with PN. From these RCTs, we can conclude that despite the fact that EN usually underdelivers calories compared with PN, it is the preferred route of nutrition delivery.

#### RANDOMIZED CONTROLLED TRIALS COMPARING EARLY AGGRESSIVE AND EARLY LOWER-DOSE ENTERAL NUTRITION

If EN is the preferred route of delivery, what evidence is there that providing more EN compared with less EN is associated with improved clinical outcomes? There have been two RCTs that have linked increased energy intake from EN that were begun early in the course

of critical illness with improved patient-centered outcomes.<sup>41,42</sup> The first was an RCT by Taylor and associates, who investigated the effects of early enhanced EN on clinical outcomes in patients with severe head injury who were mechanically ventilated.41 Eighty-two head-injured patients with Glasgow Coma Scale (GCS) scores greater than 3 were randomized to receive either standard early EN or enhanced early EN. Enteral feeding was started within 24 hours of the injury in both groups. In the control group, patients received EN starting at 15 mL per hour, which was increased incrementally as tolerated according to a predefined protocol. In the intervention group, patients received EN starting at the rate that would meet their full energy requirements. During the first week after head injury, patients in the enhanced EN group received significantly more calories than patients in the control group (59.2% versus 36.8% of caloric goal; P = .001). There was a trend toward improved neurologic outcome 3 months after injury in the intervention group (proportion with good neurologic recovery, 61% versus 39%; P = .08), but this difference was not apparent at 6 months, suggesting that the aggressively fed group had a faster time to recovery. Patients in the intervention group also had fewer overall complications, including infections, up to 6 months after the initial injury (37% versus 61%; P = .046). There was no difference in mortality (12.2% in the intervention group and 14.6% in the control group), although the study was not adequately powered for this end point.

The second RCT evaluating "dose" of nutritional support was a multicenter cluster-randomized clinical trial of algorithms for critical care enteral and parenteral therapy (ACCEPT).<sup>42</sup> This trial in 14 Canadian ICUs evaluated the impact of the implementation of evidence-based feeding algorithms on nutrition practices and patient outcomes. Four hundred ninety-nine patients 16 years of age or older who were expected to stay in the ICU at least 48 hours were enrolled in the study. At the sites assigned to the intervention group, in-service education sessions, reminders, and academic detailing (i.e., one-to-one education) were performed to implement the evidence-based nutrition support recommendations. ICUs assigned to the control group did not receive any of the interventions. Patients at both the intervention (n = 248) and control (n = 214) sites were similar with the exception that more patients at the intervention hospitals were admitted from the operating room. Although not statistically different, patients at the intervention hospitals received more calories per day than those at the control sites (1264 versus 998 kcal; P = .25) and received significantly more days of EN per 10 days (6.7 versus 5.4 days; P = .042). This difference in energy intake between the groups was associated with an improvement in clinical outcomes because patients in the intervention sites had a significantly shorter length of hospital stay (25 versus 35 days; P = .003) and demonstrated a trend toward reduced mortality (27% versus 37%; P =.058). However, length of ICU stay was not different between the two groups (10.9 versus 11.8 days; P = .7). Admittedly, it is difficult to understand how such a small difference in dose of EN is associated with such large changes in clinical outcomes. Nevertheless, in both these studies,<sup>41,42</sup> it appears that increased amounts of EN or less

energy deficit was associated with improved clinical outcomes; therefore, it may not be appropriate to underfeed the critically ill patient.

#### RANDOMIZED CONTROLLED TRIALS COMPARING EARLY AND DELAYED ENTERAL NUTRITION

Review:

During the past decade, 12 RCTs of early versus delayed EN in critically ill patients have been performed.<sup>41,43–53</sup> Five of these trials were in elective surgery patients;<sup>43–47</sup> the remainder were in trauma, head injury, and burn patients.<sup>41,48–53</sup> These RCTs, together with earlier studies,

have been included in two meta-analyses. When looking across these trials, patients in the early EN groups generally received more total calories (average, 1713 kcal) than patients in the delayed groups (average, 910 kcal) because their EN was initiated earlier. The first meta-analysis included only mechanically ventilated patients<sup>37</sup> and concluded that early EN is associated with trends toward a reduction in mortality (RR, 0.64 [95% CI, 0.41 to 1.00; P = .05]) and infectious complications (RR, 0.78 [95% CI, 0.60 to 1.01; P = .06]) (Figs. 68-1 and 68-2), but not ICU length of stay (weighted mean difference, 1.04 [95% CI, -2.09 to 4.18; P = .51]). The second meta-analysis included 19 RCTs<sup>54</sup> and found that early EN was not associated with mortality but was associated with a

Review:	Early enteral nutrition vs. delayed nutrient intake
Comparison:	01 Early EN vs. delayed nutrient intake
Outcome:	01 Mortality

Early enteral nutrition vs. delayed nutrient intake

Study or sub-category	Early EN n/N	Delayed n/N	RR (rai 95%	ndom) Weight	RR (random) 95% Cl	Year
Moore	1/32	2/31	<	3.67	0.48 [0.05, 5.07]	1986
Chiarelli	0/10	0/10			Not estimable	1990
Eyer	2/19	2/19		5.89	1.00 [0.16, 6.38]	1993
Chuntrasakul	1/21	3/17	<	4.30	0.27 [0.03, 2.37]	1996
Singh	4/21	4/22		12.96	1.05 [0.30, 3.66]	1998
Kompan 1999	0/14	1/14	<	2.08	0.33 [0.01, 7.55]	1999
Minard	1/12	4/15	←	4.79	0.31 [0.04, 2.44]	2000
Pupelis	1/30	7/30	<	4.90	0.14 [0.02, 1.09]	2001
Dvorak	0/7	0/10			Not estimable	2004
Kompan 2004	0/27	1/25	< <u>→</u>	2.03	0.31 [0.01, 7.26]	2004
Malhotra	12/100	16/100		41.90	0.75 [0.37, 1.50]	2004
Peck	4/14	5/13		17.48	0.74 [0.25, 2.18]	2004
Total (95% CI)	307	306	-	100.00	0.64 [0.41, 1.00]	
Total events: 26 (Ea	arly EN), 45 (Dela	yed)				
Test for heterogene	ity: Chi <sup>2</sup> = 4.84, d	f = 9 (P = 0.85)	$l^2 = 0\%$			
Test for overall effect	ct: $Z = 1.95 (P = 0)$	.05)				
			0.1 0.2 0.5 1	2 5 10		
		F	avors early EN	Favors delayed		

Figure 68-1. Effect of early versus delayed enteral nutrition on mortality in critically ill patients. (From http://www.criticalcarenutrition.com.)

Comparison: Outcome:	01 Early EN vs. delaye 02 Infections complica	d nutrient intake tions				
Study	Early EN	Delayed	RR (random)	Weight	RR (random)	Year
or sub-categor	y n/N	n/N	95% Cl	%	95% Cl	
Moore	3/32	9/31		4.30	032 [0.10, 1.08]	1986
Singh	7/21	12/22		10.51	0.61 [0.30, 1.25]	1998
Kompan	9/27	16/25		13.35	0.52 [0.28, 0.96]	1999
Minard	6/12	7/15		9.11	1.07 [0.49, 2.34]	2000
Malhotra	54/100	67/100		34.73	0.81 [0.64, 1.01]	2004
Peck	12/14	11/13		28.01	1.01 [0.74, 1.39]	2004
Total (95% Cl) Total events: 9 Test for hetero Test for overall	206 1 (Early EN), 122 (Dela geneity: Chi <sup>2</sup> = 8.39, df effect: Z = 1.88 ( <i>P</i> = 0.	206 lyed) = 5 ( <i>P</i> = 0.14), l <sup>2</sup> 06)	= 40.4%	100.00	0.78 [0.60, 1.01]	

Favors early EN Favors delayed

Figure 68-2. Effect of early versus delayed enteral nutrition on infectious complications in critically ill patients. (From http://www .criticalcarenutrition.com.)

significantly lower risk for infectious complications (RR, 0.45 [95% CI, 0.30 to 0.66; P < .001]) and reduced hospital length of stay (mean reduction, 2.2 days [95% CI, 0.81 to 3.63; P = .004]). Consistent with the observations from the randomized trials presented earlier, these data support the notion that more aggressive initiation of EN with increased amounts of EN provided is associated with improved clinical outcomes.

#### RANDOMIZED CONTROLLED TRIALS COMPARING ENTERAL NUTRITION ALONE AND ENTERAL NUTRITION PLUS SUPPLEMENTAL PARENTERAL NUTRITION

Five RCTs have compared combined EN and PN with EN alone, all of which started both regimens simultaneously.<sup>27,55–58</sup> We can assume that patients in the groups supplemented with PN likely achieved full energy intake more rapidly and thus had less energy debt. However, energy debt can only be calculated from a study by Bauer and associates,58 in which the prescribed calories were 25 kcal/kg per day: the combined EN and PN group reached 98% goal calories with 24.6 kcal/kg per day, and the EN-only group received 57% of prescribed calories with 14.2 kcal/kg per day. A meta-analysis of these five trials concluded that combination EN and PN has no benefit with regard to mortality (RR, 1.27 [95% CI, 0.82 to 1.94; P = .3]), infectious complications (RR, 1.14 [95%) CI, 0.66 to 1.96; P = .6]), length of hospital stay, or days on mechanical ventilation.<sup>59</sup> Therefore, despite the fact that some observational data suggest that an energy deficit may be associated with poor outcomes, there is no evidence that minimizing energy deficit with supplemental PN in addition to EN will improve clinical outcomes.

#### CONCLUSION

Observational studies examining the association between amount of energy intake and clinical outcomes suggest that providing somewhere in the range of 25% to 82% of calculated energy requirements is optimum. These observations are supported by animal studies showing that restrictive energy intake is associated with decreased inflammatory cytokines, improved metabolic profiles, and better survival compared with more liberal amounts of energy.<sup>60</sup> However, stronger inferences can be made from existing RCTs comparing different routes of delivery and timing of feeding. Evidence from these RCTs suggests that early aggressive EN, with increased amounts of EN provided, is associated with improved clinical outcomes, and that using PN in preference to EN or supplementing EN with PN does not confer any additional benefits. It is important to point out that none of the RCTs that achieved greater success with EN achieved 100% goal calories. Rather, they increased the provision of energy from about 50% closer to 100%. Consequently, given the inadequate provision of energy to critically ill patients in our ICUs, strategies to achieve goal calories with EN should be adopted. Improving adequacy of EN from between 25% and 82% to closer to goal calories may be associated with a clinical benefit. However, how close to 100% represents a shift from benefit to harm is unknown. High-quality evidence from randomized trials investigating the optimal amount of energy intake in ICU patients is still needed.

#### **AUTHORS' RECOMMENDATIONS**

- Most critically ill patients receive only 49% to 70% of their calculated energy requirements.
- The results of observational studies suggest that the optimal dose of EN is greater than 25% but less than 82% goal calories.
- RCTs of studies of route of delivery and timing of feeding suggest that early aggressive EN is associated with improved clinical outcomes, but using PN in preference to EN or supplementing EN with PN does not confer any additional benefits.
- RCT level evidence on the optimal amount of energy to provide critically ill patients is lacking.
- Strategies to achieve 100% goal calories with EN should be pursued.

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### 59 How Do I Diagnose and Manage Acute Gastrointestinal Bleeding?

#### Rachel A. Hadler, Rachel R. Kelz

Acute gastrointestinal bleeding carries a mortality rate of 5% to 10%, depending on etiology. The incidence of acute upper gastrointestinal (GI) bleeding is about 100 per 100,000 population; lower GI bleeds are seen in 20 to 27 adults per 100,000 population, although that rate increases substantially with age. Patients presenting with acute GI bleeding may present overtly or with more subtle symptoms indicative of blood loss and hypotension. Both upper and lower GI bleeding may present with hematochezia, although upper GI bleeds are more likely to present as hematemesis or melena or with weakness, dyspnea, and anemia.<sup>1</sup>

Acute GI bleeding can be classified based on point of origin, with the ligament of Treitz as the major geographic landmark distinguishing upper and lower. Predisposing factors for upper GI bleeds include pharmacologic agents such as aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and anticoagulants, as well as cigarettes and alcohol. Vascular abnormalities throughout the GI tract may generate acute bleeding, as can coagulopathies, malignancies, and any disease process causing changes to the GI mucosa (e.g., diverticulosis, inflammatory bowel disease, or esophagitis).<sup>2</sup>

Common etiologies of acute bleeding vary by location. Peptic ulcer is the most common cause of upper GI hemorrhage, generating about 50% of cases.<sup>3</sup> Other common causes include esophageal and gastric varices (seen in patients with portal hypertension). These are responsible for about 15% of cases. Arteriovenous malformations (5%), Mallory-Weiss tears (5%), tumors (5%), and Dieulafoy lesions (1%) account for most others.<sup>2</sup> Diverticular disease is the most common cause of lower GI bleeding (30%) and is seen particularly in older patients (>65 years). Angiodysplasia (8%) is another condition seen more commonly in older patients. In contrast, hemorrhoids (5%) are seen in a younger population. Other common causes of lower GI bleeding include polyps (18%), malignancies (18%), and colitis (18%). However, roughly 15% of cases are idiopathic (Tables 69-1 and 69-2).<sup>2</sup>

#### EVIDENCE

### Diagnosis and Treatment of Nonvariceal Bleeding

Nonvariceal bleeding represents most cases of upper GI bleeding. For the past two decades, endoscopic therapy has been considered the ideal treatment for nonvariceal

bleeding. A meta-analysis of 30 trials by Cook and colleagues determined that thermal contact devices, laser treatment, and injection therapy all decrease rates of rebleeding as well as mortality and the need for surgery in patients with actively bleeding or nonbleeding visible vessels.<sup>4</sup> This is not, however, the case in patients with ulcers containing flat pigmented spots or adherent clots. More recently, Barkun and associates discussed 20 themes through meta-analyses of 71 articles involving roughly 9000 patients.<sup>5</sup> These authors proposed a sequential management scheme for nonvariceal bleeding. This involved immediate resuscitation and evaluation followed by placement of a nasogastric tube for diagnosis and prognosis. Early (<24 hours after presentation) diagnostic endoscopy should be performed in all patients and should be followed by endoscopic hemostatic therapy in patients with high-risk stigma (e.g., clots in ulcer beds). No single endoscopic therapy was highlighted, although combination therapy with thermal coagulation and injection vielded the best results. No routine second-look endoscopy is required unless the patient presents with rebleeding; a surgical consult and testing for *Helicobacter pylori* are suggested for patients who fail endoscopy. Octreotide and somatostatin were not recommended for routine use in bleeding patients, nor were H<sub>2</sub> blockers. Instead, an intravenous bolus of a proton pump inhibitor (PPI) followed by continuous infusion was suggested to prevent rebleeding and to prepare patients for endoscopy.<sup>5</sup> These findings may override the results of the meta-analysis by Imperiale and Birgisson<sup>6</sup> that examined 14 papers and 1829 patients. This study suggested that somatostatin might reduce the risk for continued bleeding more effectively than octreotide, H<sub>2</sub> blockers, or placebo.

#### **Peptic Ulcers**

Initial treatment of bleeding peptic ulcers follows the same protocol as above. Once hemostasis has been achieved, a 2005 meta-analysis involving 1855 subjects<sup>7</sup> suggested using high-dose PPIs as a means of preventing rebleeding and mortality. A 2008 meta-analysis (2915 subjects)<sup>8</sup> confirmed the role of PPIs in preventing rebleeding and reducing the need for surgical intervention but suggests that this does not affect mortality. These findings have been substantiated in other studies. Gisbert and colleagues, in a 2003 meta-analysis involving 11 studies and 1352 subjects, found that pharmacologic

Table 69-1 Common Causes of GastrointestinalBleeds						
Source	Presentation	Common Causes				
Upper gastrointestinal	Hematemesis, melena, hematochezia (uncommon), hypotension	Peptic ulcer (duodenal or gastric), varices (esophageal or gastric), Mallory- Weiss tear, acute hemorrhagic gastritis				
Lower gastrointestinal	Hematochezia, melena	Diverticular disease, arteriovenous malformation, colitis, neoplasia, benign anorectal disease				

treatment may be effective even in patients who do not undergo endoscopic therapy.<sup>9</sup> A 2004 meta-analysis of 26 trials and 4670 patients by Khuroo and associates supported the use of PPIs as an adjuvant to endoscopic therapy in patients with high-risk stigma. However, Khuroo and associates suggested caution in administering PPIs to patients with multiple comorbidities, noting that their vascular and renal effects may have been the cause of a higher rate of nonulcer deaths in this intervention group, particularly in those receiving intravenous therapy.<sup>10</sup> These conclusions are supported by an earlier meta-analysis (including 1761 subjects) that further catalogued a series of high-risk indications for PPI use.<sup>11</sup> These include active bleeding, nonbleeding but visible vessel, and overlying clots categorized as high risk.

Table 69-2 Diagnosis and Treatment of GI Bleeds: Recent Meta-Analyses								
Study	No. of Trials	No. of Subjects	Intervention	Control	Outcome			
UPPER GASTROINTESTINAL BLEEDING								
Nonvariceal								
Barkun et al, 2003 <sup>5</sup>	71	9000						
Imperiale & Birgisson, 1997 <sup>6</sup>	14	1829	SST or octreotide treatment	H <sub>2</sub> -blocker or placebo	Somatostatin may reduce risk for continued bleeding.			
Cook et al, 1992 <sup>4</sup>	30		Endoscopic therapy	No endoscopic therapy	Therapy decreases rebleeding, surgery, and mortality in high-risk patients.			
Peptic Ulcers: Eso	phageal Va	arices						
Banares et al, 2003 <sup>16</sup>	8	939	Endoscopic plus drug therapy	Endoscopic therapy alone	Combined treatment reduced risk for bleeding but did not improve mortality.			
Corley et al, 2001 <sup>15</sup>	13	948	Octreotide	Other therapies	Octreotide is very effective, with fewer side effects than vasopressin.			
Grace et al, 1997 <sup>14</sup>	45		Multiple interventions	Standard sclerotherapy	Endoscopic ligation and β-blockers are most effective for treating bleeding esophageal varices.			
Laine et al, 1995 <sup>13</sup>	7	273	Endoscopic ligation	Sclerotherapy	Ligation is more likely to prevent rebleeding and mortality and also requires fewer treatments and fewer local complications.			
Prevention and Pro	ophylaxis							
Bernard et al, 2003 <sup>17</sup>	5	534	Antibiotic prophylaxis in cirrhotic patients with gastrointestinal bleeding	No prophylaxis	Prophylaxis increased mean percentage of patient free of infection and mean survival rate.			
SMALL BOWEL	EVALUAT	TION						
Horsthuis et al, 2008 <sup>22</sup>	33	1735	Multiple scanning modalities, including <sup>99m</sup> Tc-tagged red blood cells	Standard scanning modalities	Specificity of scintigraphy is less than that of ultrasound on a per-patient basis.			
Khanna et al, 2005 <sup>25</sup>	25		Embolization		Embolization is effective in treating bleeding due to diverticula, but not other lower gastrointestinal bleed sources.			
Green et al, 2005 <sup>21</sup>		100	Urgent colonoscopy	Standard treatment with expected colonoscopy	Intervention group is more likely to have an identifiable source of bleeding, more likely to receive endoscopic treatment.			

In 2004, Calvet and associates used 16 studies involving 1673 patients to analyze the question of whether a second endoscopic procedure after epinephrine injection improves outcome for high-risk bleeding peptic ulcers. The combined therapy did not appear to affect hemostasis but did reduce risk for rebleeding, particularly in patients with high-risk stigma.<sup>12</sup>

#### Treatment of Bleeding Esophageal Varices

Both endoscopic and pharmacologic therapies are recommended for treatment of acutely bleeding varices. Current teaching suggests that endoscopic ligation may provide more definitive treatment than sclerotherapy.<sup>13,14</sup> Ligation is more likely to prevent rebleeding (a 50% reduction seen with ligation relative to sclerotherapy) and mortality (number needed to treat to prevent 1 death = 10), as well as reducing the local complication rate.<sup>13</sup> A study by Grace and colleagues supports this conclusion, noting that one to three fewer treatments were required to treat varices with ligation compared with sclerotherapy.<sup>14</sup> Grace recommends endoscopic ligation and nonselective β-adrenergic blockers to treat and prevent bleeding, respectively, with shunting by transjugular intrahepatic portal shunt (TIPS) as needed to manage portal hypertension.14

Corley and coworkers' early study indicated that use of octreotide was superior to treatment with vasopressinterlipressin, with the former providing a significant improvement in achievement and maintenance of hemostasis.<sup>15</sup> Indeed, results with octreotide were comparable to immediate sclerotherapy. Octreotide use also was associated with fewer side effects and thus appeared to be a more appropriate pharmacologic treatment.

A combination of pharmacologic and endoscopic treatment may be the most effective means of controlling bleeding varices. The Banares group found a 33% increase in achievement of hemostasis over 5 days as well as a 2% reduction in 5-day mortality with the combination therapy.<sup>16</sup> Antibiotic prophylaxis also reduced infections and improved survival in this patient population.<sup>17</sup>

#### Small Bowel Evaluation

The small bowel is responsible for a relatively smaller proportion of upper and lower GI bleeds. Identification of a bleed source is particularly difficult in this region. In a 2005 meta-analysis of 14 studies,<sup>15</sup> capsule enteroscopy was found to be comparable to the gold standard practice (intraoperative endoscopy) in diagnostic value and was more accurate than either push enteroscopy or small bowel radiography. The procedure was notably effective for enhancing visualization of intravascular and inflammatory lesions.<sup>18</sup> In capsule enteroscopy, a camera within a capsule can be ingested and retrieved in order to take a video of the small intestines. Push enteroscopy is a study in which a push enteroscope with an overtube to prevent coiling can be advanced into the small bowel farther than usual (about 100 cm beyond the ligament of Treitz) to try to visualize the proximal small intestine. These findings were backed by a meta-analysis performed by Marmo and associates<sup>19</sup> (17 studies, 526 subjects), which indicated

that capsule enteroscopy is a more useful diagnostic tool than standard enteroscopy. Use of capsule enteroscopy was associated with a fourfold increase in the chance of a positive finding in patients presenting with obscure bleeds. However, these patients also faced a 16% likelihood of incomplete exploration owing to failure of the capsule to reach the cecum. Capsule enteroscopy also substantially (by 7 times) increased the chance of a positive finding in patients with Crohn disease (although the group did note concerns regarding entrapment of the capsule within strictures in this population). The procedure was found to yield the most accurate results in a prepared small bowel.<sup>19</sup> A more recent study<sup>20</sup> found capsule endoscopy to have higher yield than double balloon enteroscopy given a single insertion approach. Capsule endoscopy was also found to have a much higher rate of false positive results, possibly because of variations in study technique. A lack of study of double balloon enteroscopy visualization of more than the jejunum also limits the findings of this study; nonetheless, its results further highlight the role of capsule endoscopy in visualization of small intestine bleeds.<sup>20</sup>

#### Diagnosis and Treatment of Lower Gastrointestinal Bleeding

In a 2005 report of a randomized controlled trial involving 100 patients, Green and colleagues suggested that urgent colonoscopy may be more effective than delayed in identifying a source of lower GI bleeding. However, even urgent endoscopy use did not affect patient outcome or recurrence. These investigators cautioned against the idealization of endoscopic treatment for lower GI bleeding, noting that localization does not always result in conclusive treatment but that successful localization of a lower GI bleed might indeed enable more effective resection.<sup>21</sup>

Very few meta-analyses or randomized controlled trials have studied the value of <sup>99m</sup>Tc-tagged red blood cells and angiography in the diagnosis of acute GI bleeding. The one available meta-analysis, published in 2008 by Horsthius and colleagues, found that the specificity of scintigraphy was significantly lower than that of ultrasound.<sup>22</sup> Other modalities (ultrasound, magnetic resonance imaging, and computed tomography) were found to be roughly equal on a per-patient basis, although some variance was demonstrated at the segmental level. The study suggested that the recurrent nature of inflammatory bowel disease might argue against use of scintigraphy because patients are exposed regularly to ionizing radiation.<sup>22</sup>

More generally, a 2005 review article by Farrell and Friedman suggested that radionuclide imaging, although well tolerated by patients, is an inconsistent technique for identifying a source of localizing bleeding (24% to 91% accuracy reported).<sup>23</sup> The patient must be actively bleeding for scans to identify a source. Early scanning (<4 hours from onset of symptoms) is considered to be more effective than delayed. Radionuclide scanning does enhance the diagnostic potential of angiography by screening out patients who are not actively bleeding. According to Farrell and Friedman, scanning with <sup>99m</sup>Tc-tagged red blood cells should only be performed in hemodynamically stable patients, a factor that may also

limit its utility.<sup>23</sup> Similarly, in their review of multiple modalities of imaging GI bleeding, Singh and Alexander<sup>24</sup> found that <sup>99m</sup>Tc-labeled red blood cells have limited use in bleed localization, although they can be used for up to 24 hours and have a sensitivity of 0.1 to 0.4 cm<sup>3</sup> blood per minute. They suggest that the tagged scans may be useful in determining timing of angiography, that is, that angiography immediately following a positive acute phase bleeding scan (within 2 minutes of infusion of tagged cells) has a higher yield than angiography performed after a positive late scan (67% versus 7%). Thus, a bleeding scan may be useful in determining the utility of angiography but is not necessarily a useful modality on its own. Singh and Alexander also questioned the diagnostic value of angiography, noting that there must be substantial blood loss for sensitivity to equal that of a tagged red blood cell scan.<sup>24</sup> This highlights the importance of using scintigraphy as a means of identifying high-volume bleeds as those most amenable to angiographic visualization.<sup>24</sup>

With respect to treatment, the main controversies surround the use of endoscopy versus angiography. A 2005 meta-analysis by Khanna and coworkers<sup>25</sup> of 25 studies indicated that embolization should be used only in the treatment of acute bleeding caused by diverticular disease. Embolization was found to be 85% effective in this patient population. However, 40% of patients with nondiverticular disease experienced rebleeding. The group recommended a 2-day observation period following embolization treatment for diverticular disease.<sup>25</sup>

#### CONTROVERSIES

No single endoscopic method has been identified as superior in the treatment of upper GI bleeds. The question of appropriate treatment (e.g., epinephrine injection versus sclerotherapy versus ligation) has not been adequately answered by the research and remains a subject of debate. Concomitant use of pharmacologic agents appears to be helpful, but the ideal agent and dose have not been defined. Although ligation appears to be more effective and safer than sclerotherapy for esophageal varices, it has not been accepted as a definitive treatment, nor is it clear whether or which pharmacologic treatment (octreotide, somatostatin, vasopressin, or  $\beta$ -blockers) should be used as an adjuvant.

With respect to lower GI bleeding, controversies surround the use of capsule enteroscopy versus regular endoscopy for the diagnosis of small bowel bleeding. Additionally, the timing of colonoscopy and treatment of large bowel bleeds has not been clearly defined, nor has the role of colonoscopic versus angiographic treatment. More critical analysis of the treatment modalities is required.

#### GUIDELINES

The American Society for Gastrointestinal Endoscopy (ASGE) has published a detailed series of guidelines describing treatment for acute nonvariceal, variceal, and lower GI bleeds. The ASGE recommends endoscopic therapy for variceal and nonvariceal upper GI bleeding. Adjuvant treatment with PPIs or octreotide-somatostatin is recommended for nonvariceal bleeding only. Endoscopic therapy also is the approach of choice in patients with actively bleeding ulcers and in scenarios in which the artery is visible or in which patients are experiencing active blood loss.<sup>26</sup> Bleeding esophageal varices may be treated with endoscopic esophageal variceal ligation (EEVL), endoscopic sclerotherapy (EST), or injection of cyanoacrylate compounds, with EEVL at presentation and repeated treatment every 2 to 4 weeks until the varices are obliterated. At present, no treatment has been approved for gastric varices.<sup>27</sup>

The American College of Surgeons (ACS) Principles and *Practices* for management of upper GI bleeding are often in accordance with those of the ASGE. They recommend that bleeding ulcers initially be treated with endoscopic therapy and PPIs. If bleeding cannot be controlled, a duodenotomy or truncal vagotomy may be performed for duodenal ulcers. A wedge resection, antrectomy, or ligation of the left gastric artery is suggested for patients with refractory bleeding from gastric ulcers. Similarly, endoscopic banding or injection sclerotherapy is suggested as an initial means of controlling bleeding. However, the ACS recommends that patients demonstrating uncontrolled bleeding should be evaluated for liver transplantation. If the patient is an appropriate candidate, a TIPS should be placed while the patient awaits an organ. If the patient is not a transplant candidate, several procedures, including a distal splenorenal shunting procedure or esophageal transsection, may be performed if the patient is stable. Patients who are not stable should receive central portacaval shunting or esophageal transsection.<sup>2</sup>

The ACS *Principles and Practices* also comment on a variety of less common conditions, the treatment of which is detailed in Table 69-3.

Condition	Initial Treatment	If Bleeding Persists
Mallory-Weiss tear	Endoscopy if lesion does not stop bleeding without therapy	Anterior gastrostomy with suture ligation of tear
Acute hemorrhagic gastritis	Stop nonsteroidal anti-inflammatory drugs, give H <sub>2</sub> blockers, proton pump inhibitors, or antacids, <i>Helicobacter pylori</i> therapy	Intravenous somatostatin or intra-arterial vasopressin; if bleeding persists, total gastrectomy
Gastric neoplasm	Excise lesion; if malignant, attempt to control bleeding first	

#### Table 69-3 Treatment Recommendations for Uncommon Causes of GI Bleeding

For acute lower GI bleeding, the ASGE recommends nasogastric tube placement to identify or rule out the upper GI tract as the source. The presence of bile in the effluent is necessary to exclude the stomach and duodenum as the source. Colonoscopy after colonic preparation with polyethylene glycol solutions is recommended as the primary evaluative method. The use of upper endoscopy in addition to colonoscopy is suggested in patients with histories of NSAID use, peptic ulcers, or upper GI tract symptoms. Several endoscopic treatment modalities can be used to achieve hemostasis when a source of lower GI bleeding is identified by colonoscopy. Identification of a visible vessel or a pigmented protuberance within a diverticular segment is rare and may denote patients at high risk for persistent or recurrent bleeding. Thermal contact modalities, including heat probe and bipolar or multipolar coagulation, and epinephrine injection can be used independently or together to treat bleeding colonic diverticula. Superselective arterial embolization also is recommended. Patients with significant and untreatable bleeding should be sent to surgery for colonic resection pending localization of the source.<sup>25</sup>

The ACS *Principles and Practices* demonstrate considerable overlap with respect to initial evaluation and treatment, also recommending nasogastric tube aspiration followed by colonoscopy when the aspirate is clear or contains bile. If no bleeding source can be identified by colonoscopy, an esophagogastroduodenoscopy should be considered. If the degree of bleeding limits the value of colonoscopy, the ACS suggests performing selective mesenteric arteriography guided by radiolabeled red blood cell scanning. Lesions amenable to angiographic therapy may be treated subsequently with a vasopressin infusion. If a bleeding source can be identified by colonoscopy, endoscopic therapy should be attempted if possible. If endoscopy or angiographic therapy fails or cannot be attempted, surgical resection is required.<sup>30</sup>

The American Society of Colon and Rectal Surgeons (ASCRS) suggests that endoscopic treatment of lower GI bleeding is preferred when feasible. Surgery may be indicated in the 10% to 25% of patients who either require greater than 1500 mL of blood on initial resuscitation with ongoing bleeding or require 6 U or more of red blood cells, have ongoing bleeding for 72 hours, or rebleed within 1 week of initial cessation.<sup>31</sup>

#### **AUTHORS' RECOMMENDATIONS**

For all patients presenting with GI bleeding, we recommend the following course of action:

- Obtain appropriate intravenous access and resuscitate the patient.
- Identify the source of bleeding using nasogastric tube aspiration to rule out or in an upper GI source.
- In the case of an upper GI bleed, evaluate and identify a source using endoscopy. Attempt endoscopic treatment of esophageal varices and peptic and duodenal ulcers. If bleeding persists, surgery should be considered.
- In the case of a lower GI bleed, localize bleeding using colonoscopy or tagged red blood cell scan-guided angiography.

Endoscopic therapy should be attempted, particularly for diverticular disease and arteriovenous malformations. Surgical intervention is required for patients demonstrating excessive blood loss.

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## 70 Is Prophylaxis for Stress Ulceration Useful?

#### Ivan Hayes, Brian Marsh

For decades, acute life-threatening upper gastrointestinal bleeding from stress ulceration was considered a common and often unavoidable complication of critical illness. However, with the evolution of critical care, particularly in the 1980s,<sup>1</sup> the prevalence of gastrointestinal bleeding has fallen significantly.<sup>2–4</sup> Stress ulcer prophylaxis, a traditional cornerstone of intensive care, is now controversial.<sup>5</sup> The practicing clinician must balance the relatively low expense of this intervention with the significant patient morbidity, resulting in greater costs and length of intensive care unit (ICU) stay, associated with stress ulceration.<sup>1,6</sup> Undoubtedly, certain subsets of critically ill patients are at greater risk, and the identification and treatment of this group are likely to result in cost-effective therapy.

#### DEFINITIONS

- *Stress-related mucosal disease* (SRMD) is diffuse and superficial upper gastrointestinal mucosal damage in a critically ill patient.
- *Stress ulceration* is a discrete deeper lesion that penetrates into the submucosal layer.
- *Overt bleeding* is hematemesis, gross blood, or coffee grounds–like material in the nasogastric aspirate, hematochezia, or melena.
- *Clinically significant bleeding* (CSB) is overt bleeding complicated by hemodynamic changes or by the need for transfusion, defined as the presence of hypotension, tachycardia, or orthostasis or as a drop in hemoglobin of more than 2 g/dL.

#### PATHOPHYSIOLOGY

Under normal physiologic circumstances, defense mechanisms prevent the erosion of the upper gastrointestinal mucosal lining by the acidic intraluminal contents. A glycoprotein mucous layer lines the stomach and forms a physical barrier to hydrogen ion back-diffusion (Fig. 70-1A). Bicarbonate is trapped in this protective layer and neutralizes hydrogen ions before they reach the gastric epithelial layer. Adequate perfusion and oxygen delivery maintain intramural pH and prostaglandin synthesis, which is necessary for maintenance of the protective barrier layer. The pathophysiology of SRMD and stress ulceration is complex, and the exact mechanisms remain uncertain. Major factors necessary for ulceration are the following:

- Low gastric intraluminal pH
- Upper gastrointestinal tract intramural acidosis
- Increased permeability of the protective mucosal barrier

Gastric intraluminal acidity (pH < 4) is necessary for the generation of stress ulceration. Fasting and prolonged gastric transit times may contribute to a more acidic upper gastrointestinal tract. This increased duration and intensity of acid exposure may increase the likelihood of erosions and ulceration. Reflux of bile salts and enzymes from the duodenum and jejunum may exacerbate mucosal damage.<sup>7</sup>

Shock is common in critically ill patients, and septic shock is the most frequent cause of death in intensive care.8 Early in the systemic inflammatory response, splanchnic blood flow is reduced in order to preserve midline organs. The result is gastric intestinal mucosal hypoperfusion. This is exacerbated by absolute or relative hypovolemia and arterial hypotension. The intestinal tract possesses a lower capillary density and is unable to recruit capillaries to augment local blood flow to match increases in metabolic needs compared with other tissues. Early studies in septic animals demonstrated that intestinal O2 supply dependency occurs at a lower threshold than in other major organs<sup>9</sup> The combination of hypovolemia, redistribution of cardiac output, and intense splanchnic microvascular vasoconstriction results in low perfusion to oxygen demand ratios and subsequent tissue hypoxia. Hypoxia leads to uncoupling of oxidative phosphorylation. Energy is derived from anaerobic glycolysis and adenosine triphosphate (ATP) hydrolysis, resulting in regional lactic acidosis and a fall in the tissue pH.

Hypoperfusion initially causes an ischemic mucosal injury. Accumulation of oxygen free radicals contributes to tissue inflammation and cell death. A reduction in prostaglandin synthesis results in breakdown in the protective mucosal barrier; the epithelial layer is exposed to hydrochloric acid and pepsin, and erosions ensue (Fig. 70-1B).

Inducible nitric oxide synthetase elevates nitric oxide levels. This causes reperfusion hyperemia and cell death, an enhanced inflammatory response, and gastric and small bowel dysmotility. Animal experiments indicate that the subsequent mucosal reperfusion phase exacerbates the

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A Good blood flow and oxygen delivery

B Poor blood flow and oxygen delivery

**Figure 70-1.** Development of stress ulcers: gastric mucosa. **A**, Normal mucosal barrier function. **B**, In critical illness, normal cytoprotective mechanisms are lost, and hypoperfused mucosa is exposed to gastric acid.

initial injury. Gastric acid secretion is an active, energydemanding process. Agents such as H<sub>2</sub>-receptor antagonists and proton pump inhibitors (PPIs), by diminishing energydemanding gastric acid secretion, may protect against the development of stress ulcers related to hypoperfusion.

In the severely physiologically stressed critically ill patient, the combination of hypovolemia, activation of the sympathetic nervous system, global and regional hypoperfusion, endogenous and exogenous vasoactive agents, the release of proinflammatory cytokines, and activation of coagulation create a milieu that favors gastrointestinal ulceration and impairs protective and healing mechanisms.

#### EPIDEMIOLOGY

SRMD is almost universal in ICU patients.<sup>10,11</sup> When examined endoscopically, there is evidence of SRMD in 74% to 100% of patients within 24 hours of ICU admission.<sup>21</sup> However, clinically significant stress ulcerassociated bleeding (CSB) is much less common, occurring in about 1% to 4% of critically ill patients.<sup>10,12–15</sup> In a cohort of 2252 ICU patients, Cook and colleagues<sup>1</sup> found that 4.4% had an overt bleeding episode, and 1.5% had CSB. This was substantially reduced from reports in the decades before.<sup>2–4</sup> Mortality was greater in the patients who developed CSB than those who did not (48.5% versus 9.1%; P < .001). Of 847 patients with identified risk factors, 31 (3.7%) developed CSB. Of 1405 patients without these risk factors, 2 (0.1%) had CSB.<sup>1</sup> Retrospective analyses of trauma patients have found the incidence of stress-induced bleeding to range from 0.05% to 2.3%.<sup>16</sup> A point of prevalence survey of ICUs in Victoria, Australia, in 1997 found active stress-related upper gastrointestinal bleeding in 7 of 155 patients; when the same study was repeated in 2005, only 1 of 208 patients were reported to have active bleeding.<sup>15</sup> Improvements in critical care management such as early goal-directed therapy with rapid restoration of intravascular volume and organ perfusion pressure, use of lung protective ventilatory strategies with shorter duration of mechanical ventilation, institution of surviving sepsis campaign guidelines, and early enteral nutrition are widely believed to contribute to the reduced incidence of stress ulceration. However, the downward trajectory in prevalence preceded these developments

and probably represents a compilation of a wide variety of factors associated with critical care, hospital, and emergency medicine. Pharmacologic stress ulcer prophylaxis is now used extensively in ICU patients<sup>1,15,17</sup> and has been shown to independently reduce the incidence of stress-associated bleeding (odds ratio [OR], 0.39).<sup>14</sup>

#### **RISK FACTORS**

Not all critically ill patients are at equal risk for developing gastrointestinal hemorrhage. Increasing severity of illness is associated with a higher incidence of bleeding.<sup>18</sup> In the prospective multicenter cohort study of 2252 intensive care patients by Cook and associates,<sup>1</sup> two independent risk factors for CSB were identified: respiratory failure (requiring mechanical ventilation for more than 48 hours; OR, 15.6) and coagulopathy (platelets < 50,000; international normalized ratio [INR] > 1.5 or activated partial thromboplastin time [aPTT] > 2 times the control; OR, 4.3). There was a trend toward increased bleeding in patients with hypotension (OR, 3.7), sepsis (OR, 2.0), renal failure (OR, 1.6), and glucocorticoid use (OR, 1.5), but these did not reach statistically significant independent risk factors.<sup>1</sup> In a later study of 1077 critically ill mechanically ventilated patients, using a multivariable analysis, the same group<sup>14</sup> demonstrated that renal failure (OR, 1.16) was independently associated with CSB, whereas enteral nutrition (OR, 0.3) and prophylaxis with ranitidine (OR, 0.39) conferred significantly lower bleeding rates. Two factors that appear to be independently predictive of stress ulcer bleeding in trauma patients are severe injury, as defined by an Injury Severity Score greater than 16, and injuries to the central nervous system (brain and spinal cord).<sup>16</sup> In an observational study by Maury and coworkers,<sup>19</sup> *Helicobacter pylori* infection was found to be associated with a 20% absolute increase in risk in critically ill patients who developed upper gastrointestinal hemorrhage (36% versus 16%; P = .04) (Table 70-1).

#### MANAGEMENT

The prevention or limitation of SRMD and stress ulceration begins with restoration of splanchnic perfusion and prompt effective treatment of the underlying condition. Early

Table 70-1 Risk Factors for Stress Ulceration
Mechanical ventilation*
Coagulopathy*
Acute renal failure <sup>†</sup>
Major trauma (Injury Severity Score > 16)
Hypotension
Sepsis
Shock
Organ dysfunction
Liver failure
Cardiac arrest
Brain or spinal cord injury
Thermal injury (>35% total-body surface area)
High-dose glucocorticoids
Organ transplantation
Anticoagulation
After major surgery, with or without nasogastric tube
History of gastritis, peptic ulcer disease, gastrointestinal bleeding
*Independent risk factors. <sup>†</sup> Independent risk factor in mechanically ventilated patient

goal-directed therapy with fluid and catecholamine resuscitation has been shown to reduce mortality and multiorgan dysfunction in patients with severe sepsis and septic shock.<sup>20</sup> In shocked patients with splanchnic hypoperfusion, adequate volume loading is likely to be the most important initial intervention. The types of fluids, resuscitation end points, and monitoring techniques remain controversial. These issues are covered elsewhere in this book.

#### SPECIFIC STRESS ULCER PROPHYLAXIS

Specific pharmacologic antistress ulcer therapies can be broadly divided into four groups: antacids, cytoprotectants,  $H_2$ -receptor antagonists, and PPIs (Fig. 70-2).

Antacids act by directly neutralizing gastric acid and transiently increasing intraluminal pH. Frequent oral administration is required. Adverse effects include vomiting, constipation, metabolic alkalosis, and a range of electrolyte disturbances. Antacids are less efficacious than H<sub>2</sub>-receptor antagonists and PPIs in reducing gastric acidity and are currently not recommended as prophylaxis.

Sucralfate is the most extensively used and studied of the cytoprotectant agents. It is a sulfated polysaccharide complexed with aluminum hydroxide, which forms a protective gel layer on the gastric mucosa, reducing direct acid contact. Sucralfate is administered orally or by nasogastric tube. It is said to bind preferentially to damaged mucosa. It does not significantly alter intraluminal pH; this may confer benefit in terms of gastric bacterial colonization. Other proposed benefits of sucralfate include (1) stimulation of mucous and bicarbonate secretion, (2) stimulation of epidermal growth factor, and (3) improved mucosal blood flow and enhanced prostaglandin release. Adverse effects are reduced absorption of some medications (quinolones, theophylline, phenytoin, ranitidine, ketoconazole, digoxin), bezoar formation, clogging of nasogastric tubes, need for feeding breaks, and increased serum aluminum levels in patients receiving renal replacement therapy. Because sucralfate acts directly on the stomach, administration distal to the pylorus is ineffective. In addition, sucralfate should not be combined with other acid-reducing therapies.

H<sub>2</sub>-receptor antagonists are the most commonly used agents of stress ulcer prophylaxis in intensive care.<sup>1,15</sup> They act by reversible competitive inhibition of H<sub>2</sub>stimulated acid secretion. Enteral and parenteral formulations are available. These agents require frequent dosing, and there is some evidence to suggest that continuous infusions of the intravenous formulations may achieve better pH control than bolus administration.<sup>21,22</sup> Tolerance to H<sub>2</sub>-receptor antagonist acid inhibition develops within 72 hours of commencement.<sup>23,24</sup> Adverse effects include central nervous system disturbances, especially in elderly patients with intravenous administration. In rare instances, hematologic disorders such as thrombocytopenia have been associated with H<sub>2</sub>-receptor antagonists. Cimetidine and ranitidine cause inhibition of cytochrome P-450 metabolism that reduces the clearance of many drugs (e.g., warfarin and phenytoin). In a multicenter randomized, blinded, placebo-controlled trial in 1200 mechanically ventilated patients comparing sucralfate with ranitidine, CSB occurred in 1.7% of those receiving ranitidine compared





**Figure 70-2.** Gastric acid production and the impact of acid reduction therapy. ACh, acetylcholine; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; H<sub>2</sub>RA, H<sub>2</sub>-receptor antagonist; PPI, proton pump inhibitor.

with 3.8% of those receiving sucralfate (P = .02). There was no significant difference between the groups with regard to ventilator-associated pneumonia, the duration of stay in the ICU, or mortality.<sup>25</sup>

The use of PPIs is increasing in intensive care.<sup>15</sup> PPIs are substituted benzimidazoles that act by inhibiting the final step in acid production, H<sup>+</sup>-K<sup>+</sup> ATPase transport of H<sup>+</sup> ions. This inhibits both histamine-induced and vagally mediated acid secretion, making PPIs the most potent agents in reducing gastric acidity. PPIs irreversibly bind to the proton pump, and subsequent secretion of acid can only occur with the synthesis of new enzyme.<sup>26</sup> There are enteral and intravenous formulations available. Patients do not develop tolerance to the antacid effects of PPIs, but rebound acid hypersecretion is common after discontinuation. Adverse effects are generally mild (e.g., gastrointestinal upset or headache), but an association with *Clostridium difficile* diarrhea has been reported.<sup>27</sup> PPIs are metabolized by the cytochrome P-450 enzyme system, so there is potential for drug interaction. Omeprazole interferes with metabolism of cyclosporine, diazepam, phenytoin, and warfarin and increases the metabolism of several antipsychotic drugs and theophylline.<sup>28</sup> Pantoprazole undergoes dual-pathway metabolism in the liver to inactive metabolites through the cytochrome P-450 system and also sulfate conjugation. This results in fewer drug interactions that make pantoprazole particularly useful in critically ill patients, who typically are on numerous medications. PPIs provide the most reliable and sustained control of gastric acidity. A blinded randomized crossover trial compared ranitidine infusion and omeprazole infusion in 34 healthy volunteers.<sup>29</sup> On day 1, ranitidine raised gastric pH to about 5, but over the next 2 days, mean pH fell to less than 3. Omeprazole maintained the mean gastric pH greater than 6 for each of the 3 days.<sup>29</sup> A comparison of bolus administration of ranitidine to omeprazole had similar results.<sup>29</sup> These studies demonstrate that control of gastric pH by omeprazole, either as an intermittent or continuous infusion, is markedly superior to that provided by ranitidine.

In patients with bleeding peptic ulcers, who require a higher gastric pH to maintain clot stability, the results of two trials suggest that omeprazole infusion can maintain the intragastric pH higher than 6 for several days, whereas the initial effectiveness of the H2-receptor antagonists in keeping the pH above 6 is quickly lost, most likely as a result of tolerance.<sup>23,30</sup> A meta-analysis of 11 trials compared the efficacy of PPIs and H<sub>2</sub>-receptor antagonists in reducing the rate of rebleeding in patients with bleeding peptic ulcer disease. PPIs were found to be more effective in preventing persistent or recurrent bleeding, but there was no significant difference in the need for surgery or mortality rate.<sup>31</sup> Blood clot integrity is dependent on a pH higher than 6, which is only reliably achieved with PPIs. In a crossover trial in 10 patients taking omeprazole, 40-mg intravenous bolus was compared with an 80-mg bolus plus 8-mg-per-hour infusion with the outcome measure of mean intragastric pH. The two regimens were equivalent for the first 12 hours. When the time with intragastric pH above 6 during the first 24 hours was considered, the 80-mg bolus and 8-mg-per-hour infusion was superior.<sup>32</sup> An intragastric pH higher than 6 during most of the 24-hour period is a prerequisite for the control of bleeding in patients with active bleeding ulcers because platelet aggregation will not occur below a pH of 5.9 and is optimal at a pH of 7 to 8.<sup>33</sup>

When CSB occurs, the patient should be hemodynamically assessed and appropriate volume resuscitation instituted. Endoscopy is the procedure of choice for the diagnosis and treatment of active upper gastrointestinal bleeding and for the prevention of rebleeding.<sup>34</sup> A range of endoscopic techniques are in use. These include epinephrine injection, thermal coagulation, hemostatic clips, tissue glues, argon plasma coagulation, and combination therapies. In rare instances, surgical intervention may be required when pharmacologic and endoscopic intervention fails to achieve hemostasis.

#### RISK FOR NOSOCOMIAL PNEUMONIA WITH GASTRIC ACID SUPPRESSION

In the European Prevalence of Infection in Intensive Care (EPIC) study,<sup>35</sup> pneumonia (46.9%) and lower respiratory tract infection (17.8%) were found to be the most common ICU-acquired infections in Europe. Stress ulcer prophylaxis was one of seven risk factors identified for ICU-acquired infection.<sup>35</sup> Bacterial colonization of the aerodigestive tract and the aspiration of contaminated secretions into the lower airways are believed to contribute to the pathogenesis of ventilator-associated pneumonia (VAP).<sup>36,37</sup> Concerns have been raised that the administration of pH-altering drugs (antacids, H<sub>2</sub>-receptor antagonists, and PPIs) facilitates bacterial colonization of the stomach, particularly with gram-negative enteric organisms such as Enterobacteriaceae that cause pneumonia.<sup>25,38</sup> Continuous enteral nutrition may also raise gastric pH and facilitate bacterial colonization. A trial of acidified enteral feed (pH = 3.5)was found to maintain gastric acidity and reduce bacterial colonization in 120 critically ill patients.<sup>39</sup> These patients had a higher incidence of gastrointestinal bleeding, acidemia, and feed intolerance but had no reduction in the rate of pneumonia or mortality. Many studies have looked at the effects of acid reduction therapy on the incidence of VAP. The results are conflicting.

In a trial of 242 mechanically ventilated patients randomized to receive sucralfate, antacid, or ranitidine for stress ulcer prophylaxis, there was no statistically significant difference in nosocomial pneumonia.<sup>40</sup> A similar randomized controlled trial of 244 patients found that patients treated with sucralfate had a lower median gastric pH, less frequent gastric colonization, and a reduced incidence of late-onset nosocomial pneumonia.<sup>41</sup> A prospective randomized controlled trial compared the use of antacids, continuous intravenous cimetidine, or sucralfate in critically ill trauma patients to determine the role of gastric colonization in the development of pneumonia.<sup>4</sup> The authors concluded that the gastric biology of the three groups was nearly identical, and stress ulcer prophylactic agents that elevate gastric pH did not increase the incidence of pneumonia. A meta-analysis of eight randomized controlled trials published before 1990 found that stress ulcer prophylaxis with drugs that raise gastric pH did not increase the incidence of nosocomial pneumonia in comparison to placebo or control therapy. However, the use of sucralfate was associated with a lower incidence of nosocomial pneumonia (OR, 0.42) in comparison with agents that raised gastric pH.<sup>43</sup>

#### ENTERAL NUTRITION

Enteral feeding may reduce the incidence of overt GI bleeding due to stress ulceration,<sup>1,14,44,45</sup> but there are conflicting data.<sup>42</sup> Continuous infusion of commercially available enteral feeding solutions (pH of 6 to 7) are reported to neutralize gastric acid and raise the gastric intraluminal pH and may encourage the redistribution of blood flow to the mucosal layer. Tolerance of enteral nutrition is often poor in the critical care setting, and this may be one reason that clinical trials have been inconsistent with regard to cytoprotection.<sup>45,46</sup> As a result, enteral nutrition cannot be recommended as the sole method of prophylaxis against stress ulceration.

#### DISCONTINUATION OF PROPHYLAXIS

There are no published data on late CSB in the critical care population. Consequently, it is not possible to make recommendations regarding the timing of discontinuation of stress ulcer prophylaxis. Consideration should be made of the continued presence of risk factors, such as persistent mechanical ventilation, catabolism, and coagulation disorders. Given the low incidence of CSB in patients without specific risk factors and the cost implications, it seems reasonable to discontinue prophylaxis when the original indication has subsided.

#### **AUTHORS' RECOMMENDATIONS**

- Clinically significant stress ulcer–associated bleeding increases hospital costs and length of stay as well as patient morbidity and mortality.
- Early restoration of intravascular volume and organ perfusion may limit SRMD and progression to stress ulceration.
- Pharmacologic stress ulcer prophylaxis is not necessary in all ICU patients but is recommended in those with known risk factors for stress ulcer-associated bleeding.
- The choice of prophylaxis used should be based on whether the functional status of the gastrointestinal tract, the potential for drug interactions, local policy and resources.
- In patients with active upper gastrointestinal bleeding, PPIs are recommended because tolerance does not develop and there is superior control of gastric pH, which facilitates blood clot stability.
- When prophylaxis fails upper gastrointestinal endoscopy with endoscopic hemostasis is recommended.
- Enteral nutrition has multiple benefits in the critically ill patient and should be instituted early when possible, but there is insufficient evidence to support this as a lone anti-ulcer therapy.

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### 71 How Is Acute Liver Failure Managed (Including Hepatic Encephalopathy)?

Mark T. Keegan

Acute liver failure (ALF) is a catastrophic condition that results in multiple-organ failure. The severity of the illness and the rapidity of clinical deterioration in a previously healthy individual are alarming to patients, their families, and the health care team. Support of the patient with ALF requires the full armamentarium of therapies available in the modern intensive care unit (ICU) and may require orthotopic liver transplantation (OLT).

ALF is defined as the onset of hepatic encephalopathy (HE) and coagulopathy within 26 weeks of jaundice in a patient without pre existing liver disease. Terms that signify the duration of illness, such as *hyperacute* (<7 days), *acute* (7 to 21 days), and *subacute* (between 21 days and 26 weeks), have been used in the literature but are no longer recommended, nor are the terms *fulminant hepatic failure, fulminant hepatitis,* or *fulminant hepatic necrosis.* 

In 2005, the American Association for the study of Liver Diseases (AASLD) published a position paper detailing the management of ALF.<sup>1</sup> Recommendations of the U.S. Acute Liver Failure Study Group for the ICU management of such patients were published in 2007<sup>2</sup> (Table 71-1). Unfortunately, because of the rarity of the condition and the speed of progression, there is a paucity of randomized controlled trials evaluating therapies for ALF, and many therapies are empirical or based on expert opinion (Table 71-2).

#### EPIDEMIOLOGY

About 2000 cases of ALF occur per year in the United States.<sup>3</sup> The etiology of ALF differs depending on the geographic location. In the United States and Europe, medications are responsible for most cases. Acetaminophen is the principal culprit and accounted for 39% of the 308 cases of ALF seen at 17 referral centers in the United States between 1998 and 2001.<sup>4</sup> About three fourths of cases of ALF in this study were in women, and most patients were between 26 and 45 years of age. More recent estimates suggest that acetaminophen may account for up to 50% of cases of ALF.<sup>5</sup> In other parts of the world, viruses (especially hepatitis A, B, D, and E) are the principal causes. There are a number of other causes of ALF, as detailed in Table 71-3.<sup>6</sup>

#### **CLINICAL PRESENTATION**

Although initially a liver insult, ALF quickly becomes a multisystem disease. Loss of hepatocyte function (including host defense functions) and release of cellular debris and inflammatory mediators leads to a generalized inflammatory process. Stigmata of chronic liver disease are *absent*. HE and coagulopathy are the characteristic features of ALF, and both may progress rapidly over days or even hours. Diagnosis of ALF is made on clinical grounds, aided by laboratory analysis. Imaging studies (e.g., hepatic ultrasound to assess the patency of the liver's vascular supply) and liver biopsy may aid in the elucidation of the cause of ALF, but the latter is not usually performed.

#### INITIAL ASSESSMENT AND MANAGEMENT

Most patients are initially admitted to the hospital under the care of a general medical, gastroenterology, or liver service. When the diagnosis of ALF has been made, a referral center with a liver transplantation program should be contacted for advice on management and consideration for transfer. Some have suggested that waiting for the development of HE to diagnose ALF leads to crucial delays in treatment.<sup>7</sup> When HE develops in a patient with ALF, ICU care is usually warranted because of the potential for further deterioration and need for interventions such as intubation, mechanical ventilation, and hemodynamic support. A number of institutions have developed formal protocols for management of patients with ALF.<sup>8</sup> Although the utility of such protocols has not been studied in a controlled trial, they may help to ensure that all relevant aspects of the patient's care are addressed.

#### PROGNOSIS

In the U.S. Acute Liver Failure Study Group prospective cohort study, overall patient survival at 3 weeks was 67%, and short-term survival in transplanted patients was 84%.<sup>4</sup> Although these survival figures are much better than in the pretransplantation era, ALF remains a life-threatening disease entity. With supportive therapy,

Table 71-1 Important Summary Documents andGuidelines for the Management of AcuteLiver Failure

Study	Organization	Type of Document
Polson & Lee, 2005 <sup>1</sup>	American Association for the Study of Liver Diseases	Position paper on the management of acute liver failure
Stravitz et al, 2007 <sup>2</sup>	United States Acute Liver Failure Study Group	Recommendations for intensive care of patients with acute liver failure

some patients with ALF will spontaneously recover hepatic function, and 43% of patients in the Ostapowicz study survived without transplantation.<sup>4</sup> In many other cases, however, the patient will die without orthotopic liver transplantation (OLT). The main causes of death are cerebral edema with subsequent herniation and multiple-organ failure.

The timing of transplantation is crucial. Delay in listing for transplantation may result in the patient's demise before a donor organ is found or may result in perioperative mortality. Premature listing may result in OLT being performed in patients who might otherwise have recovered liver function spontaneously. Multiple prognostic scoring systems have been developed in an effort to identify patients at high risk for mortality.<sup>9</sup> The most commonly used criteria are those developed by O'Grady and colleagues in the United Kingdom; these are commonly known as the King's College criteria.<sup>10</sup> The King's College criteria were developed in a cohort of 588 patients with ALF who were managed medically between 1973 and 1985. The criteria differentiate between acetaminopheninduced ALF and ALF due to other etiologies. They use pH, international normalized ratio (INR), creatinine, grade of encephalopathy, age, duration of jaundice, and bilirubin level for prognostication. They have been subsequently validated.<sup>11</sup> Many other prognostic criteria have been proposed to identify patients at high risk for mortality. There

Table 71-2 Selected Randomized Studies in the Management of Acute Liver Failure							
Study	No. of Subjects (Intervention/No Intervention)	Study Design	Intervention	Control	Outcomes		
Canalese et al, 1982 <sup>50</sup>	44 patients with ALF (4 groups)	Prospective randomized controlled trial	Dexamethasone alone Mannitol alone Both dexamethasone and mannitol	Neither	Dexamethasone did not affect survival. Among patients who developed cerebral edema, survival was better in the mannitol group.		
Bhatia et al, 2004 <sup>56</sup>	42 patients with ALF (22 patients given prophylactic phenytoin, 22 controls)	Prospective randomized controlled trial	Prophylactic phenytoin administration	Usual therapy	Similar rates of cerebral edema, need for mechanical ventilation, incidence of seizures, mortality		
Gazzard et al, 1975 <sup>62</sup>	20 patients with acetaminophen- induced ALF (10 intervention, 10 controls)	Prospective randomized controlled trial	Fresh-frozen plasma, 300 mL every 6 hr	Usual therapy	No difference in morbidity or mortality between intervention and control groups		
Davenport et al, 1993 <sup>71</sup>	32 patients (12 intermittent renal replacement therapy, 20 continuous renal replacement therapy)	Prospective randomized controlled trial of patients with ALF and acute renal failure	Continuous renal replacement therapy	Intermittent renal replacement therapy	Patients in intermittent renal replacement therapy group had significantly lower cardiac indices and mean arterial pressure		
Demetriou et al, 2004 <sup>96</sup>	171 patients (85 bioartificial liver, 86 control)	Prospective randomized controlled multicenter trial in patients with severe ALF	HepatAssist bioartificial liver (patients were allowed to undergo liver transplantation)	Usual therapy (including potentially liver transplantation)	30-day survival 71% for BAL versus 62% for control (P = .26)		

ALF, acute liver failure; BAL, bronchoalveolar lavage.

#### Table 71-3 Etiologies of Acute Liver Failure

#### A. Viral

- Hepatitis A virus, hepatitis B virus ± hepatitis D virus, hepatitis E virus, herpes simplex virus, cytomegalovirus, Epstein-Barr virus, varicella-zoster virus, adenovirus, hemorrhagic fever viruses
- B. Drugs and toxins
  - Dose dependent: acetaminophen, carbon tetrachloride, yellow phosphorus, *Amanita phalloides, Bacillus cereus* toxin, sulfonamides, tetracycline, methyldioxymethamphetamine (Ecstasy), herbal remedies
  - Idiosyncratic: volatile anesthetics (especially halothane), isoniazid, rifampicin, valproic acid, nonsteroidal antiinflammatory drugs, disulfiram
- C. Vascular
  - Right heart failure, Budd-Chiari syndrome, veno-occlusive disease, shock liver (ischemic hepatitis), heat stroke
- D. Metabolic
  - Acute fatty liver of pregnancy, Wilson disease, Reye syndrome, galactosemia, hereditary fructose intolerance, tyrosinemia
- E. Miscellaneous
  - Malignant infiltration (liver metastases, lymphoma), autoimmune hepatitis, sepsis
- F. Indeterminate
  - Includes primary graft nonfunction in liver transplant recipients

are insufficient data to recommend a particular scheme because none has been found to discriminate well enough.<sup>2</sup>

The United Network for Organ Sharing (UNOS), the donor organ allocation body in the United States, has criteria that must be satisfied before a patient may be listed as a status I candidate for liver transplantation (the highest priority for organ allocation). These criteria include the onset of HE less than 8 weeks since the onset of jaundice, the absence of preexisting liver disease, ventilator dependence, dialysis dependence, or INR greater than 2. The criteria are not based on a controlled trial.

#### THERAPY FOR SPECIFIC CAUSES

The cause of the ALF should be sought because it will have implications for both therapy and prognosis.<sup>1</sup> Diagnosis of the cause of ALF requires a detailed history, multiple sero-logic and imaging tests, and potentially liver biopsy.

Based on a national multicenter study, *N*-acetylcysteine (NAC) has been shown to be effective in the treatment of acetaminophen toxicity and should be administered even if there is doubt regarding the timing or dose of ingestion or of the plasma concentration of acetaminophen.<sup>12</sup> Oral administration is satisfactory for patients with mild HE, but in patients with more severe disturbances, or if there is any concern regarding the reliability of oral intake, NAC should be administered intravenously. The duration of NAC administration is determined by clinical condition rather than by time or serum acetaminophen concentration. Dosing may need to be continued beyond 72 to 96

hours.<sup>2</sup> A prospective, multicenter study was recently performed by Larson and colleagues to further characterize acetaminophen toxicity.<sup>13</sup> Brok and colleagues from the Cochrane Collaborative summarized the evidence for therapy of acetaminophen overdose in 2002.<sup>14</sup>

Drug-induced hepatotoxicity (apart from that induced by acetaminophen) is usually idiosyncratic and typically occurs during the first 6 months of therapy. There are no specific antidotes, but the offending agent should be identified and stopped. Herbal and nutritional supplements also may cause acute liver injury, and information regarding such supplements should be sought from the patient and family.<sup>15</sup> If the cause of ALF remains indeterminate, even after liver biopsy, further investigation of potential drug or toxin exposure should be made.

Viral hepatitis has become a relatively infrequent cause of ALF in the United States but is more common elsewhere. Hepatitis A and B accounted for 8% and 12%, respectively, of cases of ALF in the U.S. multicenter study.<sup>4</sup> Acute hepatitis D may cause acute liver dysfunction in a patient with preexisting hepatitis B, and hepatitis E may cause ALF in endemic areas, especially in pregnancy.<sup>16</sup> Care of a patient with acute viral hepatitis is mainly supportive. Lamivudine has been reported to be of use for the treatment of ALF due to hepatitis B, although a clinical trial has not been performed.<sup>15</sup> Although ALF secondary to herpes simplex or varicellazoster virus infection is rare, treatment with acyclovir has been recommended for suspected or documented cases.<sup>17</sup>

ALF may develop as an acute presentation of autoimmune hepatitis.<sup>18</sup> Corticosteroids (prednisone starting at 40 to 60 mg per day) are administered in this scenario, although this practice is based on theory and case series. Transplantation may be required.

Acute fatty liver of pregnancy is a rare disease that may occur in the second half of pregnancy, most often in the third trimester. It resolves with delivery of the fetus. Liver transplantation has been performed for this condition but should not be necessary with early diagnosis and prompt delivery.<sup>19,20</sup>

Wilson disease is an uncommon cause of ALF but carries a grim prognosis without transplantation. Features of Wilson disease include low serum ceruloplasmin, high serum and urinary copper, hemolysis, Kayser-Fleischer rings (seen on slit-lamp examination), very low serum alkaline phosphatase and uric acid, and a bilirubin (mg/dL)-to-alkaline phosphatase (IU/L) ratio higher than 2.<sup>21</sup> Although penicillamine treatment may be used in Wilson disease, it is not recommended in the setting of ALF.<sup>21</sup> Rather, other measures to reduce serum copper and prevent further hemolysis (e.g., plasmapheresis) should be initiated while the patient is waiting for an emergent liver transplantation.

*Amanita phalloides* (mushroom) poisoning has been treated with penicillin G, NAC, and silibinin, although controlled trials have not been performed, and the latter is not available as a licensed drug in the United States.<sup>22</sup>

When ALF is due to an acute ischemic injury or severe congestive heart failure, treatment of the underlying cause is required, and the prognosis is related to response to therapy of the inciting insult.<sup>23</sup>

Modified from Saas DA, Shakil AO. Fulminant hepatic failure. *Liver Transplant*. 2005;11:594–605. Reprinted with permission of John Wiley & Sons, Inc.

Abdominal pain, prominent hepatomegaly, and ascites may indicate acute hepatic vein thrombosis (Budd-Chiari syndrome), which may present as ALF.<sup>24</sup> Liver transplantation is indicated based on high survival rates in case series, provided underlying malignancy is excluded.<sup>24</sup> Malignant infiltration of the liver sufficient to cause ALF is a contraindication to liver transplantation and indicates a very poor prognosis.<sup>25</sup>

#### HEPATIC ENCEPHALOPATHY

HE is one of the hallmarks of ALF. In contrast to patients with chronic liver disease, the development of HE in a patient with ALF often is associated with the development of cerebral edema and elevations in intracranial pressure (ICP). Cerebral edema is especially likely to develop in those patients with a short interval between jaundice and development of HE. Cerebral edema with subsequent herniation is the leading cause of death in patients with grade IV encephalopathy (see later) and may occur in up to 80% of these patients.

There are two main theories regarding the development of cerebral edema in ALF. It is likely that both play a role.<sup>26,27</sup> Glutamine is the end product of brain ammonia metabolism and may accumulate in astrocytes causing cerebral edema. In addition, failure of cerebral autoregulation that develops as a result of ALF leads to cerebral vasodilation with subsequent increase in cerebral blood flow and cerebral edema.<sup>28</sup> The increase in ICP leads to a decrease in cerebral perfusion pressure (CPP) and the development of cerebral ischemia. In accordance with the Monro-Kellie doctrine, cerebral edema in the fixed confines of the skull will ultimately lead to herniation and death. Hyponatremia, cytokine production, and the development of seizures each may contribute to the development of cerebral ischemia.

HE develops rapidly in patients with ALF. Alterations in mental status are initially subtle but may progress to coma. There are four grades of HE (Table 71-4), and the grade of encephalopathy correlates with the development of cerebral edema and with outcome. Cerebral edema is uncommon in grade I or II but occurs in 25% to 35% and 65% to 75% in patients with grades III and IV encephalopathy, respectively. The prognosis worsens when grade IV encephalopathy is complicated by cerebral edema and is further worsened if renal failure is present. Further, the development of infection alters the progression of HE.<sup>29</sup> Although ammonia levels correlate poorly with the severity of HE, an arterial ammonia greater than  $200 \ \mu g/dL$ , within 24 hours of the development of grade III or IV, HE is predictive of herniation.<sup>30</sup>

#### Treatment of Hepatic Encephalopathy and Elevated Intracranial Pressure

#### Grade I and II Hepatic Encephalopathy

The management of patients with HE depends on the grade. Based on the experience at the institution, patients with grade I HE may be managed on a general ward, with skilled nursing in a quiet environment, but in most institutions, such patients should be managed in an ICU. If, and when, grade II HE develops, ICU care is indicated. A computed tomography (CT) scan of the head should be performed to exclude causes of mental status change other than HE (e.g., intracranial hemorrhage, space-occupying lesion), although transport to the CT scanner may be dangerous, especially if the patient's airway is not protected. Although CT scans may demonstrate cerebral edema in patients with advanced HE, intracranial hypertension may not be detected.<sup>31</sup>

Administration of sedatives to patients with grade I or II HE should be avoided if possible because they will confound the detection of signs that might indicate progression to the next stage of encephalopathy. Nonetheless, small doses of short-acting antipsychotics (e.g., haloperidol or benzodiazepines) may be required to control agitation.

Based on a belief that ammonia plays a role in the pathogenesis of cerebral edema in patients with ALF, lactulose has been administered to patients with HE. In a study by Alba, it was associated with a small increase in survival time but no difference in the severity of encephalopathy or overall outcome. Thus, lactulose cannot be recommended at this time.<sup>32</sup> Nonabsorbable antibiotics (rifaximin, neomycin) also are not proved to be of use in ALF, and neomycin carries a risk for nephrotoxicity.<sup>33</sup>

Table 71-4 Grades of Hepatic Encephalopathy						
Grade	Mental Status	Tremor	Electroencephalogram			
I	Euphoria; occasionally depression; fluctuant mild confusion: slowness of mentation and affect; untidy; slurred speech; disorder in sleep rhythm	Slight	Usually normal			
II	Accentuation of grade I; drowsiness; inappropriate behavior; able to maintain sphincter control	Present (easily elicited)	Abnormal; generalized slowing			
III	Sleeps most of the time but arousable; incoherent speech; marked confusion	Usually present if patient can cooperate	Always abnormal			
IV	Not arousable; may or may not respond to painful stimuli	Usually absent	Always abnormal			

Modified from Sass DA, Shakil AO. Fulminant hepatic failure. Gastroenterol Clin N Am. 2003;32:1195–1211.

#### Grade III and IV Hepatic Encephalopathy

A patient who progresses to grade III HE requires endotracheal intubation for airway protection. The choice of sedative or induction agents to be administered before intubation is left to the discretion of the practitioner because there are no studies to demonstrate the advantage of one regimen over another in this circumstance. It is intuitive that a drug regimen that minimizes the risk for increasing ICP should be used. Therefore, propofol is a reasonable choice in this situation.

#### Intracranial Pressure Monitoring

The use of ICP monitoring devices in ALF is subject to ongoing debate.<sup>1,34,35</sup> Proponents of ICP monitoring argue that such monitoring will allow rational use of the therapies detailed later. Others suggest that the risks of monitoring outweigh its value. Vaquero and colleagues reviewed the experience with ICP monitoring at 24 centers in the U.S. ALF Study group.<sup>36</sup> ICP monitoring was used in 28% of 332 patients with ALF and the use of monitoring differed among centers and with the etiology of ALF. In a subset of 58 of these patients, 10% were noted to have developed intracranial hemorrhage, although half were incidental radiologic findings. The 30-day survival after liver transplantation was similar in both monitored and unmonitored groups, although patients without ICP monitoring were treated less aggressively. Although studies also have shown that ICP monitoring devices provide useful information, such observational data have not demonstrated that survival of patients with grade III or IV HE is improved by ICP monitoring.<sup>8</sup> The performance of a randomized clinical trial to answer the question of whether ICP monitoring should be used would require a relatively large number of patients and has not been performed thus far. Current recommendations are that "ICP monitor placement should be considered for all patients listed for OLT in stage III/IV HE."2

The risks for ICP monitoring include bleeding and infection. The former is especially worrisome in these coagulopathic patients. The ICP monitoring device of choice traditionally has been an epidural catheter. These have relatively low associated risks for intracranial hemorrhage but may be less accurate than other devices.<sup>37</sup> Subdural or intraparenchymal monitors provide improved reliability at the cost of increased bleeding risk. Coagulopathy needs to be treated before placement of an ICP monitor and newer agents for the treatment of coagulopathy (see later) may alter the threshold for placement of such devices. Definitive recommendations for INR or platelet count are not available.

There are insufficient data to recommend the use of transcranial Doppler (TCD) or jugular venous bulb oximetry in patients with ALF. Abdo and associates assessed cerebral blood flow by TCD in five patients with ALF and compared the patterns to a control group. A cerebral hypoperfusion pattern was found in the ALF group.<sup>38</sup> The clinical utility of TCD in patients with ALF is, as yet, undocumented. Similarly, jugular bulb oximetry has not been demonstrated to be of use in patients with ALF.<sup>39</sup>

#### Maintenance of Cerebral Perfusion Pressure

CPP is mean arterial pressure (MAP) minus ICP. The management goal for patients with cerebral edema is to limit ICP *and* to maintain CPP. Targets for CPP are subjects of debate, but a goal ICP of less than 25 mm Hg and a CPP of greater than 60 mm Hg seem reasonable. An ICP greater than 40 mm Hg and a prolonged period of time with a CPP less than 50 mm Hg are strongly associated with poor neurologic recovery in patients with ALF, although the data are not sufficient to contraindicate OLT.<sup>40–42</sup> It may be necessary to augment MAP to attain and maintain a satisfactory CPP (see "Hemodynamic Support," later). Systemic hypertension may be treated with conventional agents such as labetalol or hydralazine. Continuous infusions of nicardipine offer some theoretical advantage over the traditionally used sodium nitroprusside.<sup>43</sup>

#### Control of Elevations of Intracranial Pressure in Patients with Grade III or IV Hepatic Encephalopathy

**General Measures.** Patients with elevated ICP (defined as an ICP > 20 to 25 mm Hg for more than 1 minute or a CPP < 50 mm Hg) should be managed in a quiet environment. Head elevation to 20 to 30 degrees and avoidance of obstruction to venous return (e.g., head rotation, tight endotracheal tube ties) are recommended. Endotracheal tube suctioning should be kept to a minimum and consideration given to administration of a bolus of a sedative agent such as propofol or lidocaine before suctioning.<sup>44</sup> Hypoxemia and hypercapnia increase ICP, and every effort should be made to avoid these.

**Sedation and Analgesia.** Patients with grade III or IV HE should be sedated as one measure to control ICP. Because of its rapid onset and offset (even in patients with liver disease), propofol seems an excellent choice for sedation to control ICP in patients with ALF.<sup>45</sup> Wijdicks and Nyberg reported the use of propofol in seven patients with ALF who had ICP monitors in situ.<sup>46</sup> At a median dose of 50  $\mu$ g/kg per minute, propofol alone appeared to control ICP, although the study was observational, and there were a number of confounders. Patients with ALF may be at a higher than usual risk for the development of propofol infusion syndrome, although this is unproved.<sup>47</sup>

The induction of a "barbiturate coma" by administration of pentobarbital or sodium thiopental has been used to treat refractory intracranial hypertension in ALF, although studies are uncontrolled. Forbes and colleagues administered thiopental to patients with ALF, refractory intracranial hypertension, and poor prognosis and demonstrated reductions in ICP.<sup>48</sup> Side effects are numerous and include hemodynamic compromise and apnea.

Patients receiving infusions of propofol or barbiturates may require pressor support to maintain optimal hemodynamics.

Opiate infusions typically are used to treat discomfort and suppress airway reflexes in intubated patients. Fentanyl may be a better choice than morphine or meperidine because the last two are longer acting and have active metabolites that may accumulate in hepatic or renal dysfunction.<sup>49</sup>

Mannitol. Mannitol is the only therapy proven in a controlled trial to reduce intracranial hypertension and improve survival in patients with ALF. Canalese and colleagues randomized 44 patients with ALF to receive mannitol (1 g/kg as required), dexamethasone (32 mg intravenously, then 8 mg intravenously every 6 hours), both drugs, or neither drug for the treatment of elevated ICP.<sup>50</sup> Dexamethasone did not affect survival, but among patients who developed cerebral edema, those who received mannitol had significantly better survival than those who did not. The dose of mannitol has not been definitively established, and boluses of between 0.25 and 1 g/kg have been used, although doses on the lower end of this range are associated with fewer adverse effects. Limitations to the use of mannitol include the development of acute renal failure or hyperosmolality (serum osmolality > 320 mOsm/L).

**Hypertonic Saline.** Murphy and colleagues performed a randomized trial of the use of 30% (hypertonic) saline to maintain serum sodium concentrations between 145 and 155 mEq/L in patients with ALF and encephalopa-thy.<sup>51</sup> They demonstrated that induction and maintenance of hypernatremia can reduce the incidence and severity of intracranial hypertension. A survival benefit was not demonstrated, and the role of prophylactic hypertonic saline remains unproved. Theoretically, and based on literature in the neurosurgical population, hypotonic solutions and hyponatremia should be avoided because of the risk for worsening cerebral edema.<sup>52</sup>

**Treatment of Fever.** Fever exacerbates intracranial hypertension in patients with ALF, and measures to maintain normothermia, including cooling blankets and fans, should be used in the febrile patient (see later for a discussion of therapeutic hypothermia). Nonsteroidal antiinflammatory drugs and acetaminophen are relatively contraindicated because of the potential for nephrotoxicity and further hepatotoxicity, although their use has not been studied extensively in this population.

**Hyperventilation.** Hyperventilation to a Paco<sub>2</sub> of less than 30 mm Hg causes cerebral vasoconstriction and rapidly reduces ICP in patients with cerebral edema.<sup>53</sup> Prophylactic hyperventilation, however, did not reduce the incidence of cerebral edema in a randomized controlled trial of 20 patients with ALF.<sup>54</sup> Further, marked hypocapnia (to a Paco<sub>2</sub>  $\leq$  25 mm Hg) or sustained hypocapnia may cause cerebral ischemia. Accordingly, the use of therapeutic hyperventilation is reserved for situations in which life-threatening cerebral edema is present and has proved refractory to other measures. Use of hyperventilation in this circumstance should be temporary—for, at most, a few hours.<sup>1</sup> Maintenance of a Paco<sub>2</sub> between 30 and 40 mm Hg is a reasonable goal.<sup>2</sup>

**Seizure Prophylaxis.** The development of seizures will markedly increase cerebral oxygen requirements, will increase ICP, and may cause or worsen cerebral edema. The AASLD position paper recommends that phenytoin be given for control of seizures, although supporting data are scarce.<sup>1,2</sup> Benzodiazepines also may be administered—

for both their anti-seizure and sedative properties—but their metabolism and clearance are greatly decreased in liver failure. Subclinical seizure activity was noted in 30% of patients with ALF studied by Ellis and colleagues in a clinical trial.<sup>55</sup> Prophylactic intravenous phenytoin was shown to reduce the incidence of seizures in this group of 42 patients, but the beneficial effects of phenytoin could not be documented in a confirmatory study.<sup>56</sup> The use of *prophylactic* phenytoin is not supported by current evidence. Electroencephalography should be performed in grade III or IV HE if myoclonus is present, if a sudden unexplained deterioration in neurologic status occurs, or when barbiturate coma is being used for management of cerebral edema.<sup>2,56</sup>

**Indomethacin.** Tofteng and Larsen administered bolus doses of indomethacin to a series of 12 patients with ALF and cerebral edema and demonstrated a reduction in ICP and an increase in CPP. Further data are awaited.<sup>57</sup>

**Other.** Neither nonabsorbable disaccharides, benzodiazepine receptor antagonists, nor dopaminergic agonists have proved beneficial for the treatment of HE, according to systematic reviews of the literature.<sup>58–60</sup>

#### COAGULOPATHY

As is the case with cerebral edema, the development of a coagulopathy is a hallmark of ALF. Coagulopathy results from multiple causes. These include platelet dysfunction (both quantitative and qualitative), hypofibrinogenemia, and inadequate coagulation factor synthesis.<sup>61</sup> In the absence of bleeding, correction of coagulopathy by administration of fresh-frozen plasma (FFP) is not required and may confound assessment of progression of the disease.<sup>1</sup> More than 30 years ago, Gazzard and colleagues showed that FFP administration did not reduce morbidity or mortality in ALF.<sup>62</sup> When invasive procedures are planned, however, or when the patient is bleeding, it is appropriate to treat coagulopathy. Many clinicians would advocate treatment of extreme coagulopathy (e.g., INR > 7), even if invasive procedures are not planned.

Vitamin K (10 mg intravenously) is typically given to patients with ALF because some have subclinical vitamin K deficiency at the time of presentation. There is some debate regarding the threshold for administration of platelet, although in the absence of bleeding or plans for invasive procedures, a value of greater than 10 to  $20 \times 10^9$ /L seems acceptable.<sup>63</sup> If invasive procedures are planned a platelet count of at least  $50 \times 10^9$ /L should be attained.<sup>6</sup> Cryoprecipitate should be administered when the fibrinogen level is less than 100 mg/dL. The thromboelastogram (TEG) is commonly used to aid in the management of coagulopathy in patients with liver disease, especially in patients undergoing liver transplantation. However, TEG use has not been studied in a randomized controlled trial.

Recombinant factor VIIa ( $40 \mu g/kg$ ) was demonstrated to be of use to transiently correct the coagulopathy of ALF and allow performance of invasive procedures in a nonrandomized trial of 15 patients who met King's College criteria for liver transplantation.<sup>64</sup> Thrombosis is a potential side effect. In patients with persistent coagulopathy despite FFP administration and in those who have contraindications to recombinant VIIa, therapeutic plasmapheresis may be beneficial.<sup>65</sup>

#### INFECTION

As documented by Rolando and colleagues in a study of 50 consecutive patients, individuals with ALF are at risk for both bacterial and fungal infection.<sup>66,67</sup> Grampositive cocci, enteric gram-negative bacilli, and Candida species are the most commonly isolated organisms. Disseminated infection may be a contraindication to transplantation. Although the use of prophylactic antimicrobial therapy may reduce the incidence of infection in certain patients with ALF, a survival benefit has not been demonstrated. Recent evidence suggests that the presence of infection or the systemic inflammatory response syndrome influences the progression of encephalopathy in ALF, but currently there is no evidence to show that administration of antimicrobials alters this relationship.<sup>29,68</sup> Surveillance for symptoms and signs of infection should be part of the management of a patient with ALF, although this recommendation is empirical.<sup>1</sup> Initiation of antibiotics is recommended when surveillance cultures reveal significant isolates, in grade III or IV HE, in the presence of refractory hypotension, and when the systemic inflammatory response syndrome is present.<sup>2</sup> Broad-spectrum antibacterial agents typically are used, and vancomycin added when intravascular catheter-related bloodstream infection or methicillinresistant Staphylococcus aureus (MRSA) infection is suspected. Low-dose amphotericin is a part of ALF protocols at some institutions.

Rolando and associates studied 108 patients with ALF in a prospective randomized fashion to compare the incidence of infection in patients given intravenous antimicrobials with and without enteral antimicrobials.<sup>69</sup> The addition of enteral antimicrobials did not decrease the incidence of infection.

#### **RENAL FAILURE**

The development of acute renal failure frequently complicates ALF, is associated with increased mortality, and may be caused by a variety of mechanisms. These include hypovolemia and hypoperfusion, nephrotoxins, or hepatorenal syndrome.<sup>70</sup> Even when hemodynamics are optimized, nephrotoxins avoided, and infection promptly treated, patients may require dialysis. Davenport and coworkers performed a prospective randomized controlled trial in patients with combined acute liver and renal failure to compare the effect of various modes of dialysis on hemodynamics.<sup>71</sup> Continuous modes of dialysis were associated with less hemodynamic compromise. Further, continuous renal replacement therapy (CRRT) is less likely to provoke an elevation in ICP or pulmonary pressures than is intermittent dialysis.<sup>72</sup> CRRT may be continued in the operating room during liver transplantation.<sup>73</sup>

#### **HEMODYNAMIC SUPPORT**

Distributive shock often develops in patients with ALF and may lead to multiple-organ failure. Hypovolemia occurs secondary to decreased oral intake and transudation of fluid into the extravascular space. A pulmonary artery catheter may be used to guide hemodynamic therapy. Despite adequate fluid resuscitation, a low systemic vascular resistance may result in persistent hypotension. Hemodynamic derangements may compromise cerebral, renal, and hepatic perfusion, with subsequent worsening of organ dysfunction. The optimal choice of pressor is unknown because, despite some limited studies, there are no definitive trials to identify the best vasoactive agent. The recommended goal MAP is 65 mm Hg, although this is not supported by data. When ICP is elevated, the MAP goal may need to be altered upward to maintain a CPP between 50 and 80 mm Hg.<sup>2</sup> Norepinephrine, dopamine, and epinephrine are reasonable choices to achieve hemodynamic goals. Vasopressin may be added, but its use is controversial, and a small study of terlipressin in ALF (six patients with ALF and HE) at a dose that did not alter systemic hemodynamics demonstrated worsening of cerebral hyperemia and intracranial hypertension.<sup>7</sup>

Adrenal insufficiency may be present in patients with liver failure, and administration of corticosteroids should be considered when refractory hypotension is present. Although there are some data to support this practice, most are from patients with chronic rather than acute liver failure, and significant controversy exists regarding steroid supplementation in critically ill patients.<sup>75</sup>

#### MECHANICAL VENTILATION

Patients with ALF need airway protection when grade III encephalopathy develops and will need mechanical ventilation if respiratory failure or severe metabolic acidosis develops. It is unclear whether prophylactic use of low tidal volume in patients with ALF will delay or avoid the development of acute respiratory distress syndrome. When setting positive end-expiratory pressure, a compromise will need to be reached between the desire to avoid hepatic congestion and a desire to optimize oxygenation.<sup>76</sup>

#### GASTROINTESTINAL BLEEDING

There is a significant risk for gastrointestinal bleeding in individuals with ALF, although this risk is presumably less than in patients with cirrhosis, portal hypertension, and esophageal or gastric varices. In two controlled trials, involving 75 patients, H<sub>2</sub>-blockers, but not antacids, were associated with a decreased incidence of bleeding in patients with ALF. Accordingly, H<sub>2</sub>-blockers or, by extension, proton pump inhibitors should be administered to patients with ALF.<sup>77</sup>

#### METABOLIC CONCERNS

Metabolic derangements, often severe, occur in ALF, and frequent monitoring of acid-base status and metabolic parameters is required. Both alkalosis and acidosis may occur, and the latter may be especially refractory when ALF is accompanied by acute renal failure. Infusions of sodium bicarbonate or a nonsodium buffer, such as THAM, or initiation of CRRT with a bicarbonate-rich infusate is often required. Impaired hepatic gluconeogenesis in ALF patients makes the use of tight glycemic control potentially problematic. Hyperglycemia may worsen cerebral edema in patients with ALF, but hypoglycemia must be avoided.<sup>78</sup> Hypoglycemia may be profound and occult because of encephalopathy or sedation. Boluses of 50% dextrose solutions and continuous dextrose infusions may be required to maintain normoglycemia. Phosphate and magnesium may be low and require repeated supplementation.

#### NUTRITION

Patients with ALF manifest a catabolic state and increased energy expenditure.<sup>79</sup> Nutritional support is recommended, although studies on which to base therapy are limited. Enteral feeding should be initiated early in the course of ALF, usually by nasogastric or nasojejunal tube. Severe protein restriction should be avoided. The AASLD position paper recommends 60 g of protein per day, although in larger patients or those who are in a catabolic state, increased loads may be more appropriate.<sup>1</sup> A Cochrane Database review of the use of branched-chain amino acids in ALF and HE did not find convincing evidence of a beneficial effect, although the trials performed in this field were mostly of poor methodologic quality.<sup>80</sup> Parenteral nutrition should be used if enteral nutrition is contraindicated or not tolerated. Both enteral and parenteral nutrition reduce the incidence of stress ulceration. Lipid emulsions appear to be safe in patients with ALF.<sup>81</sup>

#### TRANSPLANTATION

Although ALF may resolve with only supportive interventions, especially in patients with acetaminophen-induced ALF, OLT is the only definitive therapy for the condition. The therapy has not been evaluated in a prospective clinical trial for patients with ALF, but there is little doubt as to its effectiveness. ALF is the only condition designated as UNOS status I (highest priority for donor liver allocation). Overall survival for patients with ALF has increased from 15% in the pretransplantation era to 60% or more in the posttransplantation era.<sup>4</sup> In the U.S. Acute Liver Failure Study Group series, 29% of patients underwent OLT, and 25% of patients listed for transplantation died on the waiting list.<sup>4</sup> In the Nordic countries experience, 73% of 315 patients listed received a transplant, and 16% died without transplant.<sup>82</sup> Although ABO-identical liver grafts are preferred, ABO-compatible grafts have similar outcomes, based on a European experience.<sup>83</sup> ABO-incompatible grafts have much lower survival rates.

#### MANAGEMENT DURING AND AFTER LIVER TRANSPLANTATION

Although there are insufficient data to recommend any specific management of patients with ALF during OLT, guidelines based on expert opinion have been published.<sup>2</sup> If an ICP monitor has been placed before OLT, it should be continuously monitored intraoperatively because ICP may increase, especially at the time of reperfusion. Intraoperative management should follow the MAP, ICP, and CPP goals used preoperatively. Whether to perform the technique of venovenous bypass is a matter of surgeon preference because no definitive data on its role in minimizing swings in CPP exist.

#### **AREAS OF CONTROVERSY**

#### Therapeutic Hypothermia

In recent years, reports of the use of therapeutic hypothermia in patients with ALF have demonstrated promise. However, therapeutic hypothermia in ALF has not been subjected to a randomized controlled trial. Jalan and colleagues studied seven patients who fulfilled criteria for poor-prognosis liver failure and had increased ICP unresponsive to other therapies.<sup>84</sup> After cooling to 32° to 33°C, ICP and cerebral blood flow were reduced, and four of the seven patients survived to liver transplantation. Subsequent studies again demonstrated the potential of moderate therapeutic hypothermia as a "bridge to transplantation" and during the transplantation procedure, perhaps because of restoration of cerebral autoregulation.<sup>85–87</sup> Potential adverse effects of hypothermia include infections, coagulopathy, and arrhythmias.

#### *N*-Acetylcysteine for Non–Acetaminophen-Induced Acute Liver Failure

Sklar reviewed the literature pertaining to the use of NAC in patients with non–acetaminophen-induced ALF.<sup>88</sup> There are not sufficient data available at present to recommend use of the agent for this purpose. The NAC study, a U.S. multicenter study, is investigating this potential therapy.

#### Hepatectomy and Auxiliary Transplantation

Some investigators have proposed that liver-derived proinflammatory cytokines may be important in producing intracranial hypertension in ALF.<sup>89</sup> The use of hepatectomy has been advocated in patients with ALF, refractory circulatory dysfunction, and intracranial hypertension, assuming that OLT will be performed thereafter. Data to support such a practice, however, are sparse and consist of case reports and uncontrolled case series. Hepatectomy cannot be recommended at this time. Auxiliary liver transplantation is a technique in which a partial liver graft is placed either heterotopically or orthotopically while leaving part of the native liver in situ. A European multicenter study demonstrated the feasibility and potential utility of this technique.<sup>90</sup> Recently, Lodge and colleagues have performed emergency subtotal hepatectomy and auxiliary OLT for acetaminophen-induced ALF with encouraging

early results in a nonrandomized case series.<sup>91</sup> However, at this time, no clear indications for auxiliary liver transplantation exist, and a randomized clinical trial has not taken place.

#### Living Donor Liver Transplantation for Acute Liver Failure

The advent of living donor liver transplantation adds a further option to the management of ALF. Kilic and colleagues reported their experience of living donor liver transplantation in 14 cases of ALF and demonstrated a 3-year graft and patient survival of 79%.<sup>92</sup> However, the ethical difficulties already associated with this procedure in patients with cirrhosis are greatly increased in the scenario of ALF, when the acuity of the situation has the potential to lead to rushed or incompletely informed decision making.<sup>93</sup>

#### Liver Support Systems

The holy grail for the treatment of ALF is a liver support device to replace the detoxification, metabolic, and synthetic functions of the liver. Such a system could be used as a bridge to liver transplantation or, preferably, complete recovery of the patient's native liver.94 Trials for the assessment of liver support devices are complicated by the fact that many patients are diverted to liver transplantation before the response to therapy with the device can be established. Further, ALF is a catchall phrase for a heterogeneous group of disorders with different etiologies and rates of progression. There have been a number of approaches to the development of an "artificial liver." The first systems removed toxins through hemodialysis, hemofiltration, or hemoperfusion. Newer systems combine hemodialysis with adsorption to albumin or charcoal. Living hepatocytes (porcine or derived form human hepatocellular cancer cells) are the basis of "bioartificial liver" devices. Kjaergard and colleagues performed a systematic review of artificial and bioartificial liver support devices for the treatment of acute and acute-on-chronic liver failure.<sup>95</sup> They identified 12 randomized trials with 483 patients. Overall, support systems had no significant effect on mortality compared with standard therapy. Stratified meta-analyses suggested that, although there may have been some beneficial effect in the treatment of patients with acute-on-chronic liver failure, the devices tested were of no utility in patients with ALF.

Since this report was published, Demetriou and colleagues published the results of a randomized clinical trial evaluating a porcine bioartificial liver in 171 patients with ALF.<sup>96</sup> Overall, survival was no different between the intervention (71% survival) and control (62%) groups. The survival gap widened when the 27 patients who had primary graft nonfunction were excluded, but did not reach statistical significance.

Studies reporting the experience with the molecular adsorbents recirculation system (MARS), a system based on albumin, have also been published since the Kjaergard meta-analysis. Uncontrolled case series suggest a survival benefit as a bridge to transplantation or as a means to improve HE. Schmidt and colleagues performed a small controlled trial that demonstrated improvements in hemo-dynamic parameters with MARS therapy.<sup>97</sup>

Plasmapheresis has been demonstrated to improve MAP in ALF with a concomitant increase in systemic vascular resistance.<sup>98</sup> A controlled trial is ongoing in Europe.

#### CONCLUSION

ALF is a complex multisystem illness that develops after a catastrophic hepatic insult. It is characterized by coagulopathy and HE accompanied by cerebral edema and elevated ICP. The etiology is dependent on geographic location, with drugs and toxins causing more than half of cases in developed countries. Care of the patient requires a multidisciplinary approach and the full armamentarium of ICU support. The rarity of the condition and the rapidity of its development mean that there is a paucity of randomized clinical trials evaluating therapies for ALF. The U.S. Acute Liver Failure Study Group has published a consensus document with recommendations for specific aspects of ICU care of these patients. Although some patients will recover spontaneously, for patients with poor prognosis, liver transplantation is the only definitive treatment. Survival rates after liver transplantation are about 75% to 90%. The efficacy of artificial liver support devices in ALF remains unproven.

#### AUTHOR'S RECOMMENDATIONS

- Diagnosis of ALF should prompt discussion with a referral center for consideration of transfer and potential liver transplantation
- The U.S. Acute Liver Failure Study Group has published recommendations for the ICU management of patients with ALF.
- The etiology of the ALF should be determined because specific therapies exist for certain conditions. Acetaminophen overdose is a common cause of ALF and should be treated with NAC. The utility of NAC in non-acetaminophen-induced ALF is under investigation.
- Assessment of prognosis is important, and the King's College criteria are often used, although they are not absolutely predictive.
- Patients with grade III HE should be intubated for airway protection.
- Although monitoring of ICP has not been demonstrated to improve mortality in patients with ALF, the practice is common. An ICP of less than 25 mm Hg and a CPP of more than 60 mm Hg should be targeted.
- Treatment for elevations of ICP includes general supportive measures, sedation, and osmotherapy with mannitol or hypertonic saline. Therapeutic hypothermia and hyperventilation are controversial.
- Coagulopathy should be treated only if invasive procedures are planned, if the patient is actively bleeding, or if the coagulopathy is extreme.
- Metabolic derangements should be treated aggressively, and nutrition should be initiated.
- Transplantation is the only definitive treatment for ALF, and provided there are no contraindications, the patient should receive a highest priority listing for liver transplantation.
- The performance of hepatectomy and auxiliary transplantation and the use of liver support devices remain unproven.

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### 72 Should Blood Glucose Be Tightly Controlled in the Intensive Care Unit?

Jean-Charles Preiser

Before 2001, the hyperglycemia found in most critically ill patients was considered a component of the stress response. Current understanding was completely changed by the publication of the first Leuven study article in 2001.<sup>1</sup> This investigation compared an intensive insulin regimen targeting a blood glucose level within the 80 to 110 mg/dL range with a "conventional" management cohort in which blood glucose was treated only when above 200 mg/dL. Van den Berghe and colleagues, the authors of the study, demonstrated a 4% decrease in the absolute mortality of critically ill patients randomized to intensive insulin therapy. These unexpectedly impressive results triggered a huge wave of enthusiasm. Recommendations to implement tight glucose control in intensive care units (ICUs) were rapidly issued by several health care agencies (Joint Commission on Accreditation of Healthcare Organization, the Institute for Healthcare Improvement, and the Volunteer Hospital Organization). Simultaneously, several different teams tried to reproduce the results and to examine the underlying mechanisms of the findings of the Leuven team. Overall, the results of the Leuven study have not been reproduced. Nonetheless, these follow-up studies have given rise to several controversies and raised important but as yet unanswered questions for the physicians taking care of critically ill patients, including, What is the optimal value of blood glucose? What are the risks associated with hypoglycemia? and What categories of patient might benefit from tight glucose control by intensive insulin therapy?

#### PATHOPHYSIOLOGY AND MECHANISM OF ACTION

It has long been recognized that critically ill patients tend to be hyperglycemic. For many years, this was attributed to stress and was believed to be a part of the host response to critical illness. Thus, hyperglycemia was believed to be a biomarker of the severity of illness. The Leuven studies started with the hypothesis that hyperglycemia was not just a biomarker. Rather, these investigators postulated that elevations in serum glucose contributed to the pathophysiology of critical illness. This proposal spawned the current field of investigation. The initial question might be reframed as, What is the optimal blood glucose concentration in the critically ill patient? Further exploration and investigation of this question are warranted.

The physiology behind "stress hyperglycemia" is complex. The elaboration of glucose, primarily by the liver, is known to be an essential component of the host's response. This reflects the energy demand that results from injury, ischemia, or other deleterious processes. White blood cells, the main effectors of the inflammatory response, are more or less obligate glucose users. Because the blood supply to injured tissue often has been interrupted or diminished, delivery is primarily through mass action across the intracellular matrix. Increases in concentration facilitate this movement. Gluconeogenesis, the process whereby the liver synthesizes glucose, is driven primarily by the direct action of glucagon and epinephrine on hepatocytes. This is enhanced by cortisol and perhaps by inflammatory cytokines. In addition, these hormones and the cytokines to some degree limit the peripheral response to insulin. This latter effect has been termed insulin resistance, although there are no data in nonseptic patients or animals to indicate that the direct responses of the insulin signaling pathway are impaired. At some point, the process becomes maladaptive in the critically ill patient. This is especially true in sepsis and multiple-organ dysfunction. Thus, the question asked above must be expanded to examine the time course of stress hyperglycemia as well as the actual glucose concentration.

In experimental conditions, concentrations of glucose higher than 300 mg/dL clearly are deleterious.<sup>2</sup> However, new insights into the cellular mechanisms of glucose toxicity suggest a link among glucose, cytopathic hypoxia, and the production of reactive oxygen and nitrogen species.<sup>3,4</sup> These concentrations, unfortunately, are clinically irrelevant, and only clinical data can be used to define the optimal value for tight glucose control. Indeed, the ultimate proof that hyperglycemia is an independent risk factor for poor outcome in critically ill patients is lacking.<sup>5</sup> Importantly, insulin exerts effects other than the promotion of glucose metabolism and utilization. These include vasodilatory, anti-inflammatory, and antiapoptotic activities that can be viewed as a homeostatic control mechanism limiting some of the processes that occur in inflammation and other potentially injurious responses. Such a role for insulin might explain some of the beneficial but unexpected effects of intensive insulin therapy.

#### PRESENTATION OF AVAILABLE DATA BASED ON SYSTEMATIC REVIEW

It has been difficult to replicate the results of the Leuven study.<sup>1</sup> This leaves several practical questions unanswered. First, it is unclear just what constitutes "normoglycemia" in critical illness.<sup>6</sup> Retrospective data and the two Leuven studies<sup>1,7</sup> clearly indicate that a blood glucose higher than 180 mg/dL cannot be considered acceptable. However, the optimal target for blood glucose concentration is still unknown. Interestingly, several retrospective trials<sup>8,9</sup> found that patients in whom blood glucose was below 150 mg/dL had a better outcome than those with higher levels.

To solve the issues of the external validity of the Leuven study and the optimal blood glucose target, large single-center and multicenter prospective trials of tight glucose control by intensive insulin therapy comparing two ranges of blood glucose were launched. The designs of these trials (Table 72-1) were similar. All aimed to compare the effects of insulin therapy titrated to restore and maintain blood glucose between 80 and 110 mg/dL. Where they differed was in the target range of blood glucose for the control (nonintensive insulin therapy) group. The Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR)<sup>10</sup> and GluControl trials<sup>11</sup> used a target value of 140 to 180 mg/dL, whereas both the Leuven studies,<sup>1,7</sup> the VISEP study,<sup>12</sup> and two other single-center large-scale trials<sup>13,14</sup> used a target value of 180 to 200 mg/dL.

The results of these trials are summarized in the Table 72-1. Basically, there was no significant difference in the vital outcomes between the two groups, with the notable exceptions of the Leuven I study<sup>1</sup> and the NICE-SUGAR study, in opposite directions. Not surprisingly, tight glucose control by intensive insulin therapy is associated with a fourfold to sixfold increase in the incidence of hypoglycemia. This represents the major concern when starting intensive insulin therapy and is the major cause of an increased workload.<sup>15</sup> In the VISEP and GluControl studies, the rate of hypoglycemia and the mortality in the patients who experienced at least one such episode (defined as blood glucose < 40 mg/dL) were higher than in patients who did not experience hypoglycemia.<sup>11,12</sup> In contrast, in both Leuven studies,<sup>1,7</sup> hypoglycemic patients had no detectable differences in outcome compared with patients who had no hypoglycemic episodes. This does not exclude the possibility that long-lasting hypoglycemia, with consequent decreases in glucose availability for tissues that are glucose dependent, may be deleterious or even life-threatening. Clearly, an accurate understanding of the consequences of hypoglycemia in critically ill patients requires further investigation.

Systematic reviews and meta-analyses including data on glucose control recorded in the ICU and in other patients are also available. The design and main results of the three meta-analyses<sup>16–18</sup> are summarized in Table 72-2. These analyses yielded different results, including the overall effects on mortality. The meta-analyses by Pittas and colleagues<sup>16</sup> and Gandhi and associates<sup>17</sup> revealed decreased short-term mortality (respective relative risks [95% confidence interval] of 0.85 [0.75 to 0.97] and 0.69 [0.51 to 0.94]). In contrast, the study by Wiener and coworkers<sup>18</sup> showed no significant effect on mortality (relative risk of hospital mortality, 0.93 [0.85 to 1.03]).

Study	No. of Subjects (Intervention/ No Intervention)	Study Design	Intervention (Blood Glucose Target)	Control (Blood Glucose Target)	Primary Outcome Variable
SINGLE CENTER TRIAL	S				
van den Berghe et al (Leuven I), 2001 <sup>1</sup>	765/783	Single-blind	80-110 mg/dL	180-200 mg/dL	ICU mortality
van den Berghe et al (Leuven II), 2006 <sup>7</sup>	595/605	Single-blind	80-110 mg/dL	180-200 mg/dL	ICU mortality
Arabi, 2008 <sup>14</sup>	266/257	Single-blind	80-110 mg/dL	180-200 mg/dL	ICU mortality
De La Rosa, 2008 <sup>13</sup>	254/250	Single-blind	80-110 mg/dL	180-200 mg/dL	28-day mortality
MULTICENTER TRIALS					
Brunkhorst et al, 2008 (VISEP) <sup>12</sup>	247/289	Single-blind	80-110 mg/dL	180-200 mg/dL	28-day mortality and SOFA
Finfer et al, 2009 (NICE-SUGAR) <sup>10</sup>	3054/3050	Single-blind	80-110 mg/dL	140-180 mg/dL	90-day mortality
Preiser et al, 2009 (GluControl) <sup>11</sup>	542/536	Single-blind	80-110 mg/dL	140-180 mg/dL	ICU mortality

Table 72-1 Summary of the Prospective Large-Scale Randomized Controlled Trials of Tight Glucose Control by Intensive Insulin Therapy

ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment.

Table 72-2 Summary of Meta-Analyses on Insulin Therapy							
Study	No. of Trials Included/ Retrieved	No. of Subjects (Intervention/No Intervention)	Intervention	Control	Outcomes		
Pittas et al, 2004 <sup>16</sup>	35/941	Not indicated: total, 8432	Insulin therapy	No insulin	Short-term or hospital mortality		
Gandhi et al, 2008 <sup>17</sup>	34/445	2192/2163	Intravenous perioperative insulin	Higher blood glucose target	Mortality and 11 outcome variables		
Wiener et al, 2008 <sup>18</sup>	29/1358	4127/4188	Tight glucose control	Usual care	Short-term mortality, septicemia, new need for dialysis, hypoglycemia		

#### **INTERPRETATION OF DATA**

The results of the different large-scale individual trials can be summarized as follows: in critically ill patients staying in an ICU, tight glucose control by intensive insulin therapy improved survival in one proof-of-concept study only (Leuven I<sup>1</sup>). There are multiple potential explanations for the discrepant results between this and other studies. These include differences in the study population and in the treatment protocol, especially with regard to the amount of intravenous glucose, which was higher in Leuven I than in the other settings. Another possible factor that could explain differences in the outcome data is the quality of glucose control. Unfortunately, at the present time, there is no agreement on the best index to assess and compare the quality of glucose control.<sup>19</sup> Finally, the statistical power of each of these individual studies is probably too low. The rate of hypoglycemia in virtually all studies is increased fivefold.<sup>18</sup> Most hypoglycemic episodes are classified as a nonserious adverse event. However, this interpretation may be questioned following the recent publication of data from a retrospective cohort of 102 patients with at least one episode of severe hypoglycemia (<40 mg/dL) matched with 306 control patients from a cohort of 5365 patients.<sup>20</sup> In this study, hypoglycemia was found to be an independent risk predictor of mortality, possibly related to neuroglycopenia.

In contrast to studies that included patients who were not critically ill,<sup>16,17</sup> the meta-analysis that focused on critically ill patients<sup>18</sup> did not demonstrate an advantage of tight glucose control. The meta-analysis of Pittas and colleagues<sup>16</sup> included patients with stroke, acute myocardial infarction, and diabetes. The results of the large trials of the effects of glucose-insulin-potassium (GIK) after acute myocardial infarction in patients with diabetes, a different intervention than tight glucose control, were included and substantially influenced the overall results. Incidentally, most large trials of GIK during myocardial ischemia were conducted before the 1990s and involved populations with diabetes and acute myocardial infarction. The positive results of some of these studies in all probability reflect the metabolic effects of insulin. This includes the ability to promote the use of glucose as a primary myocardial energy substrate. In myocytes, the delivery of insulin increases glycolytic substrate and ultimately adenosine triphosphate (ATP) synthesis. This attenuated ischemia-induced decreases in ATP. However, these effects are unrelated to glucose control because blood glucose in the GIK studies actually was not corrected. The meta-analysis by Gandhi and associates<sup>17</sup> focused on perioperative glucose control. Most of the included studies involved coronary artery bypass surgery and patients who were not critically ill. The authors of this meta-analysis acknowledged that the available mortality data represent only 40% of the optimal information size required to reliably detect a treatment effect. Further, methodologic and reporting biases may weaken inferences.<sup>17</sup>

In the third meta-analysis,<sup>18</sup> only studies performed in ICUs and aiming to reach a predefined blood glucose level were included. This analysis, however, included studies of various sizes that targeted different blood glucose levels. When evaluating the data from the largest individual prospective studies that used a 80 to 110 mg/dL blood glucose target in the intensive treatment arm,<sup>1,7,10,13,14</sup> the Leuven I study still appears as the outlier (see Table 72-1). The aggregation of individual data from participants in each of these prospective studies could solve the remaining questions.<sup>21</sup>

#### CONCLUSION

- Intensive insulin therapy titrated to restore and maintain blood glucose between 80 and 110 mg/dL was found to improve survival of critically ill patients in one pioneering proof-of-concept study performed in a surgical ICU.<sup>1</sup> This result was not confirmed in any of the subsequent trials.<sup>7,10-14</sup> The underlying reasons for this discrepancy are under investigation.
- Studies using intensive insulin therapy reveal a high rate of hypoglycemia that may alter outcome.<sup>22</sup>
- The effects of severe hyperglycemia (>180 mg/dL) are well documented.
- The choice of intermediate target appears logical to minimize the risks for hypoglycemia.
- A blood glucose target below 150 mg/dL is presently recommended by the Surviving Sepsis Campaign.<sup>23</sup>

#### **AUTHORS' RECOMMENDATIONS**

- Severe hyperglycemia is harmful.
- Intensive insulin therapy titrated to achieved a blood glucose level between 80 and 110 mg/dL was found to improve survival in one study.
- Intensive insulin therapy is labor intensive and increases the risk for hypoglycemia.
- Particularities of the case mix, usual care, and quality of glucose control in the unit where intensive insulin therapy was found beneficial compared with other ICUs might explain the differences in the effects of intensive insulin therapy.

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## Can Acute Adrenal Insufficiency Be Diagnosed in the Intensive Care Unit? If So, How Should It Be Managed?

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Physiologic and pathophysiologic perturbations initiate a well-coordinated response to maintain homeostasis.<sup>1</sup> Adaption is in part characterized by alterations in cardio-vascular function, metabolic activity, and inflammation.<sup>2</sup> This response involves activation and secretion of hormones from the adrenal cortex. However, during the course of the intense and potentially prolonged response that accompanies critical illness, acute adrenal insufficiency (AI) may develop.<sup>3</sup> This deficit may increase the mortality of critically ill or injured patients.<sup>4</sup>

#### NORMAL PHYSIOLOGY OF HYPOTHALAMIC-PITUITARY-ADRENAL AXIS FUNCTION

In healthy subjects, cortisol secretion by the adrenal gland is tightly controlled by the hypothalamic-pituitary-adrenal (HPA) axis. Corticotropin-releasing hormone (CRH) produced in the hypothalamus in response to a variety of signals (cold, fever, infection, trauma, emotional distress, burns, inflammatory agents, pain, hypotension, exercise, hemorrhage) is transferred through the hypothalamicpituitary portal system to the anterior pituitary gland. The CRH acts on specialized cells that produce and release adrenocorticotropic hormone (ACTH). ACTH, in turn, stimulates adrenal cortical cells to produce steroid hormones, including cortisol. Negative feedback, which reduces the secretion of both CRH and ACTH, is exerted by secreted cortisol at the level of both the hypothalamus and the pituitary. This ensures a tightly regulated system.<sup>5</sup>

Cortisol normally is secreted in a diurnal pattern, with a maximal circulatory level early in the morning, followed by a steady decrease throughout the day. The serum cortisol response to ACTH stimulation also is circadian. Therefore, afternoon responsiveness is greater owing to the decreased cortisol level. In addition, cortisol secretion is pulsatile and not continuous. These factors become important when interpreting random cortisol levels.<sup>6</sup> Under normal conditions, the adrenal glands release 20 to 30 mg of cortisol each day. When under physiologic stress, a normal adrenal gland can secrete about 10 to 12 times that amount.  $^{\rm 5}$ 

Ninety-five percent of the cortisol circulating in the blood is carried by cortisol-binding globulin (CBG; transcortin), albumin, or both. Five percent is unbound and thus physiologically active. It is this free cortisol that is regulated to maintain homeostasis.<sup>5</sup> Cleavage of CBG by elastase secreted from activated neutrophils results in a 10-fold decrease in its affinity for cortisol. This has been proposed as a mechanism for cortisol delivery and release to sites of inflammation.<sup>7</sup> Free cortisol levels are significantly affected by changes in CBG and albumin and affect measured cortisol levels.<sup>8</sup>

#### MOLECULAR ACTIONS OF GLUCOCORTICOIDS

Glucocorticoids regulate gene transcription in every cell of the body. These effects are summarized in Table 73-1.<sup>9-17</sup>

#### ALTERATIONS IN HYPOTHALAMIC-PITUITARY-ADRENAL AXIS FUNCTIONING DURING CRITICAL ILLNESS

The classic regulators of the axis continue to be operable in critically ill patients but with significant alterations.

#### Cytokines and the HPA Axis

Sepsis mediators alter the HPA axis. During inflammatory processes, cytokines such as interleukin-1 $\alpha$  (IL-1 $\alpha$ ), IL-1 $\beta$ , IL-6, and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) can activate the HPA axis at the level of the hypothalamus, pituitary, and adrenal cortex.<sup>18–23</sup> This increases levels of CRH, ACTH, and glucocorticoids.<sup>24–26</sup> These concentrations also may reflect impaired glucocorticoid clearance, especially in patients with impaired hepatocellular function, decreased hepatic blood flow, and depressed renal or thyroid function.<sup>27</sup> In addition, cytokines alter glucocorticoid receptor
System	Acute	Long-Term
Host defense	Protection from the potentially harmful inflammatory mediators <sup>9</sup>	Anti-inflammatory and immunosuppressive effects, influencing lymphocytes, NK cells, monocytes, macrophages, eosinophils, neutrophils, basophils, and macrophages. <sup>9</sup> Decrease the accumulation and function of these cells at inflammatory sites, stabilize lysosomal membranes, decrease release of inflammatory mediators, impair antigen processing and antibody formation by B lymphocytes. <sup>10</sup> Poor tissue repair and wound healing, immunosuppression and vulnerability to infection
Metabolism	Mobilization of energy stores: increase glycogen stores, increase blood glucose, decrease peripheral glucose uptake and metabolism, increase lipolysis, increase protein catabolism	Insulin-resistant "steroid" diabetes mellitus
	Increase hepatic gluconeogenesis, inhibit adipose tissue glucose uptake, stimulate free fatty acid release from adipose tissue and amino acid release from body proteins, in order to facilitate substrate and energy supply to the cells during stress <sup>11</sup>	Centripetal obesity, moon face Protein depletion in muscle, connective and other tissues
Musculoskeletal	Protein catabolism: alter calcium homeostasis, lower serum calcium levels by inhibition of calcium absorption from the gut, decrease renal calcium reabsorption and promotion of the shift of calcium from extracellular to intracellular compartment <sup>9</sup>	Impaired growth, muscle wasting, loss of connecting tissue, osteoporosis, and disturbed calcium homeostasis
Central nervous system	Improved cognitive function	Mood changes (depression and psychotic episodes), neurodegeneration <sup>9</sup>
Cardiovascular	Salt and water retention: inhibition of the production of vasoactive inflammatory mediators Required for normal reactivity to angiotensin II, epinephrine, and norepinephrine contributing to the maintenance of cardiac contractility, vascular tone, and blood pressure as well as for synthesis of NA <sup>+</sup> -K <sup>+</sup> ATPase, <sup>12</sup> catecholamines, and catecholamine receptors <sup>13,14</sup> Decrease the production of nitric oxide <sup>15-17</sup>	Hypertension and other cardiovascular disease
Reproductive	Inhibition of hypothalamic-pituitary-gonadal function	Menstrual irregularities, male and female infertility
Gastrointestinal tract	Reduced bicarbonate and mucus production Inhibit gastric and intestinal motility <sup>9</sup>	Increased susceptibility to ulcers
Renal	Bind to mineralocorticoid receptors and increase sodium reabsorption and excretion of potassium and hydrogen ions, while increasing free water excretion by inhibition of antidiuretic hormone release <sup>9</sup>	

#### Table 73-1 Effects of Cortisol on Organ System Function

(GR) number and activity.<sup>28,29</sup> Cytokines also, however, suppress the HPA axis and GR function.<sup>18–20,28,29</sup> Indeed, several studies have reported inappropriately low ACTH levels in patients with the systemic inflammatory response (SIRS) and severe sepsis.<sup>30,31</sup>

#### **Cortisol Response to Critical Illness**

Critical illness activates the HPA axis through different mechanisms. Pain, fever, hypovolemia, hypotension, and tissue damage all may increase corticotropin and cortisol secretion with a loss of normal diurnal variation in these hormones.<sup>32</sup> However, the activity of the HPA axis during critical illness is biphasic. In the initial, acute phase of illness, the HPA axis is activated primarily by an increase in CRH secretion and cytokine production. Therefore, plasma ACTH and cortisol are elevated. Teleologically, this response should provide energy and protect the body by increasing gluconeogenesis, maintaining intravascular volume, and inhibiting acute inflammation.<sup>32</sup>

During prolonged critical illnesses, the response differs, highlighting a wide range of cortisol levels among patients with sepsis.<sup>33</sup> Plasma ACTH concentrations decrease despite persistent hypercortisolism. This suggests that

cortisol secretion is regulated through alternative pathways.<sup>34</sup> The persistence of hypercortisolism may contribute to long-term complications, including hyperglycemia, myopathy, poor wound healing, and psychiatric alterations.<sup>35</sup> However, prolonged critical illness also may present with low cortisol levels.<sup>33</sup>

#### DEFINITION AND INCIDENCE OF RELATIVE ADRENAL INSUFFICIENCY

#### Definition

Several studies have shown that patients with sepsis and normal or high baseline cortisol levels develop a syndrome of relative AI. This is typified by a depressed cortisol response to the ACTH stimulation test.<sup>36</sup> This sepsis-associated AI is associated with increased mortality.<sup>36</sup> It has been proposed that an unstimulated cortisol level of less than 15 µg/dL (414 nmol/L) represents relative AI.<sup>37–40</sup> Some investigators believe that the rapid corticotropin stimulation test is useful in evaluating adrenocortical function in these cases.<sup>35</sup> Postcorticotropin cortisol concentrations should be greater than 20 µg/dL (550 nmol/L) or increase more than 9 µg/dL (248 nmol/L).<sup>35,41</sup> The absence of an increase of at least 9 µg/dL is hypothesized to define relative AI. Importantly, however, these data are not experimentally verifiable, and thus the appropriate cortisol concentration and increase to ACTH stimulation in sepsis and septic shock are not known.

#### Incidence

Primary AI is rare, with an incidence of less than 0.015 in the general population.<sup>42</sup> The reported incidence of AI in intensive care unit (ICU) settings varies. In the most recent study, 46.7% of patients did not have an appropriate response to corticotropin.<sup>43</sup>

#### CAUSES OF ACUTE ADRENAL INSUFFICIENCY IN THE CRITICALLY ILL

Several factors have been associated with AI in critically ill patients (Table 73-2). An inflammatory state such as sepsis is accompanied by both primary and secondary AI.<sup>44</sup> This may result from circulating cytokines.<sup>45</sup> It is important to recognize these patients because of the high mortality of this disorder if untreated.<sup>22</sup> As many as 30% of patients with septic shock<sup>44</sup> and up to 25% of critically ill patients with human immunodeficiency virus (HIV)<sup>46</sup> may acquire AI that is associated with resistance to ACTH. Both human and animal studies have shown that sepsis is associated with either a decrease in the number of GR<sup>47</sup> or decreased GR function and affinity for glucocorticoids.<sup>48,49</sup>

Several investigators observed higher cortisol levels among patients recovering from septic shock relative to levels expected in healthy adults. In addition, survivors have a more robust response to ACTH stimulation than nonsurvivors.<sup>33</sup>

Several drugs used in the ICU setting may induce AI. These include cytochrome P-450 inducers (rifampin, phenytoin) that increase cortisol metabolism. Others, like

#### Table 73-2 Causes of Adrenal Insufficiency in Critically III Patients

#### REVERSIBLE DYSFUNCTION OF THE HPA AXIS

- Sepsis, systemic inflammatory response syndrome
- Drugs (corticosteroids, etomidate, rifampin, phenytoin,
- ketoconazole)Hypothermia

#### PRIMARY ADRENAL INSUFFICIENCY

- Autoimmune
- Human immunodeficiency virus (infection, drugs)
- Cytomegalovirus infection
- Antiphospholipid syndrome
- Metastatic carcinoma (lung, breast, kidney)
- Systemic fungal infections
- Tuberculosis
- Hemorrhage (disseminated intravascular coagulation, anticoagulation, meningococcemia)

#### SECONDARY ADRENAL INSUFFICIENCY

- · Pituitary (tumors, metastasis, surgery, or radiation)
- Empty sella syndrome
- Craniopharyngioma
- Sarcoidosis, histiocytosis
- Postpartum pituitary necrosis
- Head trauma

ketoconazole or etomidate, depress glucocorticoid synthesis, secretion, or both.  $^{\rm 43,50}$ 

Several infectious agents are associated with AI. Tuberculosis, the main cause of AI in the past, has been replaced by cytomegalovirus, histoplasma, cryptococcus, or toxoplasma infections in modern ICUs. These tend to occur in HIVpositive or immunosuppressed patients.<sup>51</sup> Tumor (primary or metastatic) infiltration of the adrenal and intra-adrenal hemorrhage are additional possible but rare causes of AI.<sup>51</sup>

#### CLINICAL FEATURES OF HYPOTHALAMIC-PITUITARY-ADRENAL AXIS FAILURE

Clinical diagnosis of HPA failure in critically ill patients may be due to the combination of AI and the underlying disease. Therefore, it often is difficult to diagnose. Thus, there should be a high index of suspicion in critically ill patients requiring vasopressor support.<sup>52</sup> Laboratory assessment can help identifying patients at risk. The presence of eosinophilia may be an additional sign of AI. Clinical signs associated with AI are presented in Table 73-3.

#### DIAGNOSIS OF HYPOTHALAMIC-PITUITARY-ADRENAL AXIS FAILURE

Several tests have been proposed for the diagnosis of AI.

#### Measurement of Random Serum Cortisol Levels

A number of investigators have suggested that a random low serum cortisol level is indicative of HPA failure.<sup>53,54</sup>

## Table 73-3 Signs Suggestive of Adrenal Insufficiency in Critically III Patients

- · Sepsis, with hypotension resistant to volume resuscitation
- Vasopressor dependence
- Hyperdynamic circulation
- Weakness, fatigue
- Anorexia, weight loss
- Nausea, vomiting, diarrhea
- Anemia
- Eosinophilia
- Metabolic acidosis
- Hyponatremia and hyperkalemia
- Hypoglycemia
- Mental status changes
- Hyperpigmentation, vitiligo
- Fever

They postulate that the central nervous system–HPA axis is maximally activated in severely stressed patients. This results in a fixed response and loss of diurnal variation.<sup>32</sup> Thus, a random cortisol level provides adequate information about the integrity of the entire axis.<sup>3</sup> This approach is problematic for several reasons. First, the cortisol level that indicates failure is unknown. Values ranging from 10 to  $34 \,\mu g/dL$  have been proposed. Current thinking is that unstimulated cortisol levels less than 15 µg/dL (414 nmol/L) should be used as a cutoff for the diagnosis of relative adrenal insufficiency.<sup>16</sup> A second problem involves the high degree to which cortisol is bound to CBG and albumin. Therefore, low levels may reflect nothing more than hypoalbuminemia or redirected hepatic protein synthesis.<sup>16</sup> Finally, data correlating levels with mortality are confusing because both low (suggesting insufficient response to stress) and high (reflecting more severe stress) cortisol levels have been associated with increased mortality.<sup>41,53,55–58</sup>

#### Free Plasma Cortisol Measurement

Measurement of free plasma cortisol has been suggested. This avoids the problems associated with changes in the plasma concentrations of proteins that bind cortisol. Free cortisol may be calculated using the Coolens equation.<sup>59,60</sup> A number of studies suggest that free plasma cortisol is likely to provide a more accurate reflection of circulating glucocorticoid activity than total plasma cortisol.<sup>61</sup> This approach is supported by several important findings: (1) ACTH markedly stimulated free cortisol increments whereas total cortisol increments are nearly undetectable; (2) basal free cortisol levels are more elevated than total cortisol in septic patients; (3) after resolution of septic shock, basal free cortisol levels fell promptly, but total cortisol levels remained elevated; and (4) there is less overlap between relative AI and nonrelative AI patients when basal free cortisol levels, rather than basal total cortisol levels, were used to make the diagnosis.<sup>61</sup> Despite the logic of this approach, there are no data that directly support the use of free cortisol measurements.

#### High-Dose Adrenocorticotropic Hormone Test

This approach is designed to measure the integrity of the HPA axis. It is performed by administering 250  $\mu$ g of corticotropin intravenously. Serum cortisol levels are measured at 30 and 60 minutes.<sup>62</sup> In ambulatory healthy subjects, an increase in serum cortisol levels to 18 to 20  $\mu$ g/dL is considered normal.<sup>62,63</sup> Similarly, a level less than 18 to 20  $\mu$ g/dL or an increase of less than 9  $\mu$ g/dL is considered abnormal.<sup>64</sup> The threshold of 18  $\mu$ g/dL may be inappropriately low in critically ill patients.<sup>65</sup> Importantly, 250  $\mu$ g of corticotropin may be sufficient to override adrenal resistance to ACTH and result in a normal cortisol response even though the patient may fail to respond to stress.<sup>44</sup>

#### Low-Dose Adrenocorticotropic Hormone Test

Some clinicians have argued that a corticotropin dose of only 1  $\mu$ g is more sensitive and specific for primary and secondary adrenal insufficiency.<sup>44</sup> This eliminates concern that a large dose will elicit a response even when responses in the HPA axis are suppressed. However, this approach becomes problematic when the HPA axis is maximally stimulated. In this setting, the stressed patient may be secreting all the cortisol possible, and that amount may be appropriate. Failure to respond to stimulation would not be indicative of insufficiency.

Other tests have been proposed but are unexplored in critically ill patients.

#### DIAGNOSIS OF RELATIVE ADRENAL INSUFFICIENCY IN CRITICALLY ILL PATIENTS

The prognostic importance of adrenal insufficiency in septic shock is well described. However, it is important to systematically evaluate the value of routine testing of adrenal function and the effect of steroid replacement in the critically ill. Several randomized clinical trials (RCTs) have addressed this issue.

The recently published CORTICUS study,<sup>43</sup> the largest RCT in the field, evaluated (1) the reliability of the short corticotropin test for the diagnosis of relative AI, and (2) the effect of cortisol replacement in patients with refractory hypotension.<sup>66</sup> To reduce heterogeneity in the determination of cortisol levels, all samples were measured blindly and serially before interim and final analyses in a central laboratory using the Elecsys cortisol assay (Roche Diagnostics). The authors concluded that the short corticotropin test was not useful for determining the advisability of corticosteroid treatment in patients with septic shock. These results also raise concerns regarding the accepted definition of relative adrenal insufficiency. Indeed, the measured cortisol level was not consistent between different assays. Other studies have described the poor relationship between measurement methods.<sup>66</sup> There also is concern about the dose, timing, and type of corticotropin.43

Based on these findings, the guidelines regarding management of severe sepsis and septic shock presented in the 2008 Surviving Sepsis guidelines were modified so that an ACTH test was not used to identify the subset of adults with septic shock who needed steroids.<sup>66</sup>

#### THERAPEUTIC APPROACH TO PATIENTS WITH PRESUMED ADRENAL INSUFFICIENCY

Most of the published data on the use of steroids in critically ill patients have come from subjects with severe sepsis or septic shock. The rationale for their use in these settings is multifactorial: potent anti-inflammatory properties, inhibition of cytokine production, inhibition of migration of inflammatory cells into tissues, increase in vasoactive tone, enhancement of responsiveness to catecholamine, prevention of desensitization, or downregulation of  $\beta$ -adrenergic receptors. However, clinical trials of glucocorticoid therapy in septic patients have vielded conflicting results. Tables 73-4 and 73-5 summarize the most important meta-analyses and randomized controlled trials regarding steroid use in sepsis. It is important to emphasize that in most of the studies that contributed data to meta-analyses, pretreatment serum cortisol levels were significantly elevated relative

to accepted norms.<sup>41</sup> Additionally, even treatment with "low-dose" steroids (150 to 200 mg hydrocortisone per day) resulted in both free and total serum cortisol levels that were much higher than those noted in any group of critically ill patients.<sup>67</sup> This increases the potential for adverse effects (e.g., secondary infection with resistant organisms, myopathy, hyperglycemia, hypokalemia) when steroids are administered.

Two large randomized controlled studies have addressed current therapy of AI in critically ill patients. In a French study, the authors used an ACTH stimulation test to divide their septic patients into responders (increase of  $>9 \,\mu g/dL$  in serum cortisol) and nonresponders (increase of  $<9 \,\mu g/dL$ ). These investigators noted a benefit from steroid therapy in patients labeled as nonresponders.<sup>41</sup> However, the recently published CORTICUS study was unable to demonstrate a statistically significant mortality difference between patients who did not respond to corticotropin and those who did.43 Indeed, hydrocortisone did not alter mortality in either group but was associated with an increased rate of resistant infection. Several differences in the design of these two studies may explain these contradictory findings (Table 73-6). These include entry window, duration of hypotension needed for inclusion, the use of fludrocortisone in addition to hydrocortisone, treatment duration, and the corticosteroid weaning

Table 73-4 3	able 75-4 Summary of Meta-Analyses of Steroid Ose in Sepsis						
Study	No. of Trials	No. of Subjects	Intervention	Control	Outcomes		
Lefering & Neugebauer, 1995 <sup>69</sup>	10	1329	Clinical evidence and treatment effects of low- vs. high-dose or type of corticosteroid used in proven gram-positive or gram-negative sepsis	Placebo or supportive treatment alone	No beneficial effect of corticosteroids in septic shock was observed; there is some evidence for a positive effect in patients with gram- negative septicemia.		
Cronin et al, 1995 <sup>70</sup>	9	1232	Effect of corticosteroid therapy on morbidity and mortality in sepsis	Placebo or supportive treatment alone	No support for the use of corticosteroids in patients with sepsis or septic shock, and suggests that their use may be harmful		
Minneci et al, 2004 <sup>71</sup>	5	875	Effects of glucocorticoids on survival or vasopressor requirements	Placebo or supportive treatment alone	Short courses of high-dose glucocorticoids decrease survival during sepsis. A 5- to 7-day course of physiologic hydrocortisone doses increases survival and shock reversal in patients with vasopressor-dependent septic shock.		
Keh & Sprung, 2004 <sup>72</sup>	13	811	Impact of a low or a high dose of corticosteroids in severe sepsis and septic shock	Placebo or supportive treatment alone	Low doses of corticosteroids are recommended in vasopressor-dependent septic shock. High-dose corticosteroids are not recommended in sepsis. Addition of oral fludrocortisone is considered an optional approach.		
Annane et al, 2004 <sup>73</sup>	16	2063	Effects of corticosteroids in severe sepsis and septic shock	Placebo or supportive treatment alone	Corticosteroid use did not significantly affect mortality in septic shock. Long courses of low doses of corticosteroids decreased 28-day and hospital mortality.		

Study	No. of Subjects	Study Design	Intervention	Control	Outcomes
Wagner et al, 1955 <sup>74</sup>	Two parallel groups, 2 centers, 113 adults with pneumococcal pneumonia; shock present in only 3	Quasi-randomized	Hydrocortisone (orally 80 mg on admission followed by 60 mg 3 times on day 1, then 40 mg 4 times on day 2, 20 mg 4 times on day 3, 10 mg 4 times on day 4, and 10 mg twice on day 5)	Standard therapy (first 85 patients); placebo (last 28 patients)	Fever; pleuritic pains; patient's well-being
Cooperative Study Group, 1963 <sup>75</sup>	Two parallel groups, 5 centers, 194 adults and 135 children with vasopressor-dependent septic shock	Quasi-randomized	Hydrocortisone (intravenous infusion of 300 mg for 24 hr, then 250 mg for 24 hr, followed by 200 mg orally on day 3, then tapered off in steps of 50 mg/ day—i.e., total duration of treatment 6 days)	Placebo	Primary: hospital mortality Secondary: safety
Bennett et al, 1963 <sup>76</sup>	96 patients	Double-blind	Hydrocortisone, 300 mg $\times$ 1, then decrease by 50 mg/day	Standard treatment	Hospital mortality, complications of treatment
Klastersky et al, 1971 <sup>77</sup>	Two parallel groups, 1 center, 85 adults with disseminated cancer and life-threatening infection	Double-blind	Betamethasone (1 mg/kg/day in 2 intravenous doses for 3 consecutive days)	Placebo	30-day mortality; rate of adverse events
Schumer, 1976 <sup>78</sup>	Three parallel groups, 1 center, 172 adults with septic shock with positive blood cultures	Double-blind	Dexamethasone (3 mg/kg as a single intravenous bolus); methylprednisolone (30 mg/kg as a single intravenous bolus). Treatments might have been repeated once after 4 hr and had to be initiated at time of diagnosis.	Placebo	Primary: 28-day mortality Secondary: complication rates
Thompson et al, 1976 <sup>79</sup>	28 patients	Double-blind	Methylprednisolone, 30 mg/kg × 1 and then repeat up to 3 times within 24 hr if in shock	Standard treatment	Hospital mortality, toxicities of treatment
Sprung et al, 1984 <sup>80</sup>	Three parallel groups, 2 centers, 59 adults with vasopressor-dependent septic shock	Open-label	<ul> <li>Dexamethasone (6 mg/kg as a single intravenous 10- to 15-min infusion); methylprednisolone (30 mg/kg as a single intravenous dose 10-to 15-min infusion).</li> <li>Treatments might have been repeated once after 4 hr if shock persisted and had to be initiated at time of diagnosis.</li> </ul>	No treatment, placebo	Primary: hospital mortality; shock reversal Secondary: complications of septic shock; treatment safety

Bone et al, 1987 <sup>81</sup>	Two parallel groups, 19 centers, 382 adults with severe sepsis ( $n = 234$ ) or septic shock ( $n = 148$ )	Double-blind	Methylprednisolone (30 mg/kg 20 min intravenous infusion, every 6 hr for 24 hr). Treatments had to be initiated 2 hr from time entry criteria were met.	Placebo	Primary: 14-day development of shock for severe sepsis; shock reversal for septic shock; 14-day mortality and safety
Veterans Administration Systemic Sepsis Cooperative Study Group, 1987 <sup>82</sup>	Two parallel groups, 10 centers, 223 adults with severe sepsis or septic shock ( $n = 100$ )	Double-blind	Methylprednisolone (30 mg/kg as a single intravenous 10-15 min infusion, followed by a constant infusion of 5 mg/kg/hr for 9 hr). Treatments had to be initiated within 2 hr.	Placebo	Primary: 14-day mortality Secondary: complications
Lucas & Ledgerwood, 1984 <sup>83</sup>	Two parallel groups, 1 center, 48 adults with septic shock	Open-label	Dexamethasone (2 mg/kg as a single intravenous bolus followed by a maintenance infusion of 2 mg/kg/24 hr for 2 days)	Standard treatment	Primary: 14-day mortality (unclear) Secondary: improvement in hemodynamics; improvement in pulmonary function; safety
Luce et al, 1988 <sup>84</sup>	Two parallel groups, 1 center, 75 adults with septic shock	Double-blind	Methylprednisolone (30 mg/kg 15 min intravenous infusion, every 6 hr for 24 hr); placebo	Placebo	Primary: 28-day mortality Secondary: complication rates
Slusher et al, 1996 <sup>85</sup>	Two parallel groups, 2 centers, 72 African children aged 1 to 16 yr with severe sepsis or septic shock	Double-blind	Dexamethasone (0.20 mg/kg every 8 hr for 2 days) Treatments might have been repeated once after 4 hr if shock persisted and had to be initiated 5-10 min before first dose of antibiotic.	Placebo	Primary: hospital mortality (unclear) Secondary: hemodynamic stability at 48 hr; complications
Bollaert et al, 1998 <sup>86</sup>	Two parallel groups, 2 centers, 41 adults with vasopressor- and ventilator-dependent septic shock	Double-blind	Hydrocortisone (100 mg intravenous bolus every 8 hr for 5 days, then tapered over 6 days) Treatments had to be initiated after 48 hr or more from shock onset.	Placebo	Primary: shock reversal Secondary: 28-day mortality; improvement in hemodynamics; safety
Briegel et al, 1999 <sup>87</sup>	Two parallel groups, 1 center, 40 adults with vasopressor- and ventilator-dependent septic shock	Prospective randomized double-blind, single- center	Hydrocortisone (100 mg 30-min intravenous infusion followed by 0.18 mg/kg/hr continuous infusion until shock reversal and then tapered off) Treatments had to be initiated within 72 hr from shock onset.	Placebo	Primary: shock reversal Secondary: 28-day mortality; improvement in hemodynamics; organ system failure; safety

Continued

Study	No. of Subjects	Study Design	Intervention	Control	Outcomes
Chawla et al, 1999 <sup>88</sup>	Two parallel groups, 1 center, 44 adults with vasopressor-dependent septic shock	Double-blind	Hydrocortisone (100 mg intravenous bolus every 8 hr for 3 days, then tapered over 4 days) Treatments had to be initiated after 72 hr or more from shock onset.	Placebo	Primary: shock reversal Secondary: 28-day mortality; improvement in hemodynamics; safety
Annane et al, 2002 <sup>41</sup>	Two parallel groups, 19 centers, 300 adults with vasopressor- and ventilator-dependent septic shock	Double-blind	Hydrocortisone (50 mg intravenous bolus every 6 hr for 7 days + fludrocortisone 50 g taken orally every 24 hr for 7 days) Treatments initiated within 8 hr from shock onset	Respective placebos	Primary: 28-day mortality in nonresponders Secondary: 28-day mortality in responders and all patients; intensive care unit mortality; hospital mortality; 1-year mortality; shock reversal; organ system failure-free days; safety
Yildiz et al, 2002 <sup>89</sup>	Two parallel groups, 1 center, 40 adults with sepsis ( $n = 14$ ), severe sepsis ( $n = 17$ ), and septic shock ( $n = 9$ )	Double-blind	Prednisolone (2 intravenous bolus, 5 mg at 6 am and 2.5 mg at 8 pm for 10 days)	Placebo	Primary: 28-day mortality Secondary: complications
Keh et al, 2003 <sup>68</sup>	40 adults with vasopressor-dependent septic shock	Double- blind crossover design	Hydrocortisone (100 mg 30-min intravenous infusion followed by 10 mg/hr continuous infusion for 3 days) All patients received hydrocortisone for 3 days	Preceded or followed by placebo for 3 days	Primary: immune response Secondary: improvement in hemodynamics and organ system failure; safety
Oppert et al, 2005 <sup>90</sup>	Single-center study, 48 patients	Prospective randomized double-blind	Patients were randomized to receive low-dose hydrocortisone (50-mg bolus followed by a continuous infusion of 0.18 mg/kg/hr)	Placebo	Time to cessation of vasopressor support (primary end point) Secondary end points were cytokine response, 28-day survival, and the Sequential Organ Failure Assessment (SOFA) score

#### Table 73-5 Summary of Randomized Controlled Trials on Steroid Use in Sepsis\*-Cont'd

Continued

Confalonieri et al, 2005 <sup>91</sup>	6 centers, 46 patients	Randomized double-blind	Patients with clinical and radiographic evidence of pneumonia were randomly assigned in a 1:1 manner to receive hydrocortisone infusion (intravenous 200-mg loading bolus) followed by an infusion (hydrocortisone 240 mg in 500 mL 0.9% saline) at a rate of 10 mg/hr for 7 days)	Placebo	Primary end points: improvement in Pao <sub>2</sub> / Fio <sub>2</sub> and multiple-organ dysfunction syndrome, and development of delayed septic shock Secondary end points: duration of mechanical ventilation, length of intensive care and hospital stay, survival to hospital discharge and to 60 days
Sprung et al, 2008 <sup>43</sup>	52 intensive care units, 499 patients	Randomized double-blind	Patients received either 50 mg of intravenous hydrocortisone or placebo every 6 hr for 5 days; the dose was then tapered during a 6-day period.	Placebo	Primary outcome: 28-day mortality among patients who did not have a response to corticotropin test

\*No meta-analyses available.

Table 73-6 Comparison between the French

and CORTICUS Studies				
	French Study (Annane et al, 2002 <sup>41</sup> )	CORTICUS Study (Sprung et al, 2008 <sup>43</sup> )		
Entry window	8 hr	72 hr		
SBP < 90 mm Hg	>1 hr	<1 hr		
Additional prescription	Fludrocortisone	None		
Treatment duration	7 days	11 days		
Hydrocortisone weaning	No	Yes		
SAPS II	$59\pm21$	$49\pm17$		
Nonresponders	76.6%	47%		
Resistant infection	No	Increased		

SAPS, Simplified Acute Physiology Score; SBP, systolic blood pressure.

procedure. These differences may have affected the severity of patients recruited to either study (see Table 73-6).

The contrasting findings in these two large randomized controlled studies are reflected in recently published guidelines regarding the management of severe sepsis and septic shock.<sup>66</sup> It is important to note that some of these recommendations are based on common practice with little evidence to support them. The Surviving Sepsis Campaign recommends the following:

- 1. Intravenous hydrocortisone is administered only for adult septic shock patients with blood pressure that is poorly responsive to fluid resuscitation and vasopressor therapy. Although corticosteroids promote reversal of shock, they fail to reduce sepsis-related mortality.
- 2. Corticosteroids should not be given to septic patients in the absence of shock. However, there is no contraindication to continuing steroid therapy if the patient's history or endocrine status warrants.
- 3. Doses of corticosteroids for septic shock should be not higher than 300 mg per day.
- In patients with septic shock, hydrocortisone is preferable to dexamethasone because it may lead to immediate and prolonged suppression of the HPA axis.
- 5. Fludrocortisone should be considered if hydrocortisone, which has some mineralocorticoid activity, is not available.
- 6. Weaning from steroid therapy occurs when vasopressors are no longer required. Tapering the dose is recommended because there may be an increase in proinflammatory mediators and hemodynamic deterioration after abrupt cessation of corticosteroids.<sup>43</sup>

Patients with inadequate adrenal reserve and those receiving chronic steroid therapy should receive sufficient steroid during severe stress or critical illness. Although not supported by data, the accepted practice is to provide glucocorticoid therapy based on type of surgery. Recommendations are as follows:

- 1. For minor surgery, a dose of 25 mg hydrocortisone daily  $^{3}$
- 2. For moderate surgical stress, a dose of 50 to 75 mg hydrocortisone for 1 to 2 days<sup>3</sup>
- 3. For major procedures, 100 to 150 mg hydrocortisone for 2 to 3 days<sup>3</sup>

It has been recommended that doses be increased to maximal stress dose (300 mg/day) in patients who remain hypotensive or deteriorate during recovery from surgery.<sup>3</sup> However, this recommendation is unsupported by data.

#### **AUTHORS' RECOMMENDATIONS**

- The response of the HPA axis is altered by critical illness. This
  in part reflects the ability of cytokines to activate responses.
- Despite disagreement regarding definitions and diagnosis, AI may develop during critical illness.
- AI in critically ill patients is associated with poor outcome.
- Randomized clinical trials are at odds regarding the use of corticosteroids in critically ill patients. The differences may reflect study design or the replacement regimen used.
- Virtually all trials show that corticosteroid administration improves hemodynamics in critically ill patients.
- The ACTH stimulation test gives inconsistent results and should not be the basis for starting corticosteroids.
- In hemodynamically compromised patients who are not responsive to fluid or vasopressor and inotropic therapy, a trial of corticosteroids is warranted.

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Is There a Mineralocorticoid Deficiency in Critically III Patients? How Can It Be Diagnosed? Should It Be Treated?

Djillali Annane

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The role of adrenal function in the pathophysiology of critical illness is a frequently addressed topic. However, definitions, diagnosis, and treatment are challenging and controversial. Recent guidelines published by a multidisciplinary, multispecialty group of experts indicate that adrenal insufficiency occurs during critical illness, that it can be diagnosed by a change in the total serum cortisol of less than 9 µg/dL following adrenocorticotropic hormone (ACTH; 250 µg) administration or a random total cortisol of less than 10  $\mu$ g/dL, and that in such cases treatment (hydrocortisone 50 mg 4 times per day or a continuous infusion of 10 mg/hour for 5 to 7 days) is warranted for patients with septic shock poorly responsive to fluids and vasopressors.<sup>1</sup> This stands in contrast to the findings and recommendations detailed in the CORTICUS trial.<sup>2</sup> In addition, although the CORTICUS study does not address the replacement of mineralocorticoids, the Society of Critical Care guidelines suggest that mineralocorticoid replacement also is indicated. This last issue is addressed in this chapter.

#### PHYSIOLOGIC BASIS FOR REPLACING MINERALOCORTICOID IN CRITICALLY ILL PATIENTS

#### Definition

The term *mineralocorticoid* is used to designate a group of adrenal steroids, most notably aldosterone in humans, that are highly active in the control of mineral and water metabolism.

#### **Regulation of Synthesis**

Mineralocorticoids are synthesized in the zona glomerulus, the region situated just beneath the adrenal capsule (Fig. 74-1). Endogenous mineralocorticoids include desoxycorticosterone (the first mineralocorticoid identified), progesterone, and aldosterone (the most potent). About 100 to 150 µg per day of aldosterone are secreted under normal conditions. A cytochrome P-450 enzyme, CYP11B2 (aldosterone synthase, CYP11B2), catalyzes synthesis by converting desoxycorticosterone to corticosterone and subsequently to aldosterone.<sup>3</sup> Of note, aldosterone can be synthesized in the brain,<sup>4</sup> blood vessels,<sup>5</sup> and heart.<sup>6</sup> Aldosterone synthesis is regulated primarily by the renin-angiotensin system through adrenal angiotensin I receptors. Small changes in blood electrolyte levels also affect production. Potassium acts directly on aldosterone-secreting cells. ACTH has little effect normally but may become important under specific conditions.

## Mode of Action and Mineralocorticoid Receptors

Mineralocorticoids primarily act on the kidney, where they cause sodium and water retention and active excretion of potassium and protons. This effect is modulated by hormone binding to epithelial mineralocorticoid receptors (MRs) in collecting tubules. It is thought that aldosterone effects are mediated by genomic interaction with the Na<sup>+</sup>-K<sup>+</sup> ATPase pumps and nongenomic increases in the permeability of cells to  $Na^+$  and protons.^7 The essential role of MRs in salt and water homeostasis and in survival is demonstrated by MR disruption or adrenalectomy in mice. The former results in markedly reduced weight, a severe dehydration due to failure of sodium reabsorption, hyperkalemia, hyponatremia, a strongly activated renin-angiotensin system, and premature death.<sup>8</sup> Treatment of the latter with mineralocorticoids increases plasma volume and systemic arterial pressure and prolongs survival in adrenalectomized animals.<sup>7</sup>

Importantly, glucocorticoids and mineralocorticoids have similar affinity for MRs. This is problematic because cortisol, the primary glucocorticoid in humans, is much more abundant than aldosterone and thus may prevent



Figure 74-1. Anatomic view of the adrenal gland.

aldosterone binding and also might overstimulate salt and water retention. However, evolution has provided an enzyme, 11 $\beta$ -hydroxysteroid dehydrogenase type 2 (11 $\beta$ -HSD2), that converts cortisol to its inactive form, cortisone.<sup>9</sup> This enzyme is present mainly in mineralocorticoidresponsive tissues such as the kidney, the intestine, and the salivary glands.<sup>7</sup> The inactivation of cortisol thus renders these tissues sensitive to mineralocorticoids only.

#### EVIDENCE FOR ABNORMAL MINERALOCORTICOID LEVELS DURING CRITICAL ILLNESS

#### Prevalence of Mineralocorticoid Insufficiency in Critical Illness

Several investigators have reported a dissociation between plasma renin and aldosterone levels in critically ill patients<sup>10–20</sup> (Table 74-1). In these studies, although plasma renin activity was consistently elevated, aldosterone levels paradoxically were low in a substantial

Study	Population	Study Design	Prevalence of an PA/PRA Ratio < 2	Clinical Consequence	Treatment
Zipser et al, 1981 <sup>10</sup>	28 critically ill and hypotensive adults	Prospective cohort study	18/28 (64%)	Mortality, 78%	None
Stern et al, 1983 <sup>11</sup>	14 critically ill patients 9 healthy controls	Case control study	8/14 (57%)		None
Davenport & Zipser, 1983 <sup>12</sup>	100 critically ill adults	Prospective cohort study	22/100 (22%)	Hypotension more frequent (91% vs. 53%)	None
Findling et al, 1987 <sup>13</sup>	83 critically ill adults	Prospective cohort study	24/59 (41%)	Mortality was higher (75% vs. 46%)	None
du Cheyron et al, 2003 <sup>19</sup>	46 adults with septic shock	Prospective cohort study	22/46 (48%)	Longer intensive care unit length of stay, greater proportion or renal failure and of patients requiring renal replacement therapy	Hydrocortisone + fludrocortisone
Manglik et al, 2003 <sup>18</sup>	100 adults with sepsis and septic shock	Prospective cohort study	9/100 (9%)	Hypotension more likely	Hydrocortisone
Lichtarowicz- Krynska et al, 2004 <sup>17</sup>	60 children with acute meningococcemia (group 1: $n = 31$ ) or after major surgery with lung infection (group 2: $n = 29$ )	Prospective cohort study	12/15 (80%)	Not available	None
du Cheyron et al, 2008 <sup>20</sup>	50 adults critically ill with liver cirrhosis	Prospective cohort study	26/50 (52%)	Greater disease severity and organ dysfunction scores, higher levels of serum interleukin-6, and a greater intensive care unit mortality rate PA/ PRA < 2 was an independent predictor of 30-day mortality	

PA/PRA ratio, plasma aldosterone-to-plasma renin activity ratio.

number (22% to 64%) of cases and possibly in up to 97% of children with acute meningococcal disease.<sup>17</sup> The lack of correlation between renin activity and aldosterone levels has been interpreted to represent mineralocorticoid deficiency and is consistent with the sort of peripheral resistance characteristic of the behavior of other hormones in critically ill patients.<sup>21</sup> The mineralocorticoid deficiency may complicate a broad variety of critical illnesses and appears to occur more frequently in hypotensive patients.<sup>10,12,13</sup>

#### Diagnosis of Mineralocorticoid Insufficiency

The loss in mineralocorticoid activity should result in increased renal sodium excretion, dehydration, metabolic acidosis, and hyperkalemia. Although general management of critically ill patients is designed to either prevent or rapidly correct overt electrolyte disorders, <sup>10,12,13</sup> some cases may present with severe hyponatremia.<sup>14</sup> In addition, du Cheyron and colleagues showed that, compared with 24 patients with septic shock with appropriate aldosterone levels, 22 patients with septic shock and hypoaldosteronism had greater fractional excretion of sodium and requested larger amounts of fluid replacement.<sup>19</sup>

Davenport and Zipser proposed that the critical illness–associated hyperreninemic hypoaldosteronism is defined by a plasma aldosterone–to–plasma renin activity (PA/PRA) ratio of less than 2, which corresponds to the 98th percentile of the control population.<sup>12</sup> This definition has been broadly endorsed.

#### Outcome Associated with Mineralocorticoid Insufficiency

Compared with 78 patients with a PA/PRA ratio above 2, 22 patients with the so-called hyperreninemic hypoaldosteronism syndrome were more likely (91% versus 53%) to present with persistent hypotension.<sup>12</sup> This relationship between mineralocorticoid insufficiency and shock has been confirmed in various critical illnesses.<sup>10,11,13,14,19,20</sup> In septic shock, aldosterone levels correlated negatively with serum creatinine levels and mineralocorticoid deficiency was associated with an increased risk for developing acute renal failure and an increased likelihood of requiring renal replacement therapy.<sup>19</sup> Mineralocorticoids levels also correlated with multiple organ failure<sup>20</sup> and interleukin-6 levels.<sup>20,22</sup> Finally, in a cohort of 66 intensive care unit patients, 21% had low aldosterone levels and a significantly higher mortality rate (75% versus 46%) than those with a normal PA/PRA ratio.<sup>13</sup> The poor prognosis associated with hyperreninemic hypoaldosteronism remains controversial, with an associated increased mor-tality confirmed in some studies,<sup>10,20</sup> but not in others.<sup>12,22</sup>

#### Mechanisms and Causes of Critical Illness– Associated Mineralocorticoid Insufficiency

Chronic hypoxia in rats was associated with a dramatic reduction in plasma aldosterone levels, although blood pressure, plasma renin activity, and ACTH levels were unaffected.<sup>23</sup> In these animals, acute hemorrhage resulted in a rapid and sustained increase in ACTH and corticosterone levels while aldosterone levels remained low. Similarly, chronic stress induced by repeated immobilization and repeated intraperitoneal injection of hypertonic saline resulted in a sustained activation of the hypothalamic-pituitary-adrenal axis and increased plasma renin activity with low aldosterone levels.24 Chronic exposure of cultured bovine adrenal zona glomerulus cells to ACTH enhanced 17α-hydroxylase and produced a shift of steroid production from aldosterone to cortisol with cortisol production indistinguishable from that of fasciculata cells.<sup>25</sup> These data suggested that the hyperreninemic hypoaldosteronism syndrome may be an adaptive phenomenon to allow the synthesis of more cortisol during prolonged stress. However, in critically ill patients, an abnormal PA/PRA ratio was found to be independent of cortisol or ACTH levels.<sup>13,17,19</sup> In most cases, aldosterone levels failed to increase after angiotensin II or ACTH infusions. This suggests that damage to the zona glomerulus is a cause of the hyperreninemic hypoaldosteronism syndrome.<sup>10,11</sup> Because this syndrome has been shown to be transient, with recovery of normal PA/PRA ratio in survivors,<sup>1,19</sup> necrosis of the zona glomerulus is unlikely. Other factors may be involved, including inhibition of the aldosterone synthase by free oxygen radicals,<sup>26</sup> cytokines,<sup>27</sup> and dopaminergic stimulation.<sup>28</sup>

#### SHOULD CRITICAL ILLNESS-ASSOCIATED MINERALOCORTICOID INSUFFICIENCY BE TREATED?

Systematic mineralocorticoid replacement has been investigated in only one randomized controlled trial.<sup>29</sup> In this trial, 300 patients with septic shock were allocated to a 7-day treatment with an intravenous bolus of 50 mg of hydrocortisone or placebo every 6 hours and 50 µg of fludrocortisone through the gastric tube daily. This trial showed survival benefit from hormone replacement in patients with adrenal insufficiency, although mineralocorticoid insufficiency was not specifically reported. Other trials of low-dose corticosteroids in sepsis or other critical illness have used only hydrocortisone.<sup>1</sup> However, it is not clear that 200 mg per day of intravenous hydrocortisone provides sufficient activity to correct mineralocorticoid deficiency in critically ill patients. Indeed, the 11β-HSD2 enzyme converts cortisol into its inactive form to prevent its binding to mineralocorticoid receptors. The plasma cortisol-to-cortisone ratio was increased following trauma, burns, or sepsis and remained elevated for several days, suggesting enhanced activity of the 11β-HSD2.<sup>30</sup> There are two ongoing multicenter trials comparing hydrocortisone alone versus hydrocortisone plus fludrocortisone for the treatment of septic shock (NCT00368381, NCT00320099). These trials should clarify the need for mineralocorticoid replacement therapy in critical illness.

#### GUIDELINES

Recently, the Society of Critical Care Medicine and the European Society of Intensive Care Medicine convened a multidisciplinary, multispecialty group of experts to establish guidelines for the diagnosis and management of corticosteroid insufficiency in critical illness.<sup>1</sup> The guidelines, however, did not address the definition of mineralocorticoid insufficiency. The guidelines identified two groups of critically ill patients who might benefit from treatment with low-dose corticosteroids. These are patients with septic shock poorly responsive to vasopressors and patients with acute respiratory distress syndrome. These guidelines suggest that dexamethasone, which lacks mineralocorticoid activity, should not be given, implicitly endorsing mineralocorticoid replacement. The guidelines also suggested that fludrocortisone administration is optional in the presence of hydrocortisone at a dose of 200 to 300 mg per day because this should provide sufficient mineralocorticoid activity.

#### **AUTHORS' RECOMMENDATIONS**

- Whether critical illness is associated with altered adrenal function and whether adrenal insufficiency contributes to poor outcome in critically ill patients remain controversial.
- There is a dissociation between plasma renin activity and aldosterone levels in a broad variety of critical illnesses, particularly in patients with persistent hypotension.
- A body of evidence suggested that the so-called hyperreninemic hypoaldosteronism syndrome is associated with an increased risk for organ dysfunction and death in critically ill patients.
- Recent guidelines suggested that corticosteroid therapy in patients with septic shock poorly responsive to vasopressor should include a compound with sufficient mineralocorticoid activity.

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## 75 How do I Diagnose and Manage Acute Endocrine Emergencies in the ICU?

Carrie A. Sims

Endocrine emergencies are frequently encountered in the intensive care unit (ICU). This chapter focuses on several of the more common disorders. These include diabetic hyperglycemic states, thyroid storm, myxedema coma, and adrenal insufficiency. Adrenal insufficiency will be discussed in separate chapter. Understanding the pathophysiology of these different disease states will enable the intensivist to make a rapid diagnosis, initiate proper therapy and monitoring, and avoid major pitfalls.

#### DIABETIC KETOACIDOSIS

Diabetic ketoacidosis (DKA) is a life-threatening hyperglycemic condition that accounts for more than 115,000 hospital admissions each year.<sup>1</sup> With improved therapy, the age-adjusted mortality rate has fallen dramatically in the past 20 years and is currently less than 5%.<sup>2</sup> Nonetheless, DKA represents a heavy health care burden, and the cost of caring for patients with decompensated diabetes may exceed \$1 billion annually.<sup>3</sup>

Although DKA is considered a pathognomonic complication of insulin-dependent diabetes (type 1), 5% to 30% of type 2 diabetic patients may also present with this condition. The defining features of DKA include metabolic acidosis (arterial pH < 7.35 with bicarbonate < 16 mEq/L), hyperglycemia (typically >250 mg/dL), and ketonemia. The severity of DKA can be graded as mild, moderate, or severe based on the degree of metabolic acidosis and the presence of an altered mental status (Table 75-1).<sup>4</sup>

#### Pathophysiology

DKA is a proinflammatory, dysregulated catabolic state that occurs in the setting of insulin deficiency coupled with high levels of counterregulatory hormones, including glucagon, cortisol, catecholamines, and growth hormone.<sup>5</sup> This hormonal imbalance results in impaired glucose use, increased gluconeogenesis, and increased lipolysis. As the serum glucose increases, water is shifted from the intracellular to the extracellular compartment in order to compensate for the increase in osmolality. With marked hyperglycemia, the kidney cannot effectively reabsorb glucose, and an osmotic diuresis ensues. Hypovolemia and profound electrolyte depletion soon follow.

In addition to hyperglycemia, DKA is defined by the development of acidosis. The combination of insulin deficiency and the increase in counterregulatory hormones promotes lipolysis and the liberation of free fatty acids. The liver oxidizes the free fatty acids as an alternative energy source and in the process generates acetone,  $\beta$ -hydroxybutyrate, and acetoacetate. As relatively strong acids, these ketones deplete the body's buffering capacity and produce a metabolic acidosis.<sup>6</sup>

#### **Clinical Presentation**

The symptoms of DKA develop early and are primarily related to the findings of hyperglycemia and acidosis. The osmotic effect of hyperglycemia results in polyuria, polydipsia, and dehydration. The degree of volume depletion, however, is variable, and patients frequently demonstrate tachycardia with or without hypotension. Nausea, vomiting, and abdominal pain are common and are thought to be secondary to the generation of ketoacids.<sup>7</sup> The metabolic acidosis also triggers compensatory hyperventilation. Classically, the patient's breath has the fruity odor of acetone, which is primarily excreted through the lungs. Although an increased white blood cell count is common even in the absence of an infection, a fever is rare and should prompt an aggressive search for a concomitant infection. Similarly, an altered mental status is not typical and warrants further investigation.

#### Therapy

The management of DKA is directed toward correcting fluid and electrolyte abnormalities, treating hyperglycemia with insulin, identifying precipitating causes, and monitoring therapy. In 2006, the American Diabetes Association (ADA) published a consensus statement regarding the management of DKA (Fig. 75-1).<sup>4</sup>

#### Fluid and Electrolyte Replacement

Volume replacement is the initial therapy and should be directed toward the re-expansion of intravascular volume and the restoration of renal perfusion. Isotonic saline (0.9% NaCl) should be infused rapidly (1 to 2 L/hour).

Table	75-1	Diagnostic Criteria for	Diabetic Ketoacidosis and Hy	vperosmolar Hyperglycemic State
IUDIC	101	Blaghostio Officilia for		

Criteria	Diabetic Ketoacidosis			Hyperosmolar Hyperglycemia
	Mild	Moderate	Severe	
Plasma glucose (mg/dL)	>250	>250	>250	>600
Arterial pH	7.25-7.30	7.00-7.24	<7.00	>7.30
Serum bicarbonate (mEq/L)	15-18	10 to <15	<10	>15
Urine ketones*	Positive	Positive	Positive	Small
Serum ketones*	Positive	Positive	Positive	Small
Effective serum osmolality <sup>†</sup>	Variable	Variable	Variable	>320
Anion gap <sup>‡</sup>	>10	>12	>12	Variable
Alteration in sensoria or mental obtundation	Alert	Alert/drowsy	Stupor/coma	Stupor/coma

\*Nitroprusside reaction method.

<sup>†</sup>Effective serum osmolality = 2[measured Na<sup>+</sup>] + glucose/18

<sup>\*</sup>Anion gap =  $(Na^+) - (Cl^- + HCO_3^-)$ .

Adapted from the 2006 American Diabetes Association consensus statement. Kitabachi AE, Umpierrez GE, Murphy MB, Krieshberg RA. Hyperglycemic crisis in adult patients with diabetes: A consensus statement from the American Diabetes Association. *Diabetes Care*. 2006;29:2739-2748.

Even if the serum sodium is elevated, initial fluid replacement should not be hypotonic. The hypernatremia will improve with intravascular volume replacement. After adequate intravascular volume repletion, fluids can be changed to 0.45% NaCl if the serum sodium is at least 140 mEq/L. The hourly rate of infusion depends on the patient's hydration state. Once the intravascular volume has been restored, the total-body water deficit should be judiciously corrected over the next 24 hours.

Almost all patients with DKA have a potassium deficit primarily due to urinary losses. Serum potassium, however, is often elevated on presentation because of the extracellular shift of potassium in response to the insulin deficiency and hyperosmolality. With insulin therapy, potassium is transported intracellularly, and profound hypokalemia can result. Potassium replacement should be initiated when the serum potassium concentration falls below 5.3 mEq/L and if the patient has good urine output (>50 mL/hour).<sup>4</sup>

Similarly, although phosphate levels may be initially elevated on presentation, DKA is associated with a phosphate deficiency. With insulin therapy, phosphate levels may fall dramatically. In randomized prospective trials, however, standard phosphate replacement was not associated with improved clinical outcomes.<sup>8,9</sup> Nonetheless, it seems prudent to provide supplementation when the serum phosphate concentration is less than 1 mg/dL in order to avoid cardiac and respiratory muscle weakness.<sup>4</sup>

Despite significant acidosis (pH > 7.0), supplemental bicarbonate is rarely, if ever, needed. Not only does bicarbonate administration contribute to a worsening intracellular acidosis, it also increases the risk for hypokalemia and cerebral edema.<sup>10,11</sup> In a small prospective randomized trial, supplemental bicarbonate did not prove beneficial in patients with an initial arterial pH between 6.9 and 7.0. There are no prospective studies evaluating the benefit of bicarbonate in DKA with an initial pH less than  $6.9.^{12}$  Given the paucity of available data regarding the

management of DKA with profound acidosis, the ADA consensus statement recommends bicarbonate supplementation when the presenting arterial pH is less than 7.0.<sup>4</sup>

#### Insulin Therapy

Insulin therapy should only be initiated after adequate volume replacement. Premature initiation of insulin can exacerbate intravascular volume depletion and precipitate hypotension by causing an intracellular shift of glucose and water. Additionally, the serum potassium should be at least 3.3 mEq/L before insulin therapy. Insulin will shift potassium into the cell and worsen hypokalemia.

After initial volume resuscitation, a continuous insulin infusion should be started. Traditionally, a bolus of insulin (0.1 U/kg body weight) followed by a continuous infusion at 0.1 U/kg per hour has been used. Recently, a randomized trial has demonstrated that this "priming" bolus is unnecessary and that effective glycemic control can be achieved by starting the insulin drip at 0.14 U/kg per hour.<sup>13</sup> Glucose levels should decrease by 50 to 70 mg/dL per hour. If the serum glucose does not decrease by at least this value within the first hour, the insulin infusion rate should be doubled every hour until a steady decline is achieved. Glucose should be monitored by fingerstick hourly and confirmed by frequent serum glucose will normalize before ketoacid production stops.

To prevent a worsening acidosis, insulin therapy should be continued, along with supplemental glucose, until the anion gap normalizes. An abrupt discontinuation of insulin will lead to a recurrence of hyperglycemia and ketoacidosis. When serum glucose falls to 250 mg/dL or less, intravenous fluids should be changed to include 5% dextrose, and the insulin infusion should be adjusted appropriately to prevent hypoglycemia. The insulin infusion can be tapered and a subcutaneous insulin regimen



Complete initial evaluation. Check capillary glucose and serum/urine ketones to confirm hyperglycemia and ketonemia/ketonuria. Start IV fluids: 1.0 L of 0.9% NaCl per hour.<sup>†</sup>

**Figure 75-1.** Protocol for managing patients with diabetic ketoacidosis (DKA). (*Adapted from the 2006 American Diabetes Association consensus statement. From Kitabachi AE, Umpierrez GE, Murphy MB, Krieshberg RA. Hyperglycemic crisis in adult patients with diabetes: A consensus statement from the American Diabetes Association. Diabetes Care. 2006;29:2739-2748.*)

initiated when the patient's serum glucose is less than 200 mg/dL, the serum anion gap is less than 12 mEq/L, the serum bicarbonate is at least 18 mEq/L, and the venous pH is greater than  $7.30.^5$  The insulin infusion should be continued for 1 to 2 hours after the subcutaneous regimen is initiated to ensure adequate insulin levels.

Subcutaneous insulin therapy using rapid-onset insulin analogs may be an effective alternative to intravenous insulin for the treatment of uncomplicated DKA. In a randomized prospective trial, subcutaneous insulin lispro was not only as effective as intravenous insulin but also was associated with a 39% reduction in hospital charges, primarily because patients could be treated in the general wards and did not require ICU admission.<sup>14</sup> In a similar randomized prospective study that in part involved the use of subcutaneous insulin, Umpierrez and associates reported no differences in mortality, length of hospital stay, total amount of insulin administration, or episodes of hyperglycemia compared with an intravenous regimen.<sup>15</sup> Patients with mild to moderate uncomplicated DKA may be treated with an initial injection of 0.2 U/kg followed by 0.1 U/kg every hour or an initial dose of 0.3 U/kg followed by 0.2 U/kg every 2 hours until the blood glucose is less than 250 mg/dL. The insulin is then decreased by half (0.05 U/kg or 0.1 U/kg, respectively) and administered every 1 to 2 hours until DKA is resolved.<sup>4</sup>

#### Precipitating Factors

In most cases, a precipitating cause of DKA can be identified. Although noncompliance or inadequate insulin therapy can certainly initiate a hyperglycemic crisis, DKA is frequently associated with urinary tract infections or pneumonia. Appropriate laboratory tests, imaging, and cultures should be performed to rule out an infectious source, and antibiotic therapy should be initiated early. Other physiologic stressors such as myocardial ischemia, stroke, or other acute medical illness can also precipitate a diabetic crisis and should be carefully investigated. Finally, DKA has been associated with the use of glucocorticoids, second-generation antipsychotics, and sympathomimetic agents, including cocaine.<sup>5,16,17</sup>

#### Monitoring Therapy

Measuring serum levels of  $\beta$ -hydroxybutyrate, the predominant ketone in DKA, is the preferred method of monitoring ketogenesis.<sup>4,18</sup> This method, however, is not universally available. Instead, ketones are frequently measured using a nitroprusside method. This will detect acetoacetate and acetone, but not  $\beta$ -hydroxybutyrate, in the blood or urine. Using the nitroprusside method, appropriate insulin therapy may result in a paradoxical rise in total serum ketones as the unmeasurable β-hydroxybutyrate is converted to the measurable acetoacetate. In the absence of directly measuring β-hydroxybutyrate, the resolution of the ketoacidosis may be followed by monitoring the anion gap and total carbon dioxide rather than the level of serum ketones. As the remaining ketones are excreted in the urine, the anion gap will normalize. The acidosis will resolve as bicarbonate is regenerated by the kidney. Interestingly, ketonemia and ketonuria may persist for more than 36 hours despite resolution of the ketoacidosis owing to the slow removal of acetone.

Serum glucose should be monitored hourly with bedside point-of-care testing. Electrolytes, blood urea nitrogen (BUN), venous pH, creatinine, and glucose should be monitored every 2 to 4 hours until stable. Criteria for the resolution of DKA include a serum glucose of less than 200 mg/dL, serum bicarbonate at least 18 mEq/L, and venous pH greater than 7.3.<sup>4</sup>

#### Complications

Careful monitoring for complications is an important aspect of caring for the patient with DKA. The most common complications are relatively minor and easily treated (e.g., hypoglycemia, hyperglycemia, and hypokalemia). Major complications are rare and frequently attributable to underlying medical conditions.

Cerebral edema is an uncommon (0.5% to 1%) but serious complication that primarily develops in children with DKA.<sup>19</sup> Clinical symptoms include headache, behavioral changes, or a decrease in level of consciousness. With progressive edema and brainstem herniation, symptoms may rapidly progress to seizures, coma, and death. If neurologic findings progress beyond lethargy and behavioral changes, the mortality rate is more than 70%, with only 7% to 14% of patients recovering without permanent disability.<sup>19</sup> Treatment is primarily supportive, although mannitol (0.25 to 1 g/kg), and hypertonic saline (3%, 5 to 10 mL/kg over 30 minutes) have been used.<sup>20</sup> This devastating complication can be minimized by gradually correcting the sodium, water, and glucose abnormalities.

Pulmonary edema as the result of overzealous fluid replacement, poor cardiac function, or reduced osmotic pressure occurs occasionally. Supportive care with oxygen and judicious diuretics as needed is generally all that is required.

#### AUTHOR'S RECOMMENDATIONS

- Fluid replacement with normal saline should restore intravascular volume within the first few hours of therapy. Estimated water and sodium deficits should be gradually corrected over the first 24 hours. To minimize the risk for cerebral edema, plasma osmolality should not be reduced by more than 3 mOsm/kg per hour.
- For uncomplicated, mild to moderate DKA, either intravenous insulin or subcutaneous regimens are equally as effective. Intravenous insulin therapy is recommended for severe or complicated DKA.
- Dextrose should be added to the intravenous fluids once serum glucose levels reach 200 mg/dL. Serum glucose levels should be maintained at 200 mg/dL or higher until ketogenesis resolves.
- The intravenous insulin infusion (or the hourly subcutaneous insulin regimen) may be tapered and transitioned to a multipledose subcutaneous insulin schedule when the serum glucose is below 200 mg/dL, the anion gap is less than 12 mEq/L, the serum bicarbonate is greater than 18 mEq/L, and the venous pH is greater than 7.30.
- The resolution of DKA can either be assessed by directly measuring β-hydroxybutyrate or by measuring the serum anion gap.
- Potassium depletion is universal. Supplemental potassium chloride should be given when the serum potassium concentration is 5.3 mEq/L or less. Potassium replacement should be given before starting insulin therapy if the serum concentration is 3.3 mEq/L or less.
- Sodium bicarbonate therapy is rarely indicated in patients with an arterial pH higher than 7.00.
- Routine phosphate supplementation is not supported; however, severe hypophosphatemia (<1.0 mg/dL) should be treated.
- Glucose should be monitored hourly. A basic chemistry profile, plasma osmolality, and venous pH should be measured every 2 to 4 hours until stable.

#### HYPEROSMOLAR HYPERGLYCEMIC STATE

There is a spectrum of hyperglycemic emergencies with significant overlap between DKA and the hyperosmolar hyperglycemia state (HHS). Up to one third of patients with decompensated diabetes have features of both DKA and HHS.<sup>21</sup> Although a variety of terms have been used to describe this disorder, including *hyperglycemic hyperosmolar nonketotic state* and *hyperglycemic hyperosmolar nonketotic coma*, the term *hyperglycemic hyperosmolar state* has been universally adopted in order to capture the range of clinical variability.<sup>22</sup>

Most patients with HHS have type 2 diabetes, although 20% of patients presenting with this endocrine emergency

have no previous history of diabetes, according to the ADA 2006 guidelines. Compared with DKA, HHS occurs infrequently and accounts for less than 1% of all diabetes-related hospital admissions. The mortality rate of HHS, however, is much higher (11% versus <5%), especially if coma or hypotension is present.<sup>23,24</sup> Patients usually do not die because of the severe hypertonicity seen in HHS but rather as the result of the comorbidities that may have either precipitated or developed during the treatment of HHS.<sup>25</sup>

The hallmark features of HHS are hyperglycemia (glucose > 600 mg/dL), hyperosmolality (>320 mOsm/kg), and volume depletion, with an average total-body water deficit of 9 L.<sup>26</sup> Unlike DKA, HHS is not associated with a significant acidosis. A mild acidosis may occur (pH > 7.30) but is usually secondary to hypoperfusion, with the generation of lactic acid rather than creation of significant ketoacids. Mild ketonemia, however, does not preclude the diagnosis (see Table 75-1).

#### Pathophysiology

The pathogenesis of HHS is similar to DKA. Traditionally, the relative availability of insulin has been the defining difference between these disorders. In HHS, serum insulin levels may be adequate to prevent the ketogenesis seen in DKA, but not high enough to prevent hyperglycemia. This theory, however, is not supported by measurements of serum insulin. More likely, the lack of ketosis is related to the lower levels of counterregulatory hormones (e.g., glucagon and catecholamines) seen in HHS.<sup>27</sup>

As with DKA, an insulin deficiency coupled with an altered counterregulatory hormone profile leads to increased gluconeogenesis and impaired glucose utilization. As large amounts of glucose saturate the urine, the concentrating capacity of the kidney is impaired, and significant free water diuresis occurs. If adequate fluid intake is preserved and renal perfusion is maintained, major hyperglycemia will not develop. However, if renal function deteriorates because of underlying kidney disease or intravascular volume depletion, plasma glucose levels will markedly rise, and hyperosmolality will develop. Profound hyperglycemia (glucose > 600 mg/dL) and hyperosmolality (>320 mOsm/kg) lead to a robust osmotic diuresis with severe intracellular and extracellular dehydration. Elderly patients are particularly at risk because of an altered thirst response, physical limitations that may impede free access to water, and overall diminished renal function.<sup>28</sup>

#### **Clinical Presentation**

Although HHS typically occurs in elderly patients, it may occur at any age. As with DKA, HHS is frequently associated with a precipitating event such as infection, myocardial infarction, or acute medical illness. The onset of HHS, however, is insidious and usually evolves over the course of days to weeks. Clinical symptoms are primarily related to hyperglycemia (e.g., polydipsia, polyuria, fatigue, and visual disturbances) and profound dehydration (e.g., weakness, anorexia, weight loss, dizziness, confusion, and lethargy). The most common clinical presentation is altered mental status, and neurologic symptoms are frequently seen when the effective plasma osmolality exceeds 230 to 330 mOsm/kg.<sup>29</sup> Central nervous symptoms range from headache to agitation to seizures or coma. Signs of dehydration, tachycardia, and hypotension are universal, and volume contraction may result in acute renal failure. A fever is common and suggests an underlying infection.<sup>30</sup>

Electrolyte deficits are more profound than those seen with DKA but may not be appreciated on the initial chemistry values. Because glucose osmotically draws water out of the intracellular compartment, the serum sodium may initially be low. A normal or elevated serum sodium indicates profound intracellular dehydration. Serum potassium levels may be elevated secondary to the relative lack of insulin despite significant total-body potassium depletion.<sup>4</sup>

#### Therapy

Although there are some important differences that will be emphasized, treatments of DKA and HHS are very similar. The clinical management of HHS involves the evaluation and correction of significant fluid and electrolyte deficits, the institution of insulin therapy, the identification and treatment of precipitating conditions, and the careful monitoring of therapy in order to prevent complications.

#### Fluid and Electrolyte Replacement

Volume resuscitation is the first priority and mainstay of therapy. Volume resuscitation can lower serum glucose by as much as 50% primarily because improved renal perfusion results in increased renal excretion of glucose. Rapid infusion of 1 to 2 L of 0.9% saline in the first several hours may be necessary to correct severe hypovolemia. After this initial resuscitation, a corrected serum sodium should be calculated using the following equation:

Corrected Na<sup>+</sup> = 
$$1.6 (glucose - 100)/100$$

Based on the corrected serum sodium, either 0.9% or 0.45% normal saline can be infused at a rate of 250 to 500 mL per hour, depending on the adequacy of intravascular hydration. It is not uncommon for patients to require between 4 and 6 L of normal saline during the initial phase of resuscitation. The goal is to replace one half of the fluid deficit within the initial 12 hours followed by the remainder over the next 12 to 24 hours.<sup>4</sup> Given the risk for cerebral edema in children, fluid replacement in patients younger than 20 years should be more gradual, and total deficits should be replaced over 48 hours.<sup>31</sup> The free water deficit can be estimated using the follow-ing formula:

Free water deficit = TBW  $\times ([Na_{calc}^+/Na_{normal}^+] - 1)$ ,

where TBW (total-body water) = body weight (kg)  $\times$  0.6 for males (or 0.5 for females).

Elderly patients and those with underlying heart disease should be monitored closely for the development of congestive heart failure. Fluid therapy, however, should not be delayed or diminished for fear of over-resuscitation.

Although the initial potassium levels may be normal or elevated, all patients with HHS have a significant potassium

deficit. After the initial resuscitation and when urine output is at least 50 mL per hour, potassium replacement should be initiated when serum values are between 3.3 and 5.3 mEq/L.

Phosphate and magnesium stores will be decreased, although initial serum levels may be high or normal. As with DKA, there is no evidence that aggressive supplementation is needed unless levels are extremely low.<sup>32</sup>

#### Insulin Therapy

Adequate intravascular volume resuscitation should precede instituting insulin therapy. Premature insulin therapy can shift both glucose and water into the intracellular space and lead to vascular collapse. As with DKA, a potassium level of 3.3 mEq/L or less should be treated before initiating insulin therapy to decrease the risk for profound hypokalemia.

The 2006 ADA consensus statement recommends treating HHS with an initial insulin bolus (0.1 U/kg) followed by a continuous intravenous insulin infusion (0.1 U/kg per hour). If serum glucose does not decrease by 50 to 70 mg/dL within the first hour, the infusion dose should be doubled. When the serum glucose reaches 300 mg/ dL, the insulin infusion should be decreased to 0.05 to 0.1 U/kg per hour. The serum glucose should be maintained between 250 and 300 mg/dL until the plasma osmolality is 315 mOsm/kg and less and the patient is mentally alert (Fig. 75-2).<sup>4</sup> The use of a subcutaneous insulin protocol to treat HHS has not been investigated.

Complete initial evaluation. Check capillary glucose to confirm hyperglycemia. Start IV fluids: 1.0 L of 0.9% NaCl per hour.<sup>†</sup>



**Figure 75-2.** Protocol for the management of patients with hyperosmolar hyperglycemic state (HHS). (*Adapted from the 2006 American Diabetes Association consensus statement. From Kitabachi AE, Umpierrez GE, Murphy MB, Krieshberg RA. Hyperglycemic crisis in adult patients with diabetes: A consensus statement from the American Diabetes Association. Diabetes Care. 2006;29:2739-2748.)* 

When the patient is clinically stable and the episode of HHS has resolved, a subcutaneous insulin regimen may be initiated. To ensure adequate plasma insulin levels, the insulin infusion should be continued for an additional 1 to 2 hours after initiating subcutaneous therapy.<sup>4</sup>

#### Precipitating Factors

Although serious complications are more frequently the result of underlying comorbidities, the pathophysiology and management of HHS have been associated with several complications. Increased hypercoagulability secondary to dehydration and hyperviscosity is associated with an increased risk for thromboembolic events. Vascular complications can be minimized by aggressive hydration and standard prophylaxis with low-dose subcutaneous heparin. Full heparinization is warranted only with clinically evident thromboembolic disease.<sup>36</sup>

The two most common precipitating factors in the development of HSS are inadequate insulin therapy and infection.<sup>33</sup> Because infection is the cause in almost 60% of HHS cases, appropriate cultures should be taken, and antibiotics should be instituted early.<sup>34</sup> Other acute medical illnesses such as myocardial infarction or stroke also may provoke the release of counterregulatory hormones and promote gluconeogenesis. Moreover, any illness that predisposes to dehydration may encourage the development of HHS. Medications that affect carbohydrate metabolism (e.g., glucocorticoids, thiazide diuretics, phenytoin,  $\beta$ -blockers) may play a contributing role.<sup>32</sup> An association with alcohol and cocaine use has been demonstrated.<sup>35</sup>

#### Monitoring Therapy

Serum glucose should be monitored hourly with bedside point-of-care testing. Electrolytes, BUN, creatinine, and glucose should be monitored every 2 to 4 hours until stable. Criteria for the resolution of HHS include a serum glucose between 250 and 300 mg/dL and a plasma osmolality of 315 mOsm/kg or less.<sup>4</sup>

#### Complications

Subclinical rhabdomyolysis is a common finding in patients with HHS and elevated levels of creatinine kinase correlate with increasing osmolality.<sup>37</sup> HHS-induced rhabdomyolysis may contribute to acute renal failure and has been associated with a malignant hyperthermia-like syndrome.<sup>38–40</sup> Although the pathophysiology is unclear, hypophosphatemia has been implicated in the development of rhabdomyolysis. Depleted phosphate stores may result in inadequate adenosine triphosphate concentrations and the loss of cellular membrane integrity and function.<sup>41</sup>

Cerebral edema is a rare but devastating complication that occurs more frequently in children with DKA. Fatal cases, however, have been reported with HHS.<sup>42</sup> Preventive measures include the gradual replacement of sodium and water deficits. Additionally, a glucose level of 250 to 300 mg/dL should be maintained with a dextrose infusion, if necessary, until the patient's mental status normalizes and the hyperosmolarity resolves.<sup>4</sup>

#### AUTHOR'S RECOMMENDATIONS

- Fluid replacement with normal saline should restore intravascular volume within the first few hours of therapy. Estimated water and sodium deficits should be gradually corrected over the first 24 hours. To minimize the risk for cerebral edema, plasma osmolality should not be reduced by more than 3 mOsm/kg per hour.
- Intravenous insulin therapy is recommended, and an initial insulin bolus (0.1 U/kg) followed by a continuous intravenous insulin infusion (0.1 U/kg per hour) should be initiated after fluid resuscitation.
- Dextrose should be added to the intravenous fluids once serum glucose levels reach 300 mg/dL. Serum glucose levels should be maintained between 250 and 300 mg/dL until the osmolality is 315 mOsm/kg or less and the patient is mentally alert.
- Potassium depletion is universal. Supplemental potassium chloride should be given when the serum potassium concentration is 5.3 mEq/L or less. Potassium replacement should be given before starting insulin therapy if the serum concentration is less than 3.3 mEq/L.
- Routine phosphate supplementation is not supported; however, severe hypophosphatemia (<1.0 mg/dL) should be treated to decrease the risk for rhabdomyolysis.
- Glucose should be monitored hourly. A basic chemistry profile, plasma osmolality, and venous pH should be measured every 2 to 4 hours until stable.

#### **THYROTOXIC CRISIS**

Thyrotoxic crisis, or thyroid storm, is an acute, potentially life-threatening state that typically occurs in patients with untreated or partially treated hypothyroidism. Although the incidence of hyperthyroidism ranges between 0.05% and 1.3%, only 1% to 2% of patients with thyrotoxicosis develop thyroid storm.<sup>43–45</sup> Signs and symptoms of thyroid storm are essentially exaggerated features of hyperthyroidism, including fever (>38.5°C), significant tachycardia, hypertension, altered mental state, agitation, nausea, vomiting, diarrhea, and in severe cases, jaundice. If left untreated, the mortality from thyroid storm can be extremely high (90%). With early management, the mortality rate is less than 20%.<sup>45,46</sup>

#### Pathophysiology

Thyroid hormone secretion is tightly regulated by the hypothalamic-pituitary-thyroid axis. Thyrotropin-releasing hormone (TRH) is released from the hypothalamus and stimulates the synthesis and secretion of thyroid-stimulating hormone (TSH). TSH, in turn, controls the synthesis and secretion of the thyroid hormones, thyroxine (T<sub>4</sub>) and triiodothyronine (T<sub>3</sub>). More than 99.5% of T<sub>4</sub> and T<sub>3</sub> are protein bound in the serum and are, thus, metabolically inactive. The small percentage of free T<sub>4</sub> and T<sub>3</sub> influences metabolic function and modulates the release of both TRH and TSH using a negative-feedback system.<sup>47</sup>

Interestingly, although the thyroid gland primarily produces  $T_4$ , this is a biologically inactive hormone. To gain biologic function,  $T_4$  must be converted to the active hormone  $T_3$  in peripheral tissues such as the kidney and

liver. More than 80% of the available  $T_3$  is synthesized through this extrathyroidal deiodination process. Thyroid hormone exerts cellular control when  $T_3$  directly binds to cytoplasmic thyroid hormone receptor complexes. In the presence of additional regulatory elements, these complexes migrate to the nucleus and directly activate or inhibit transcription of genes that modulate cellular metabolism, adrenergic responsiveness, and thermoregulation.<sup>48</sup>

The excessive levels of  $T_4$  and  $T_3$  seen in hyperthyroidism typically result from an overproductive thyroid nodule or gland. Less commonly, excessive pituitary secretion of TSH or the overingestion of thyroid hormone can result in hyperthyroidism.<sup>49</sup>

The pathologic transition from hyperthyroidism to thyroid storm is not fully understood but usually is associated with a precipitating event such as surgery, sepsis, injury, or other acute medical illness.<sup>50</sup> Although total thyroid hormone levels may not be significantly higher than those observed in uncomplicated thyrotoxicosis, higher levels of free thyroid hormone and lower levels of binding protein have been demonstrated.<sup>51</sup> Elevated catecholamines in acute illness or trauma may further stimulate the synthesis and release of thyroid hormone, which in turn promotes the upregulation of  $\beta$ -adrenergic receptors and enhances the catecholamine effect.<sup>52</sup>

#### **Clinical Presentation**

Thyroid storm can occur in the setting of hyperthyroidism from any cause but most frequently occurs as a complication of Graves disease. Most patients will have a precipitating event such as infection or trauma that triggers a transition from stable hyperthyroidism to thyrotoxic crisis (Table 75-2). Classically, patients with thyroid storm present with fever (>38.5°C) and profound tachycardia. Other cardiac findings may include atrial fibrillation, congestive heart failure, hypotension, and shock.<sup>53</sup> Gastrointestinal symptoms may include nausea, vomiting, diarrhea, diffuse abdominal pain, and occasionally, liver failure.<sup>54</sup> Gastrointestinal fluid losses may be profound, and dehydration may contribute to multiorgan failure. Central nervous symptoms are common and range from confusion to psychosis to coma.<sup>47</sup> Younger patients are able to tolerate this hypermetabolic state better than older patients. Elderly patients are more likely to present with atrial fibrillation, congestive heart failure, and depressed mental status.<sup>55</sup>

#### Table 75-2 Factors Associated with the Precipitation of Thyroid Storm

- Cessation of anti-thyroid medications
- Iodinated contrast dyes or <sup>131</sup>I therapy
- · Sepsis or infection
- Trauma or burn injury
- Diabetic ketoacidosis
- Pulmonary embolism
- · Myocardial infarction or cerebral vascular accident
- Hypoglycemia
- Childbirth
- Vigorous palpation of thyroid gland
- Emotional stress

An elevated  $T_4$  and decreased TSH are the only laboratory findings needed to make the diagnosis of hyperthyroidism. The transition from uncomplicated hyperthyroidism to thyroid storm, however, can be difficult to determine. Because serum T<sub>4</sub> or T<sub>3</sub> values cannot be used to differentiate thyrotoxicosis from thyroid storm, the diagnosis must be made on clinical grounds. Burch and Wartofsky have developed a clinical scoring system to standardize the diagnosis based on the severity of thermoregulatory dysfunction, central nervous system effects, gastrointestinal-hepatic dysfunction, cardiovascular compromise, and the presence of precipitant history<sup>46</sup> (Table 75-3). A score of 45 or higher is highly suggestive of thyroid storm, a score of 25 to 44 is concerning for impending thyroid storm, and a score less than 25 makes thyroid storm unlikely.

In addition to altered thyroid parameters, patients with decompensated hyperthyroidism frequently have other abnormal laboratory values. These include an elevated BUN and creatinine, anemia, thrombocytopenia, leukocytosis, and hyperglycemia. Liver function tests (e.g., lactate dehydrogenase, transaminases, alkaline phosphatase, and bilirubin) are frequently elevated. As with any acute illness, serum cortisol should be elevated. A normal cortisol value should raise concern for concomitant adrenal insufficiency, especially in the setting of Graves disease.<sup>49</sup>

#### Treatment

The therapeutic goals of treating thyroid storm are to (1) decrease hormone production and secretion, (2) block the conversion of  $T_4$  to  $T_3$ , and (3) antagonize the catecholaminergic effects of thyroid hormone (Table 75-4). Supportive care is essential and best provided in an intensive care environment. Additionally, any precipitating illness should be identified and treated. After resolution of the crisis, a definitive plan for treating the patient's hyperthyroidism is warranted.

#### Decrease Hormone Production and Secretion

Thioamides such as propylthiouracil and methimazole will effectively block new thyroid hormone synthesis within several hours of administration and can be given either orally or as a rectal suspension.<sup>56,57</sup> Propylthiouracil is generally preferred because it also inhibits the peripheral conversion of  $T_4$  to  $T_3$ . Decreased conversion theoretically reduces  $T_3$  levels faster and leads to quicker clinical recovery. Thioamides also have immunosuppressive properties, including decreased expression of anti-thyrotropin receptor antibodies.<sup>47</sup>

Thioamides, however, do not prevent the release of stored thyroid hormone. High-dose iodine administration can acutely block the release of  $T_4$  and  $T_3$ . Either Lugol solution or saturated solution of potassium iodide (SSKI) can be given. Iodine products, however, should only be given after thyroid synthesis has been blocked for several hours. If synthetic function is not adequately inhibited, the iodine bolus will enhance thyroid hormone synthesis and can exacerbate the thyrotoxicosis.<sup>58</sup> Further, the iodine enrichment will complicate postcrisis treatment options. Treatment with radioiodine ablation will need to be

### Table 75-3 Diagnostic Scoring System for Thyroid Storm

Physiologic Parameters	Assigned Points
THERMOREGULATORY DYSFUNCTION	
Temperature (°F)	
99-99.9	5
100-100.9	10
101-101.9	15
102-102.9	20
103-103.9	25
≥104.0	30
CENTRAL NERVOUS SYSTEM DYSFUNC	ΓΙΟΝ
Absent	0
Mild (agitation)	10
Moderate (delirium, psychosis, extreme lethargy)	20
Severe (seizures, coma)	30
GASTROINTESTINAL-HEPATIC DYSFUNC	TION
Absent	0
Moderate (nausea, vomiting, diarrhea, abdominal pain)	10
Severe (unexplained jaundice)	20
CARDIOVASCULAR DYSFUNCTION	
Tachycardia (beats/min)	
90-109	5
110-119	10
120-129	15
≥140	25
CONGESTIVE HEART FAILURE Absent	0
Mild (pedal edema)	5
Moderate (bibasilar rales)	10
Severe (pulmonary edema)	15
Atrial fibrillation	
Absent	0
Present	10
PRECIPITATING EVENT	
Absent	0

Adapted from Burch HB, Wartofsky L. Life-threatening thyrotoxicosis: Thyroid storm. Endocrinol Metab Clin North Am. 1993;22:263-77.

10

Present

delayed until the iodine load is cleared, and enriched thyroid hormone stores increase the risk for recurrent perioperative thyroid storm.

Iopanoic acid and other iodinated oral radiographic contrast agents have extremely high iodine concentrations and can be used instead of iodine solutions. In addition to decreasing thyroid hormone release, these agents attenuate the effects of thyroid hormone by decreasing the hepatic uptake of  $T_4$ , inhibiting the peripheral conversion of  $T_4$  to  $T_3$ , and blocking the cellular binding of  $T_4$  and  $T_3$ .<sup>49</sup> Thyroid synthesis should be blocked before use to prevent enriched thyroid hormone production.

Lithium carbonate also can block the formation and release of thyroid hormone and is an option for patients who are allergic to iodine. Serum lithium levels should be checked daily with the goal of maintaining the concentration between 0.6 and 1.0 mEq/L.<sup>47</sup> Because of this narrow therapeutic window, lithium is not considered a first-line therapy.

#### Decrease Peripheral Conversion of $T_4$ to $T_3$

Glucocorticoids can effectively reduce the peripheral deiodination of  $T_4$  to  $T_3$  and may be helpful in treating underlying Graves disease. Given the risk for coexisting adrenal insufficiency, it has become standard practice to treat severe thyrotoxicosis with glucocorticoids, and even with "normal" cortisol level, steroid therapy may improve survival.<sup>59,60</sup>

In addition to their effects on thyroid hormone formation and release, both PTU and iopanoic acid decrease the peripheral deiodination of  $T_4$  to  $T_3$ . Cholestyramine also can reduce circulating thyroid hormone by inhibiting binding hormone secreted into the gastrointestinal tract and inhibiting enterohepatic recirculation.<sup>61</sup> As a final option, there are case reports describing the use of plasmapheresis, hemoperfusion, and plasma exchange as methods for rapidly reducing thyroid hormone levels in critically ill patients.<sup>62–64</sup>

#### Antagonize Adrenergic Effects of Thyroid Hormone

β-Adrenergic blockade remains a mainstay of therapy but should be used cautiously in patients with congestive heart failure. Propranolol (either orally or intravenously) is the preferred agent. In addition to its antiadrenergic effects, propranolol also inhibits the peripheral conversion of T<sub>4</sub> to T<sub>3</sub>. Alternatively, esmolol can be used when rapid titration is needed to minimize potential side effects.<sup>65</sup> After the initiation of β-blockade therapy, patients demonstrate remarkable and rapid clinical improvement. In addition to the expected cardiac effects, there is marked improvement in agitation, confusion, psychosis, diaphoresis, diarrhea, and fever.<sup>49</sup>

Diltiazem, a calcium channel antagonist, may provide an alternative method of controlling adrenergic symptoms. In two small clinical trials, diltiazem improved the signs and symptoms of hyperthyroidism and was as effective as propranolol.<sup>66,67</sup> Although its use in thyroid storm has not been rigorously investigated, diltiazem may be an option when  $\beta$ -blockade is contraindicated.

Reserptine and guanethidine are both antiadrenergic agents that inhibit the formation and release of catecholamines. Before the development of  $\beta$ -receptor antagonists, these agents were frequently used to treat thyrotoxicosis. Side effects such as hypotension, diarrhea, and sedation, however, limited their utility.

Medication	Mechanism of Action	Dosage			
Propylthiouracil	Inhibits new hormone synthesis; decreases $T_4$ to $T_3$ conversion	200 to 400 mg PO q 6-8 hr			
Methimazole	Inhibits new hormone synthesis	20-25 mg PO q 6 hr			
Lugol solution	Blocks release of hormone from gland	4-8 drops PO q 6-8 hr			
Saturated solution of potassium iodide (SSKI)	Blocks release of hormone from gland	5 drops PO q 6 hr			
Iopanoic acid	Blocks release of hormone from gland; inhibits $T_4$ to $T_3$ conversion	1 g PO q 8 hr for 24 hr, then 500 mg PO q 12 hr			
Lithium carbonate	Blocks release of hormone from gland; inhibits new hormone synthesis	300 mg PO q 8 hr			
Cholestyramine	Decreases enterohepatic resorption of thyroid hormone	4 g PO qid			
Propranolol	$\beta\text{-}Adrenergic blockade; decreases T_4 to T_3 conversion$	1-2 mg IV q 10-15 min 20-120 mg PO q 4-6 hr			
Esmolol	β-Adrenergic blockade	50-100 μg/kg/min			
Diltiazem	Decreases adrenergic symptoms	5-10 mg/hr IV 60-120 mg PO q 6-8 hr			
Reserpine	Decreases secretion of catecholamines	2.5-5 mg IM q 4-6 hr			
Guanethidine	Decreases secretion of catecholamines	30 to 40 mg PO q 6 hr			
Hydrocortisone	Decreases $T_4$ to $T_3$ conversion; vasomotor stability	100 g IV q 8 hr			

#### Table 75-4 Pharmacologic Management of Thyroid Storm

#### Supportive Care

Supportive care is essential and should be provided in an intensive care environment. Many patients require vigorous fluid resuscitation as the result of vomiting, diarrhea, hyperpyrexia, and diaphoresis. Patients with cardiac dysfunction or congestive heart failure, however, may require less fluid or even diuresis. If hypotension persists despite adequate volume resuscitation, vasopressors may be needed, and hydrocortisone supplementation should be strongly considered. In addition to dramatically improving vasomotor tone, glucocorticoids temporize thyroid storm by inhibiting the conversion of  $T_4$  to  $T_3$ .

Hyperpyrexia should be treated with external cooling methods and acetaminophen. Aspirin can inhibit hormone-protein binding, increase free hormone levels, and worsen the crisis.

#### Precipitating Factors

An infection or acute medical illness may precipitate the development of thyroid storm. Thyrotoxicosis, however, can also be exacerbated by events or acute illnesses associated with an increase in circulating catecholamines (e.g., surgery, trauma, sepsis, pregnancy, emotional stress) or the use of sympathomimetic medications (e.g., pseudo-ephedrine, cocaine).<sup>68</sup>

Interestingly, Sherman and colleagues conducted a retrospective study of patients hospitalized for thyroid storm in order to determine whether clinical and socioeconomic factors influenced the development of complicated thyrotoxicosis. Almost half of the 95 patients studied had been previously diagnosed with hyperthyroidism but were noncompliant with their prescribed medication. Patients who were poor and uninsured were at higher risk for developing complicated hyperthyroidism. These authors suggested that barriers to health care may contribute to noncompliance, diagnostic delays, and worse outcomes.<sup>69</sup>

#### **Definitive Treatment**

After resolution of the acute events, patients with a history of thyroid storm should undergo definitive treatment. Depending on the etiology, patients with hyperthyroidism are often treated with either radioactive iodine ablation or surgical thyroidectomy. If iodine was used in management of the acute crisis, radioactive ablation should be postponed several months until the iodine stores are depleted. Surgical resection can be performed after treatment with iodine, although there is an increased risk for perioperative thyroid storm. This risk is substantially decreased if thyroid hormone levels are carefully monitored and normalized before surgery.

#### **AUTHORS' RECOMMENDATIONS**

- Thyroid storm is a rare condition that presents with exaggerated features of hyperthyroidism.
- Thyroid function tests cannot be used that differentiate thyrotoxicosis from thyroid storm. The diagnosis relies on clinical presentation.

- Pharmacologic treatment of thyroid storm includes a thioamide to decrease hormone synthesis, a β-blocker to antagonize the adrenergic effects, a steroid to decrease peripheral hormone conversion, and occasionally iodine to prevent hormone release.
- Propylthiouracil is generally the preferred thioamide because it decreases thyroid hormone synthesis, inhibits the peripheral conversion of  $T_4$  to  $T_3$ , and exhibits immunosuppressive effects.
- Propranolol is the preferred β-adrenergic antagonist. In addition to its antiadrenergic effects, it inhibits peripheral conversion of T<sub>4</sub> to T<sub>3</sub>. Clinical improvement, including decreased heart rate, decreased agitation, and decreased fever, can be seen within minutes to hours of initiating therapy.
- Hydrocortisone is given for the increased risk for concomitant adrenal insufficiency and to inhibit the peripheral conversion of T<sub>4</sub> to T<sub>3</sub>.
- The use of inorganic iodine is effective at preventing the release of thyroid hormone but may complicate the definitive management of the patient's hyperthyroidism.
- Intensive care is essential and includes fluid resuscitation, cardiac monitoring, cooling measures, and acetaminophen. Aspirin can worsen thyroid storm by inhibiting hormone-protein binding.
- A precipitating factor (e.g., infection, acute illness, medication) should be investigated. Barriers to health care, including poverty and lack of insurance, may increase the risk for complications.
- After resolution of the crisis, patients should be evaluated for definitive management (e.g., radioiodine ablation or surgical thyroidectomy).

#### MYXEDEMA COMA

Myxedema coma is the result of severe, decompensated hypothyroidism leading to a depressed mental status, hypotension, and hypothermia. It is a serious, but rare, medical emergency that carries a high mortality rate (30% to 60%), even with early diagnosis and appropriate therapy.<sup>70,71</sup> Elderly patients and those with cardiac disease are particularly at risk. Myxedema coma can occur insidiously as the result of severe long-standing hypothyroidism, or it can be precipitated by an acute event such as infection, myocardial infarction, cold exposure, or certain medications (e.g., opiates, lithium, amiodarone). Because hypothyroidism is eight times more common in women and frequently occurs in the later decades of life, most patients presenting with myxedema coma are elderly women.<sup>71</sup>

#### Pathophysiology

Thyroid hormone is critical for cellular metabolism, and all organ systems are affected if hypothyroidism is severe and prolonged. Decreased thyroid function results in a depressed basal metabolic rate, decreased oxygen consumption, and impaired energy production. The cardiovascular system is particularly susceptible. Decreased  $\beta$ -adrenergic responsiveness and diminished thermogenesis lead to increased systemic vascular resistance, diastolic hypertension, and decreased blood volume.<sup>72,73</sup> Additionally, depressed myocardial contractility and bradycardia result in low cardiac output, profound hypotension, and diminished cerebral perfusion.<sup>74</sup> Primary hypothyroidism occurs when there is permanent loss or atrophy of thyroid tissue and accounts for 90% to 95% of cases of myxedema coma. Most patients have an elevated serum TSH level and low free  $T_4$  values. Myxedema coma secondary to hypothalamic or pituitary dysfunction (central hypothyroidism) is extremely rare and occurs in less than 5% of cases.<sup>71</sup> These patients have a normal or low TSH value in the setting of a low free  $T_4$  concentration.

#### **Clinical Presentation**

Patients with myxedema coma demonstrate the classic features of severe hypothyroidism, including dry skin, thin hair, periorbital swelling, nonpitting edema of the hands and feet, a hoarse voice, macroglossia, and delayed deep tendon reflexes. Progression to myxedema coma, however, is characterized by mental status changes and hypothermia. Despite the name, patients do not typically present in coma. More commonly, they are confused, lethargic, obtunded, or frankly psychotic.<sup>75,76</sup> Focal and generalized seizures have also been reported.<sup>77</sup>

Hypothermia is universal and often the first clinical indication of myxedema coma. In a retrospective review of 24 patients, 88% presented with a temperature lower than  $94^{\circ}F/36.6^{\circ}C$ , and core temperatures of less than  $80^{\circ}F/26.6^{\circ}C$  have been reported.<sup>78</sup> The mortality of myxedema correlates directly with the degree of hypothermia, and a core temperature of less than  $90^{\circ}F/32.2^{\circ}C$  is associated with a worse prognosis.<sup>71</sup>

Cardiovascular findings include bradycardia and depressed cardiac contractility. Although decreased thermogenesis initially leads to vasoconstriction, patients frequently present with hypotension as the result of decreased intravascular volume and cardiovascular collapse.<sup>74</sup> Without the administration of thyroid hormone, profound hypotension may be refractory to vasopressor support.

Central depression and respiratory muscle weakness result in hypoventilation, respiratory acidosis, and hypoxemia.<sup>79,80</sup> Most patients require mechanical ventilation for at least the initial 24 to 48 hours of therapy, although some may require support for several weeks.<sup>71</sup>

Gastrointestinal complaints are common in patients with myxedema coma. Anorexia, nausea, abdominal pain, constipation, and decreased gastrointestinal motility may limit the use of oral medications and enteral nutrition. Given the risk for malabsorption, all medications, including thyroid hormone, should be given intravenously.

Laboratory values are often notable for hyponatremia and hypoglycemia. Low serum sodium results from excessive vasopressin secretion and impaired free water excretion.<sup>81,82</sup> Significant hyponatremia ( $\leq 125 \text{ mEq/L}$ ) is common and may contribute to mental status changes. Decreased gluconeogenesis and hypoglycemia may occur with hypothyroidism alone or in conjunction with adrenal insufficiency.<sup>83</sup> Although infection is frequently a precipitating cause of myxedema coma, an elevated white blood cell count is frequently absent, although a left shift may be observed.

#### Therapy

Given the lethality of untreated myxedema coma, therapy should be instituted without waiting for laboratory confirmation. Before initiating therapy, however, thyroid function tests should be drawn. In addition to measuring serum TSH and free T<sub>4</sub>, a cortisol level should be obtained to investigate the possibility of concurrent adrenal insufficiency. Appropriate hormonal supplementation will normalize the basal metabolic rate and reverse all symptoms and signs of hypothyroidism.<sup>84</sup> Although significant clinical improvement should occur within hours to days, some neuromuscular and psychiatric symptoms may take months to disappear.<sup>85</sup>

#### Hormonal Replacement Therapy

Because myxedema coma is a rare condition, there are no randomized clinical trials comparing different treatment regimens, and the optimal strategy for thyroid replacement remains controversial. Although thyroid hormone therapy is critical for survival, rapid replacement may precipitate cardiac arrhythmias or myocardial ischemia. As such, therapy should be tailored in elderly patients and in those with a cardiac history. Additionally, thyroid replacement may unmask coexisting adrenal insufficiency and precipitate an adrenal crisis.<sup>86</sup> Hydrocortisone should be given in conjunction with thyroid replacement for several days and then tapered based on clinical improvement and assessment of adrenal function.<sup>71</sup>

Because the deiodinase conversion of T<sub>4</sub> to T<sub>3</sub> is impaired in severe hypothyroidism, intravenous T<sub>3</sub> may be preferable given its greater biologic availability. T<sub>3</sub> rapidly achieves effective tissue levels and may positively affect survival.<sup>87</sup> Moreover, T<sub>3</sub> crosses the blood-brain barrier more readily than  $T_4$  and may hasten the improvement of neurologic symptoms.  $^{88}$  Both temperature and oxygen consumption increase within 2 to 3 hours after administration of intravenous T<sub>3</sub>, and significant clinical improvement can be seen within 24 hours of initiating therapy.<sup>89</sup> The rapid onset of T<sub>3</sub> may increase the risk for treatment-associated complications such as myocardial infarction or arrhythmias. In a small retrospective study of 11 patients with myxedema coma, mortality was associated with increased age and high serum T<sub>3</sub> concentrations during treatment.<sup>90</sup> This study estimated, but did not directly measure, serum T<sub>3</sub> levels. Nonetheless, caution is warranted in elderly patients and those with cardiac disease. Intravenous  $T_3$  can be given as an initial 10- to 20-µg dose, followed by 10 µg every 4 hours for the first 24 hours and then 10 µg every 6 hours for 1 or 2 additional days. With clinical improvement, patients can be transitioned to oral thyroid replacement.

Treatment with intravenous  $T_4$  is associated with a slower onset of action because the patient's inherent tissue deiodinase activity is required to convert  $T_4$  to  $T_3$ . Although significant clinical improvement may take 1 to 3 days, the slower onset of action theoretically decreases that likelihood of cardiac complications. In a small randomized trial of 11 patients, a loading dose of 500 µg of  $T_4$  followed by a daily dose of 100 µg was associated with a

lower mortality rate than daily treatment (100  $\mu$ g) without a loading dose. This small study, however, was underpowered, and mortality differences did not reach statistical significance.<sup>91</sup>

A third treatment option is to supplement both  $T_4$  and  $T_3$ . In theory, this provides  $T_3$  at a subtherapeutic dose for immediate action as well as a loading dose of  $T_4$ .  $T_3$  is given as an initial intravenous dose of 10 µg, followed by 10 µg every 8 to 12 hours until there is clinical improvement and the patient is able to take maintenance oral doses of  $T_4$ . Additionally, a loading dose of 200 to 300 µg of  $T_4$  is given intravenously, followed by 100 µg 24 hours later, and then a daily dose of 50 µg. The daily maintenance dose should then be adjusted based on laboratory findings and clinical improvement. Although there are no clinical studies validating this approach, this regimen attempts to provide physiologic balance between efficacy and safety.<sup>71</sup>

#### Hemodynamic Support

Hypotension is common and arises from both volume depletion and low circulating thyroid hormone. Patients should be resuscitated with isotonic fluids. The initiation of thyroid hormone therapy will improve the patient's hemodynamic status, but significant clinical improvement may take hours to days. After judicious fluid resuscitation, severe hypotension may require vasopressor support until therapeutic hormone levels are reached. Supplemental hydrocortisone may also improve hemodynamic stability.

#### Hypothermia

The core body temperature should be monitored using a low reading thermometer to achieve accurate measurements. Hypothermia should be treated gradually with passive rewarming techniques, including a heating blanket, warmed intravenous fluid, and a heated ventilatory circuit. Actively rewarming the patient should be avoided because this may promote vasodilation and worsen hypotension.

#### Fluids and Electrolytes

Patients in myxedema coma frequently have fluid and electrolyte abnormalities. They may be hyponatremic and hypervolemic as a result of excessive vasopressin production, or they may be hypotensive and intravascularly dry. Hypotensive patients should be resuscitated with isotonic saline. If the serum sodium concentration is less than 120 mEq/L, a small volume of hypertonic saline (3% sodium chloride) can be used. Hyponatremia in the normotensive patient should be treated with fluid restriction. Supplemental dextrose should be added to all maintenance fluids.

#### Precipitating Factors

The presence of a precipitating infection or concurrent acute illness should be investigated. The initial evaluation should include a chest radiograph, complete blood count with a differential, chemistry panel, cardiac enzymes, electrocardiogram, urinalysis, blood cultures, arterial blood gas, and head computed tomography scan. Typical signs of infection (e.g., fever, tachycardia) may not be present in the patient with myxedema coma, and patients who die often have unrecognized infection and sepsis.<sup>71</sup> Given the possibility of underlying infection, empirical antibiotics are warranted until cultures are proved negative.

Hypothyroidism alters the metabolism of sedatives, narcotics, antidepressants, hypnotics, and anesthetics. These medications can either precipitate or worsen the symptoms of myxedema. Because of the increased risk for sedation and respiratory insufficiency, these medications should be used cautiously in hypothyroidism.

#### Monitoring Therapy

Patients should be carefully monitored for the development of tachyarrhythmias or myocardial ischemia during intravenous thyroid administration. After clinical improvement, intravenous thyroid hormone supplementation can be converted to daily oral dosing (about 1.6 mcg/kg in adults). Initially, TSH and free T<sub>4</sub> levels should be closely followed to prevent overtreatment. After a stable daily dose is adopted, patients should have their thyroid function re-evaluated in 4 to 6 weeks. With primary hypothyroidism, the goal is to restore the TSH value to the low-normal range (about 1.0 mIU/L). In patients with central hypothyroidism, TSH levels will not reflect the adequacy of treatment, and free T<sub>4</sub> levels should be monitored and maintained in the high-normal range.

#### AUTHORS' RECOMMENDATIONS

- Treatment of myxedema coma should be based on clinical suspicion and initiated without waiting for the results of thyroid function tests.
- The optimal strategy for thyroid replacement remains controversial. Regimens include intravenous T<sub>3</sub>, T<sub>4</sub>, or a combination of both hormones. Given the risk for treatment-associated complications (tachyarrhythmias, myocardial ischemia), cardiac monitoring is mandatory. Dosing should be adjusted in elderly patients and those with a history of cardiac disease.
- Until the possibility of a concurrent adrenal insufficiency has been excluded, intravenous hydrocortisone should be given in conjunction with thyroid hormone replacement.
- Underlying infection or sepsis is common, and an aggressive investigation is warranted. Empirical antibiotics should be initiated until cultures are proved negative.
- Supportive care is essential to survival and includes passive rewarming, hemodynamic support with isotonic fluids and vasopressors if necessary, mechanical ventilation, supplemental dextrose, and empirical antibiotics. Treatment of myxedema coma is best provided in an intensive care environment.
- Hyponatremia should be anticipated and may contribute to an altered mental status. Hypotonic fluids should be avoided. The patient's intravascular volume status should guide resuscitation with isotonic fluids or hypertonic saline. Fluid restriction may be necessary to correct the hyponatremia.

#### NONTHYROIDAL ILLNESS SYNDROME (SICK EUTHYROID SYNDROME)

Nonthyroidal illness syndrome is a common, albeit very controversial, diagnosis in the ICU. When measured, most hospitalized patients have low serum T<sub>3</sub> concentrations, and interpreting thyroid function tests in critically ill patients can be challenging. During illness and starvation, serum thyroid hormone levels decline in direct proportion to the severity of illness. With mild illness, only T<sub>3</sub> levels drop. As the severity of the illness increases, however, a decrease in both  $T_3$  and  $T_4$  is observed. Previously, these changes in thyroid function were considered an adaptive means of decreasing unnecessary energy expenditure, and the term *euthyroid sick syndrome* was coined.<sup>92</sup> Increasing evidence suggests that the thyroid abnormalities seen in critical illness may, in fact, reflect a maladaptive state of central hypothyroidism.<sup>93</sup> As such, the designation of euthyroid sick syndrome has been abandoned in preference of the more metabolically neutral term nonthyroidal illness syndrome (NTIS).

#### Pathophysiology

There is significant controversy regarding the pathophysiology and significance of NTIS. Under normal conditions,  $T_4$  is converted by tissue 5'-monodeiodinase to  $T_3$ , a metabolically active hormone. During periods of carbohydrate deprivation or illness, an alternative pathway of deiodination predominates, and  $rT_3$ , a biologically inactive hormone, is created.<sup>94,95</sup> Additionally, the clearance of  $rT_3$  is impaired because of the inhibited 5'-monodeiodinase activity.<sup>96</sup> High circulating levels of proinflammatory cytokines and increased serum cortisol concentrations may promote this shift in deoidination.<sup>97–100</sup> Additionally, medications frequently used in the ICU (e.g., amiodarone, glucocorticoids, propranolol) contribute to depressed  $T_3$ concentrations by inhibiting tissue 5'-monodeiodinase activity (Fig. 75-3).



**Figure 75-3.** Changes in the hypothalamic-pituitary-thyroid axis in critical illness. TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone. (*Adapted from Peeters RP, Debaveye Y, Fliers E, Visser TJ. Changes within the thyroid axis during critical illness.* Crit Care Clin. 2006;22:41-55.)

With increasing severity of illness, both serum  $T_3$  and  $T_4$  concentrations become depressed. Low  $T_4$  levels may be related to a concurrent decrease in thyroxine-binding globulin (TBG) production, poor  $T_4$ -globulin binding, an increase in TBG cleavage, or a decrease in  $T_4$  production.<sup>93</sup> Free  $T_4$  concentrations theoretically reflect the amount of hormone available at the tissue level. However, assays vary in their reliability, and measurements may be confounded by low TBG levels, free fatty acids, and medications (e.g., subcutaneous heparin).<sup>101,102</sup>

Suppressed T<sub>4</sub> levels in NTIS also may be caused by a transient state of hypothalamic-pituitary dysfunction or central hypothyroidism.<sup>92</sup> In critically ill patients, TSH concentrations do not appear to reflect the degree of T<sub>4</sub> depression. TSH levels may be normal, mildly decreased, or markedly suppressed. Additionally, the normal diurnal pulsations of TSH may be dampened or lost in NTIS.<sup>93,103</sup> Medications such as glucocorticoids, dopamine, and dobutamine markedly suppress TSH production and may contribute to a state of central hypothyroidism.<sup>104</sup> Recovery from the underlying illness is associated with a normalization of thyroid function, with TSH values recovering before an improvement in T<sub>4</sub> levels is observed.<sup>105</sup>

Regardless of the pathophysiology, NTIS is associated with increased mortality and worse clinical outcome.<sup>106,107</sup> Whether the relationship between NTIS and increased risk for dying is causative or merely an epiphenomenon remains to be determined.

#### **Clinical Presentation**

A characteristic clinical presentation of NTIS is difficult to describe because the diagnosis represents a spectrum of thyroid function abnormalities. Moreover, the clinical features of hypothyroidism are frequently absent or masked by other clinical processes. Typically, the diagnosis is entertained in a critically ill patient with findings suggestive of hypothyroidism or in those who fail to make clinical improvement. The risk for thyroid dysfunction in critical illness is substantially increased in patients with a history of previous thyroid disease, head or neck irradiation, severe head trauma, Down syndrome, or autoimmune disease. The use of amiodarone, dopamine, glucocorticoids, lithium, interleukin-2, and  $\alpha$ -interferon also increases the risk for hypothyroidism.<sup>104</sup>

Because most critically ill patients have transient or nonspecific abnormalities, routine thyroid function surveillance is not recommended. Thyroid function testing should be reserved for at-risk patients and those whose clinical picture suggests thyroid dysfunction. The diagnosis of NTIS should not be made using a single measurement of thyroid function, and the initial laboratory evaluation includes  $T_3$ ,  $T_4$ , and TSH measurements.

Although  $T_3$  levels are universally low in NTIS,  $T_4$  and TSH values are variable. The diagnosis of thyroid dysfunction, therefore, should be made in the context of the  $T_4$ -TSH relationship. TSH should be measured using a third-generation assay with a functional sensitivity limit of 0.01 to 0.02 mIU/L in order to differentiate NTIS from underlying thyroid dysfunction.<sup>108</sup> Using this more sensitive assay, most hospitalized patients with hyperthyroidism will have a TSH value less than 0.01 mIU/L, and those with NTIS will have values between 0.01 and 0.1 mIU/L.<sup>109</sup> Both total  $T_4$  and free  $T_4$  have been used to evaluate NTIS. Assays for free T<sub>4</sub> theoretically provide information about the concentration of biologically active hormone; however, the technical difficulties of measuring free hormone levels in critical illness may limit its usefulness.<sup>110</sup> T<sub>4</sub> levels in NTIS range from normal to markedly suppressed and correlate with mortality. In one study of 86 ICU patients, a T<sub>4</sub> concentration of less than 3  $\mu$ g/dL (38.7 nmol/L) was associated an 84% mortality rate, whereas a level of more than 5  $\mu$ g/dL (64.5 nmol/L) was associated with only a 15% mortality rate.<sup>111</sup> Because of the dramatically different half-lives of T<sub>4</sub> and TSH (1 week versus 1 hour), measured levels may not represent a steady-state relationship, and any abnormality should be rechecked before initiating therapy.

#### Therapy

The use of supplemental thyroid hormone in NTIS remains controversial. Without treatment, most patients with NTIS normalize their thyroid parameters as they recover from the underlying illness. Nonetheless, because severely ill patients with very low  $T_4$  concentrations are at increased risk for dying, the potential benefit of thyroid hormone supplementation has been investigated. The results, however, do not provide a compelling support for or against supplementation.

Studies investigating the administration of intravenous  $T_4$  have failed to demonstrate any improvement in the mortality or morbidity of critically ill patients.<sup>112,113</sup> Moreover, its use in patients with acute renal failure may be associated with increased mortality.<sup>114</sup> Interestingly, these studies either did not measure serum  $T_3$  or reported persistently low  $T_3$  concentrations. Because the conversion of  $T_4$  to  $T_3$  is inhibited in NTIS, it is not surprising that supplemental  $T_4$  therapy was ineffective.

The results of clinical trials investigating the use of  $T_3$  administration are mixed. In critically ill neonates, daily therapy with  $T_4$  and  $T_3$  was associated with a decreased mortality rate.<sup>115</sup>  $T_3$  administration has been shown to improve cardiac function after cardiac surgery in some studies but not in others.<sup>116–119</sup> Similarly, therapy with  $T_3$  has been associated with improved mortality after cardiac surgery in some studies but not in others, supplemental  $T_3$  may improve pulmonary function in sepsis and does not appear to increase the metabolic demand in burn patients.<sup>121,122</sup>

Van den Berghe and colleagues have suggested that the thyroid function abnormalities seen in prolonged critical illness reflect a maladaptive depression of neuroendocrine drive that should be treated at the hypothalamic level. In a clinical trial of 20 critically ill adult patients, the co-infusion of TRH and growth hormone–releasing peptide-2 resulted in the return of pulsatile TSH secretion and the normalization of thyroid hormone concentrations.<sup>123</sup> Further clinical studies are needed to establish the efficacy and benefit of this treatment strategy in NTIS.

Although administration of  $T_3$  does not appear harmful, the available data do not support the routine use of thyroid supplementation in NTIS. Therapy should be reserved for patients with documented or suspected hypothyroidism and potentially those whose  $T_4$  values (<4  $\mu$ g/dL, 51.6 nmol/L) predict a high mortality rate.<sup>93</sup> The recommended replacement dose of  $T_3$  is 50  $\mu$ g/day given in divided doses. Every 48 hours, levels of total  $T_3$  and  $T_4$  should be measured, and the dose of  $T_3$  should be adjusted to achieve a low normal serum  $T_3$  level. Additionally, it may be appropriate to start oral  $T_4$ , gradually decreasing  $T_3$  administration and increasing  $T_4$  replacement as tissue deiodination improves.<sup>93</sup>

#### AUTHORS' RECOMMENDATIONS

- NTIS is very common in the ICU. With mild illness, only T<sub>3</sub> levels are low. As the severity and duration of the illness increase, a decrease in both T<sub>3</sub> and T<sub>4</sub> is observed.
- Medications frequently used in the ICU can contribute to low thyroid concentrations by markedly suppressing TSH production (e.g., glucocorticoids, dopamine, dobutamine) or by inhibiting the peripheral conversion of T<sub>4</sub> to T<sub>3</sub> (e.g., amiodarone, glucocorticoids, propranolol).
- NTIS is associated with increased mortality and worse clinical outcome.
- Because most critically ill patients have transient or nonspecific abnormalities, routine thyroid function surveillance is not recommended. Testing should be reserved for at-risk patients and those whose clinical picture suggests thyroid dysfunction.
- Initial laboratory evaluation of NTIS should include T<sub>3</sub>, T<sub>4</sub>, and TSH measurements. TSH should be measured using a thirdgeneration assay with a functional sensitivity limit of 0.01 to 0.02 mIU/L to differentiate NTIS from underlying thyroid dysfunction.
- The use of supplemental thyroid hormone in NTIS is controversial, and there is no compelling support for or against supplementation.
- Therapy should be reserved for patients with documented or suspected hypothyroidism and potentially those whose  $T_4$  values (<4  $\mu$ g/dL, 51.6 nmol/L) predict a high mortality rate.
- If therapy is initiated,  $T_3$  should be supplemented at 50 µg/day given in divided doses. Every 48 hours, levels of total  $T_3$  and  $T_4$  should be measured, and the dose of  $T_3$  should be adjusted to achieve a low-normal serum  $T_3$  level.

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## 76 What Is the Best Way to Sedate Critically III Patients?

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Unlike the clearly defined goals of operating room anesthesia, the goals of sedation in the intensive care unit (ICU) vary widely. As in the operating room, sedation (and analgesia) is frequently administered in critical care settings to allow invasive or painful procedures. However, many other diverse uses exist. These include reducing anxiety, treating pain or delirium, facilitating sleep, preventing harm to self or caregivers, controlling vital signs, preventing consciousness during use of muscle relaxants, and facilitating mechanical ventilation. As a result, existing evidence regarding best ICU sedation practices spans a wide variety of patients, indications, approaches, and end points. Because much of the literature specific to critical care sedation focuses on the mechanically ventilated patient, this chapter specifically addresses the use of sedation and analgesia in intubated patients undergoing mechanical ventilation in an ICU setting. Therefore, we include a review of existing evidence on choice of sedative agents, monitoring of sedative depth, and complications of sedation as well as evidence-based strategies to address those complications.

#### AGENTS

A comprehensive list of agents that have been used to sedate critically ill patients would be too exhaustive for this review. It is likely that any agent capable of depressing central nervous system function has been used. Nevertheless, most intubated, mechanically ventilated patients are sedated using a combination of opioids and benzodiazepines, propofol, dexmedetomidine, or major tranquilizers such as haloperidol. Inhalation agents such as desflurane or isoflurane and barbiturate infusions also have been used in exceptional circumstances.<sup>2</sup>

Because end points to sedative administration are variable and often subjective, few data exist to recommend one sedative over another. Three literature-based observations can be made about individual sedatives. First, although midazolam is a reliable short-term sedative-anxiolytic in operative settings, it becomes much more unpredictable in ICU settings, with clinical effects that linger beyond what would be expected from operating room use.<sup>3</sup> Second, recovery from propofol sedation is more predictable than recovery from sedation with midazolam.<sup>4</sup>

This finding is consistent with the known pharmacology of propofol, which combines a vast terminal volume of distribution with an extensive and rapid metabolism.<sup>5</sup> Finally, individual sedatives may affect the incidence of ICU delirium differently, with dexmedetomidine possibly producing less delirium than lorazepam,<sup>6</sup> and midazolam surfacing as a potential risk factor for delirium.<sup>7</sup> Because the identification of drug-specific differences in ICU sedation is inconsistent with an anesthesia literature that has historically found no clinically meaningful advantage of any one anesthetic over another, further work is required to clarify these findings.

In agreement with the anesthesia literature, however, studies of caregiver satisfaction generally find no difference among specific benzodiazepines or between benzodiazepines and propofol.<sup>8</sup> Likewise, specific sedative agents largely are indistinguishable with respect to the quality or utility of sedation. The development of validated sedation scales, however, may facilitate the identification of clinically relevant differences between agents. Recent observations that some agents may be easier to titrate than others in some circumstances suggests that, as end points to sedation evolve, our ability to clarify the choice of sedative may improve.<sup>6</sup>

Although technically not sedatives, opiates are the mainstay of treatment for pain in the ICU patient. Use of these agents should be strongly considered in any critically ill patient who might be experiencing pain. This is important even if sedatives are being given because low doses of many anxiolytics and sleep-inducing drugs (barbiturates and benzodiazepines, in particular) potenti-ate the perception of pain.<sup>9</sup> The most commonly used opioids are fentanyl and morphine. Disadvantages of these compounds include tachyphylaxis to fentanyl and the production of morphine-6-glucuronide, an active, renally cleared metabolite. For these reasons, hydromorphone has become a popular alternative. Seizureinducing metabolites make meperidine a poor choice for ICU sedation, and rapidly acting opiates such as sufentanil and remifentanil offer no specific advantages. Rapid development of tolerance also makes sufentanil a less attractive alternative. Intermittent administration of longer-acting opiates such as methadone may also have a role, limiting tolerance to more rapidly acting narcotics<sup>10,11</sup> and facilitating the use of opiates in long-term patients in most ICUs.

Less commonly used agents include haloperidol, risperidone, and diphenhydramine. These agents generally serve narrow, problem-focused roles. Haloperidol commonly is used to treat agitation or delirium, and risperidone has been proposed as a substitute for haloperidol to control acute psychosis.<sup>12</sup> Diphenhydramine is used frequently to facilitate sleep. Few data exist to inform the evidence-based use of any of these agents, although in comparative trials, diphenhydramine was not as effective as benzodiazepines.<sup>13</sup>

#### ADMINISTRATION STRATEGIES

Much of currently active research in ICU sedation focuses not on drug selection but on dosing strategy. Issues have included intermittent versus continuous administration, how best to monitor the clinical effect of sedatives, the use of sedation scales, the role of daily sedative interruption, and the coordination of sedation with other ICU strategies such as extubation.

Existing data are unclear on the role of sedation scales in the management of intubated, critically ill patients. Such scales attempt to quantify the depth or efficacy of sedation, usually by correlating observed patient behavior to a predefined set of end points. Because ICU sedation strategies initially evolved from operating room anesthesia, in which experienced anesthesiologists titrate drug doses without established scales, early sedation scales such as the Glasgow Coma Scale and the Ramsay Sedation Scale were adopted (from trauma and research environments, respectively) for ICU use.<sup>14</sup> Ongoing experience with these adopted scales allowed recognition of challenges specific to ICU sedation. These included the need to incorporate assessments of agitation, pain, and multiple dimensions of cognitive function. This experience ultimately produced the Richmond Agitation-Sedation Scale, currently the most widely used and validated instrument.<sup>15</sup> It should be noted that a number of other scales exist and their familiarity may dictate that they be used in place of the Richmond Agitation-Sedation Scale.

Importantly, all these scales provide additional descriptive richness to evaluate sedation and arousal, facilitate drug titration, improve consistency within and between caregivers, and improve clinical utility. It remains unclear, however, whether such scales improve the care of ICU patients. Few data exist comparing a management strategy using or not; one 1999 study found benefit to sedation scales, but in the context of a system in which decisions to change the level of sedation required the nurse to call the physician before acting.<sup>16</sup> Such a dosing strategy limits the potential effectiveness of non–scale-based decision making and demonstrates the challenges in discriminating between sedation tools and their use in studying the effect of such scales on outcome.

In addition to drug selection and clinical assessment, specific drug dosing strategies play a role. Such strategies include intermittent versus continuous dosing and daily sedative interruption.

When compared with intermittent dosing, a continuously administered and titrated agent should produce a more stable level of sedation. Considerable experience, however, suggests that use of a continuous strategy in the ICU prolongs the sedated state and results in slower emergence compared with approaches in which sedative administration is periodically stopped<sup>17</sup> or in which sedation is administered in intermittent boluses.<sup>18</sup> These observations have led to a general recommendation that sedatives be periodically interrupted to allow accumulated drug to dissipate, allow the patient to periodically regain some degree of consciousness, and facilitate emergence. A relatively large body of evidence recommends this practice and also dispels suggestions that periodically stopping sedative infusions may lead to increased complications because of uncontrolled patient agitation.<sup>19</sup>

The mechanism underlying a more rapid recovery with periodically interrupted sedative dosing is unclear. It appears unlikely that administering operating room anesthesia using such a strategy would lead to more rapid emergence. One possibility is that, in contrast to anesthesiologists in the operating room, who can focus on one patient at a time, caregivers in the ICU must divide their attention among patients. This difference would lead ICU caregivers to maintain deeper levels of sedation (to avoid inadvertent "spikes" in patient activity) than operating room anesthesiologists, who may be more willing to titrate the dose of sedation downward during periods of unstimulating surgical activity. A reluctance to titrate sedatives downward in the ICU could lead to increased drug accumulation and prolonged emergence issues.

Regardless of mechanism, it is likely that prudent use of sedatives in the ICU should include some sort of strategy to decrease the dose of sedatives when they are not clearly needed.

Finally, debate exists regarding the best way to monitor sedative action. As discussed previously, modern sedation scales are better at assessing clinically relevant aspects of sedative effect than their predecessors. Although most ICUs use sedation scales to titrate sedatives, the recent introduction of brain function monitors allows a more quantitative assessment. These devices were initially developed for operating room use but recently have undergone trials in the ICU setting. The results are mixed.<sup>20</sup> Generally, existing data suggest that brain function monitor readings trend with existing, clinical assessments of sedative depth, that they are able to quantify the depth of sedation even when clinical scales have bottomed out, and that high-frequency interference and certain states of neurologic injury can cause these monitors to produce readings that diverge from clinical assessments. Taken together, it is not clear that such monitors add significantly to the use of clinical assessment scales. They may, however, provide additional information when clinical scales cannot be used effectively, for example, when paralytics are coadministered or when the depth of sedation must be quantified even if the patient is already comatose.<sup>21</sup>

#### AUTHORS' RECOMMENDATIONS

Use of sedatives in the ICU differs significantly from use of anesthetics in the operating room. A body of evidence unique to the ICU is now available to guide the sedation of critically ill, mechanically ventilated patients. This evidence can be reasonably summarized as follows:

- Choice of sedative plays little role in ease of use or efficacy of sedation, although propofol appears to promote a more reliable emergence than benzodiazepines. Recent preliminary data suggest that use of dexmedetomidine results in less delirium, but these data have not been confirmed by subsequent trials.
- Because most ICU sedatives do not have analgesic properties, attention to treatment of pain is an important priority when sedating patients.
- Many sedation scales exist, and all have been used successfully. These instruments allow caregivers to communicate using a common language and are useful for charting purposes. Currently, the most widely validated instrument is the Richmond Agitation-Sedation Scale.
- When compared to operating room anesthesia, there is less incentive to titrate sedatives downward in the ICU because caregivers often divide their attention among multiple patients. The daily interruption of sedative administration allows accumulated sedative agent to dissipate, permits the patient to recover consciousness for assessment purposes, and facilitates recovery from the sedated state.

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# What Is the Role of $\alpha_2$ -Adrenergic Receptor Agonists in the Intensive Care Unit?

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Although  $\alpha_2$ -adrenergic receptor agonists were initially introduced into clinical practice as antihypertensive agents, this class of compounds has subsequently found therapeutic applications for alcohol and drug withdrawal, anesthesia, pain management, and sedation of patients in the intensive care unit (ICU). This chapter concentrates on intensive care uses of this class of drug. Such uses have advanced greatly since the development of dexmedetomidine, an agonist that has the greatest  $\alpha_2/\alpha_1$ -adrenergic receptor subtype selectivity. In 1999, dexmedetomidine was approved by the U.S. Food and Drug Administration for use as a sedative for up to 24 hours in critically ill patients. Since then, understanding of both the molecular mechanisms and the clinical application of the unique sedative profile of this class of agents has advanced rapidly.<sup>1</sup> The hallmark of the sedation is a comfortable patient who is easily rousable.<sup>2,3</sup> The versatility of the  $\alpha_2$ -adrenergic receptor agonists is also remarkable; they provide analgesia, anxiolysis, and a blunted stress response without respiratory depression.<sup>4</sup> Finally,  $\alpha_2$ adrenergic receptor agonists also exert organ-protective qualities that potentially add to their already salubrious profile.<sup>5–9</sup> Further clinical studies are required to formally evaluate these organ-protective effects and to understand the extent of their clinical impact.

#### MOLECULAR MECHANISM OF ACTION

Activated  $\alpha_2$ -adrenergic receptors transduce their responses through either cholera-sensitive (Gs) or pertussinsensitive (Gi) coupling proteins. However, the pertussis toxin–sensitive  $\alpha_2$  adrenergic receptors mediate the anesthetic actions.<sup>10</sup> Lakhlani and colleagues used genetically modified mice expressing dysfunctional  $\alpha_{2A}$ -adrenergic receptors to show that  $\alpha_2$ -adrenergic receptor agonist antinociception and sedation were dependent on this receptor subtype.<sup>11</sup> The mutation did not affect morphine analgesia but inhibited dexmedetomidine sedation and analgesia. It has subsequently been shown that the neuroprotective effects of dexmedetomidine also are  $\alpha_{2A}$ -adrenergic receptor dependent.<sup>5</sup>

Activation of  $\alpha_{2A}$ -adrenergic receptors coupled to Gi proteins leads to inhibition of adenylyl cyclase and effects on ligand-gated ion channels, including inhibition of calcium channels and activation of potassium channels and the Na<sup>+</sup>/H<sup>+</sup> antiporter.<sup>4</sup> In aggregate, activation of  $\alpha_{2A}$ -adrenergic receptors reduces neuronal excitability and produces hyperpolarization of cells in key neuronal nuclei that mediate the hypnotic-sedative and analgesic responses.<sup>1,4</sup>

#### ANALGESIA

 $\alpha_2$ -adrenergic agonists provide superior analgesia when administered neuraxially (by regional anesthesia techniques) than via intravenous administration.<sup>12</sup> However, several randomized controlled trials establish that systemically administered dexmedetomidine reduces postoperative opioid requirements.<sup>13–16</sup> In one study of 295 patients after coronary artery bypass grafting, only 28% of patients receiving dexmedetomidine required morphine supplementation for analgesia, as opposed to 69% of patients given propofol (P < .001).<sup>14</sup> In addition, fewer patients in the dexmedetomidine group received nonsteroidal antiinflammatory drugs (P < .001). In this particular paradigm, the sympatholytic properties of  $\alpha_2$ -adrenergic receptor agonists without the side effect of respiratory depression make them attractive opioid-sparing drugs. As analgesicbased sedation is currently considered the optimal method for sedation in the ICU,<sup>17</sup> and the analgesic effects of dexmedetomidine with or without opioid supplementation are an important asset to sedation in this setting.

#### SEDATION

The neural networks underlying dexmedetomidine sedation overlay those responsible for producing non-rapideye-movement (NREM) sleep. In both states, the major pontine noradrenergic nucleus, the locus ceruleus (LC), is inhibited.<sup>1</sup> Activation of the  $\alpha_{2A}$ -adrenergic receptor inhibits neuronal activity in the LC. This leads to
disinhibition (activation) of GABAergic and galaninergic neurons in the ventrolateral preoptic (VLPO) nucleus in the anterior hypothalamus, the nucleus that initiates and maintains sleep.<sup>1</sup> The effect is release of the inhibitory neurotransmitter GABA, leading to the inhibition of excitatory (arousal promoting) histaminergic systems. It is likely that other excitatory systems are inhibited, although at present these have not been further evaluated. Interestingly, gabazine (a GABA<sub>A</sub> antagonist) can attenuate both  $\alpha_2$ -adrenergic receptor agonist and GABAergic (e.g., propofol) drug-induced sedation-hypnosis,<sup>18</sup> yet  $\alpha_2$ -adrenergic receptor antagonists can only reduce  $\alpha_2$ -adrenergic receptor agonist-induced sedation/hypnosis (and not that induced by GABAergic drugs).<sup>19</sup> This is because these GABAergic drugs act downstream of the LC at the tuberomammillary nucleus to potentiate the inhibitory neurotransmission from the VLPO. There are also multiple differences in the quality and type of sedation produced by these two types of drugs. Notably, the electroencephalogram (EEG) and pattern of cerebral blood flow are more similar to natural sleep with dexmedetomidine than with benzodiazepines.<sup>4,20</sup> This suggests that  $\alpha_2$ -adrenergic receptor agonists may produce a more restful state of sedation, with less sleep deprivation, than that produced by other immobilizing agents; sleep deprivation is a significant problem in critical care because it may predispose to immunologic and cognitive compromise.<sup>21</sup>

During both dexmedetomidine sedation and NREM sleep, the arousal system appears intact. This preserved arousal state may have significant utility in the ICU. Daily wake-up trials have been advocated after the demonstration of a shortened duration of ventilation and ICU stay with this sedation strategy.<sup>16,22</sup> Therefore, the use of drugs that facilitate arousability, with the ability to revert to the sedated state when unstimulated, would appear to be particularly attractive.<sup>23</sup> An added advantage is that increased patient arousability also facilitates neurologic assessment of the critically ill patient.

ICU-related delirium occurs in up to 80% of ICU patients and significantly increases patient mortality.<sup>24</sup> Although the etiology of this condition is complex, sedation plays a critical role in its development and represents the most easily modifiable factor. A recent prospective cohort study analyzed the influence of different sedative and analgesic agents on the incidence of delirium. Lorazepam achieved significance as an independent risk factor for precipitating delirium, with other GABAergic and opioid agents, showing a trend toward significance.<sup>25</sup> This finding, combined with advances in the scientific understanding of the critical differences between sedation produced by  $\alpha_2$ -adrenergic receptor agonists and GABAergic agents, <sup>1,18</sup> led to the Maximizing Efficacy of Target Sedation and Reducing Neurological Dysfunction (MENDS) study to evaluate the role of dexmedetomidine in this context.<sup>3</sup>

The MENDS study enrolled 106 patients in a doubleblind randomized controlled trial comparing lorazepam (maximal dose,  $10 \text{ mg/h}^{-1}$ ) and dexmedetomidine (maximal dose,  $1.5 \mu\text{g/kg}^{-1}/\text{h}^{-1}$ ) infusions (maximal duration, 120 hours) on the incidence of delirium and coma in mechanically ventilated patients in the ICU.<sup>3</sup> Remarkably,

patients sedated with dexmedetomidine had more days alive and free of delirium and coma (7 versus 3, P = .01). The prevalence of coma was reduced in dexmedetomidine-treated patients (63% versus 92%, P < .001). There also was a trend toward lower 28-day mortality (17% versus 27%, P = 0.21), although the study was not powered for this end point. This trial may prove to have a large impact on critical care sedation because delirium is also an independent predictor of mortality and prolonged ICU stay.<sup>24</sup> In a secondary analysis of this trial, we found that septic patients sedated with dexmedetomidine had lower mortality rates than their lorazepam-sedated comparators. This impressive finding may be related to effects on inflammation, organ protection, and improved immune function (either by the unique sedative effects of the  $\alpha_2$ -adrenergic receptor agonists or even improved bacterial clearance by macrophages; see later). A further larger study is planned to evaluate the potential benefits highlighted in this trial.

It also is of interest that in a retrospective analysis of postoperative cardiac surgery patients, the addition of dexmedetomidine to sedative regimens was associated with reduced cost, length of hospital and intensive therapy unit stay, length of mechanical ventilation, and mortality (although the dexmedetomidine group was biased toward younger patients).<sup>26</sup>

### HEMODYNAMIC EFFECTS

The ubiquitous expression and distribution of  $\alpha_2$ -adrenergic receptors explains the diversity of responses that occur after administration of  $\alpha_2$ -adrenergic receptor agonists. Their sympatholytic effects are predominantly centrally mediated through the presynaptic inhibition of norepinephrine.<sup>10</sup> Systemic and pulmonary hypertension may occur if these drugs are administered too rapidly or in too high a concentration (an effect mediated by  $\alpha_{2B}$ adrenergic receptors in the periphery).

### ANTI-INFLAMMATORY AND IMMUNOLOGIC EFFECTS

A study of septic animals by Taniguchi and colleagues indicated that activation of  $\alpha_2$ -adrenergic receptors may modulate inflammatory cytokine signaling.<sup>27</sup> These data have been replicated in a small, unpowered clinical study.<sup>28</sup> Serum levels of both interleukin-6 (IL-6) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) were reduced relative to saline<sup>27</sup> in animals and midazolam in patients.<sup>28</sup> A nonsignificant reduction in serum IL-6 levels was noted in an earlier underpowered clinical study.<sup>29</sup> Preoperative clonidine reduced TNF- $\alpha$  levels in plasma and cerebrospinal fluid in patients undergoing peripheral revascularization.<sup>30</sup>  $\alpha_2$ -Adrenergic receptor agonists may also relatively increase the anti-inflammatory mediator IL-10.<sup>31</sup>

To what extent dexmedetomidine's modulation of central cytokine signaling protects against delirium is not known. In fact, the beneficial or possible deleterious effect of modulation of proinflammatory cytokines in the critical care setting is still a matter of significant debate and research. We believe that the presence of a mild antiinflammatory agent may have benefit in settings such as a systemic immune response syndrome, including septic shock. To support this postulate, dexmedetomidine improved hemodynamics in animals treated with lipopolysaccharide.<sup>27</sup> This improved stability correlated with the observed anti-inflammatory effect.

 $\alpha_2$ -Adrenergic receptor agonists also improve phagocytic function of macrophages, increasing clearance of bacteria in vitro,<sup>32</sup> which may, at least in part, explain the mortality benefit we have uncovered in dexmedetomidine-treated septic patients (Pandharipande and colleagues, unpublished observations). However, it is possible that dexmedetomidine also protects against septic organ injury because it has been shown to inhibit pathogenic apoptosis in multiple tissues.

### **ORGAN-PROTECTIVE EFFECTS**

 $\alpha_2$ -Adrenergic receptor agonists can ameliorate cardiac, renal, and neuronal injury in certain paradigms. The importance of these effects in the intensive care environment is only beginning to be realized.<sup>3,4</sup>

### CARDIOPROTECTION

The appropriate use of  $\alpha_2$ -adrenergic receptor agonists provide hemodynamic stability with a negative chronotropic effect and modest hypotension that may be exacerbated in the volume-depleted patient. The sympatholytic properties of  $\alpha_2$ -adrenergic receptor agonists have been used perioperatively in both cardiac and noncardiac surgery to reduce the incidence of postoperative cardiac morbidity and mortality. Wallace and colleagues conducted a prospective randomized, placebo-controlled trial of clonidine to reduce cardiac risk in noncardiac surgery patients.<sup>7</sup> Clonidine significantly reduced plasma epinephrine and norepinephrine levels and the incidence of perioperative myocardial ischemia. Thirty-day and 2-year mortality rates were reduced in the clonidine-treated group, a result comparable to preoperative  $\beta$ -blockade. An earlier meta-analysis supports these findings.<sup>6</sup> This meta-analysis appears to suggest that this is a "class benefit" of  $\alpha_2$ -adrenergic receptor agonists, with the benefit probably accorded by sympatholysis, although myocyte targets may also contribute. Whether improved cardiac outcomes occur in the ICU after sedation with dexmedetomidine awaits investigation.

### RENOPROTECTION

Acute kidney injury (AKI) in the ICU is associated with high morbidity and mortality rates.<sup>33</sup> Thus, significant attention has been given to the maintenance of renal perfusion and glomerular filtration. Hypoxic-ischemic, septic, or inflammatory injury, combined with other factors such as contrast nephropathy, all contribute to AKI in the ICU. Agents that are capable of preventing this injury by providing hemodynamic stability or preventing acute tubular necrosis and apoptosis may be particularly useful.

 $\alpha_2$ -Adrenergic receptor agonists have a well-established diuretic effect as they oppose the action of arginine vasopressin (AVP) in the collecting duct of the nephron.<sup>34</sup> Activation of  $\alpha_{2A}$ -adrenergic receptors, signaling through a reduction in cAMP levels and protein kinase activation, provokes a reduction of aquaporin-2 receptor expression and causes aquaporin-2 receptor redistribution with a consequent reduction in water and sodium transport. A second non–AVP-dependent pathway enhances osmolal clearance.<sup>35</sup> Nonetheless, either increasing free water clearance or changing the solute balance of urine does not necessarily equate to preserved renal function in the face of a renal insult.

In a prospective double-blind randomized controlled trial of 48 cardiac surgical patients, preoperative clonidine  $(4 \,\mu g/kg^{-1}$  intravenously) preserved creatinine clearance on the first postoperative night.<sup>8</sup> A similar report has suggested efficacy with intraoperative administration of dexmedetomidine during coronary artery bypass grafting.<sup>36</sup> Further, a placebo-controlled randomized trial designed to assess postoperative pain control showed that dexmedetomidine-treated patients had lower serum creatinine concentrations for 7 days after surgery than placebotreated controls.<sup>9</sup> Although the etiology of these injuries may represent hypoxia-ischemia, and therefore we should be cautious about extrapolating these findings to the heterogeneous syndrome of AKI, these studies provide early evidence for a renoprotective effect of  $\alpha_2$ -adrenergic receptor agonists.

### NEUROPROTECTION

Extensive preclinical evidence suggests that  $\alpha_2$ -adrenergic receptor agonists provide neuroprotection against a variety of cerebral insults.<sup>4,5</sup>

Administration of dexmedetomidine before a hypoxicischemic neurologic insult significantly lowered plasma catecholamine levels and improved neurologic outcome in rats.<sup>37</sup> Maier and colleagues, in a transient focal model of cerebral ischemia in rabbits, demonstrated a neuroprotective effect even when dexmedetomidine (at a steadystate plasma concentration of 4 ng/mL) was administered after the insult.<sup>38</sup> Recent evidence suggests that dexmedetomidine reduces circulating catecholamine levels but does not alter brain norepinephrine or glutamate levels.<sup>39</sup> This information indicates that the neuroprotective effect may not be due to central noradrenergic mechanisms and suggests a possible post-synaptic mechanism of action (similar to sedative and analgesic responses).<sup>10</sup>

 $\alpha_2$ -Adrenergic receptor agonists also show efficacy in models of perinatal asphyxia. Clonidine reduced the size of hypoxic-ischemic cortical infarct and mortality rate induced by unilateral carotid artery ligation compared with animals treated with the  $\alpha_2$ -adrenergic receptor antagonist yohimbine.<sup>40</sup> Dexmedetomidine also inhibits neuronal injury provoked by oxygen-glucose deprivation

and pharmacologic toxins in vitro and in an in vivo neonatal asphyxia rat model<sup>41</sup>; application of an  $\alpha_{2A}$ -adrenergic receptor antagonist attenuated these effects.

Excitotoxic and apoptotic cell death occur in animal models of neuronal ischemia.  $\alpha_2$ -adrenergic receptor agonists are able to inhibit both modes of injury<sup>4,5</sup> and may also reduce any subsequent inflammatory reaction.<sup>27</sup> Despite the efficacy of these drugs at therapeutic levels, supratherapeutic concentrations of  $\alpha_2$ -adrenergic receptor agonists have been associated with lack of neuroprotective efficacy, and therefore it is important to stay within doses targeted at the  $\alpha_2$ -adrenergic receptor.<sup>42</sup>

### SUMMARY OF INTENSIVE CARE RANDOMIZED CONTROLLED TRIALS

The principal clinical trials evaluating dexmedetomidine sedation in the ICU are outlined in Table 77-1. The development of dexmedetomidine sedation for the ICU has demanded multiple small trials evaluating its sedative and analgesic qualities. Recent phase 4 trials have defined these effects well and demonstrated a reduction in analgesic requirements and satisfactory sedation. One trial also found reduced diuretic requirements and more hemodynamic stability with dexmedetomidine administration,<sup>13</sup> complementing the evidence presented earlier. The MENDS study demonstrated that dexmedetomidinetreated patients had more days alive and more days free of delirium and coma with a reduced prevalence of coma when compared with those sedated with lorazepam. We attribute this finding to the unique sedative profile of dexmedetomidine, although neuroprotective qualities may have contributed. Future studies to further evaluate the effect of dexmedetomidine on delirium, morbidity, and mortality are required.

In one study, dexmedetomidine was not found to improve patient satisfaction compared with propofol for short-term sedation after coronary artery bypass grafting.<sup>43</sup> An advantage may be realized with longer periods of dexmedetomidine sedation because its reduced amnestic capabilities (relative to propofol or the benzodiazepines) may reduce the incidence of posttraumatic stress disorder in the ICU.<sup>16</sup> Long-term follow-up of the critically ill patients treated with dexmedetomidine may reveal this theoretical difference.

### CONCLUSION

The MENDS study has reaffirmed the potential of  $\alpha_2$ adrenergic receptor agonists to significantly alter intensive care practice. Recent advances in the understanding of the importance of analgesic-based sedation and patient arousability have highlighted the role of dexmedetomidine as an ICU sedative. Indeed, dexmedetomidine's unique sedative profile lends it as the ideal sedative agent in the ICU in many circumstances. The ability to protect against organ dysfunction, notably myocardial, renal, and neuronal, may yet prove to be the defining characteristic of this class of drug. Further clinical and preclinical studies are required to inform us about the diversity of therapeutic applications of  $\alpha_2$ -adrenergic receptor agonists. The pivotal role of the  $\alpha_{2A}$ -adrenergic receptor subtype in the analgesic, sedative, sympatholytic, and neuroprotective properties of  $\alpha_2$ -adrenergic receptor agonists indicates that development of more subtype-selective agonists is warranted.

### AUTHORS' RECOMMENDATIONS

- $\alpha_2$ -Adrenergic receptor agonists provide effective analgesia and sedation in the ICU.
- Their unique sedative profile reduces delirium and coma.
- They may provide organ protection, and this requires further evaluation.
- Their side effects are predictable from their pharmacodynamic actions.

Table 77-1 Summary of Randomized Controlled Thats							
Study	No. of Subjects (Intervention/ No Intervention)	Study Design	Intervention	Control	Outcomes		
Pandharipande et al, 2007 <sup>3</sup>	106 (52/51)	DB	Dex	Lorazepam	Dex patients: more days alive and free of coma		
Corbett et al, 2005 <sup>43</sup>	89 (43/46)	OL	Dex	Propofol	No difference in patient satisfaction		
Venn & Grounds, 2001 <sup>13</sup>	20 (10/10)	OL	Dex	Propofol	Dex patients: reduced analgesic, β-blocker, diuretic, epinephrine use		
Herr et al, 2003 <sup>14</sup>	295 (148/147)	OL	Dex	Propofol	Dex patients: reduced analgesic requirements		
Venn et al, 1999 <sup>2</sup>	98 (47/51)	OL	Dex	Saline	Dex patients: reduced analgesic and sedative requirements		

DB, double-blind; Dex, dexmedetomidine; OL, open-label.

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## 78 How Does One Prevent, Diagnose, and Treat Delirium in the Intensive Care Unit?

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Delirium, a disturbance of consciousness and cognition, is associated with increased in-hospital mortality, prolonged hospital stay, and three times the likelihood of discharge to a nursing home.<sup>1</sup> Delirium in the intensive care unit (ICU) results in increased time on mechanical ventilation, increased ICU length of stay, prolonged neuropsychological dysfunction, and increased mortality.<sup>2</sup>

This chapter aims to broadly define delirium, discuss the associated subtypes and risk factors, and provide the basis for clinicians to develop strategies aimed at preventing and treating delirium in their practice settings.

### DEFINITION

Delirium is diagnosed in as many as 20% to 80% of mechanically ventilated patients in medical, surgical, and trauma units.<sup>2–4</sup> Delirium is defined by the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV*) as "a disturbance of consciousness that is accompanied by a change in cognition that develops over a short period of time, usually hours to days, and tends to fluctuate during the course of the day."<sup>5</sup> The most important criteria for the diagnosis of delirium are the temporal relationship to the disturbance and its involvement of both "consciousness" and "cognition," with inattention being an important diagnostic feature.<sup>5</sup>

### MOTORIC SUBTYPES

Delirium has been further differentiated according to the level of alertness; the *motoric* subtypes consist of hyperactive, hypoactive, and mixed subtypes.<sup>6</sup> Distribution of delirium in medical and surgical patients suggests that the hypoactive subtype, characterized by a flat affect, withdrawal, apathy, or lethargy, is the most prevalent. The hyperactive delirious patient is described as agitated, restless, violent, or emotionally labile. Although challenging to manage clinically, the weight of evidence suggests a better overall prognosis for the hyperactive patient compared with the hypoactive delirious patient.<sup>7,8</sup> Nevertheless, two published studies contradict these findings, suggesting either that the hyperactive subtype carries a poorer prognosis<sup>9</sup> or that there is no difference in outcomes by subtype.<sup>10</sup>

### **RISK FACTORS**

Patients in the hospital at a higher risk for developing delirium include patients with dementia, chronic illness, advanced age, existing infection, and depression. Modifiable risk factors such as hypertension, poor nutrition, substance withdrawal, and tobacco use have also been shown to be associated with development of delirium in the hospital.4,11,12 Iatrogenically modifiable factors include hypoxia, metabolic and electrolyte disturbances, infection, dehydration, hyperthermia, sepsis, psychoactive medications, and sleep deprivation<sup>12–14</sup> (Table 78-1). There has been much research on postoperative delirium, especially in those undergoing cardiopulmonary bypass, with a recent retrospective study showing a decreased incidence of delirium in patients receiving statins before their bypass.<sup>15</sup> Additionally, the advent of beating heart surgery without cardiopulmonary bypass appears to confer an advantage in decreasing delirium, suggestive of electrolyte or metabolic disturbances playing a role in the development of delirium.<sup>16</sup>

### PATHOGENESIS

The pathogenesis of delirium is complex, and research is in its infancy. Maldonado has postulated that the different mechanisms that may play a role in delirium are all "complementary, rather than competing" theories.<sup>17</sup>

### Neurotransmitter Imbalance and Cholinergic Deficiency

Imbalances in the normally delicately balanced neurotransmitters are associated clinically with symptoms of delirium.<sup>18</sup> Multiple neurotransmitters, including acetylcholine, dopamine, glutamate,  $\gamma$ -aminobutyric acid (GABA), serotonin (5-HT), and norepinephrine (NE) have been implicated in delirium.<sup>17,19</sup> Disruptions in neurotransmitter homeostasis may lead to decreased or increased excitability of the brain, lending a plausible explanation to the observation that delirium has a variety of presentations, as manifested in its motoric subtypes. The increases in neuron-exciting molecules such as dopamine, norepinephrine,

Table	78-1	Risk	Factors	for De	lirium,	Classified
Accor	ding t	to Lev	el of Po	otential	Modif	ication

Baseline	Patient-	Clinician-
Characteristics	Modifiable	Modifiable
Dementia Chronic illness Advanced age Depression Infection	Hypertension Substance withdrawal Tobacco use Poor nutrition	Hypoxia Metabolic disturbances Infection Dehydration Hyperthermia Sepsis Sedative and analgesics Sleep deprivation

and glutamate, coupled with the decrease in excitability produced by GABA and acetylcholine, can lead to an overall reduction in cholinergic function.<sup>17</sup> These theories are supported biochemically by the additional finding that hypoxia, a factor mentioned later, directly affects acetylcholine levels as well as GABA and glutamate.<sup>20</sup> Acetylcholine alone has been extensively studied, although some studies have not supported it as directly related or specific to delirium.<sup>21</sup>

### Impaired Oxidative Metabolism

Oxygen deprivation in the brain through either hypoxia or hypoperfusion has been implicated in delirium. Engel and Romano discussed delirium as a state of "cerebral insufficiency" as early as 1959, when they showed that delirium was accompanied by diffuse slowing on electroencephalogram (EEG), suggesting a reduction in brain metabolism.<sup>22</sup> This may be further accentuated in the patient who already has compromised blood flow secondary to vascular dementia. Decreases in oxidative metabolism, as well as acetylcholine release, have been demonstrated in the aging brain,<sup>23</sup> and preexisting cognitive dysfunction in the elderly patient, suggestive of chronic changes from vascular insufficiency, has been shown to be the most significant predictor of the development of delirium in the postoperative period.<sup>24</sup>

### Increased Inflammatory Mediators

Inflammatory mediators such as cytokines and chemokines are readily expressed in critical illness, trauma, sepsis, and after surgical interventions. Animal studies have demonstrated that the release of endogenous inflammatory mediators correlates with exacerbated cognitive and motor symptoms<sup>25</sup> and increased vascular permeability in the brain.<sup>26</sup> A small study of 23 patients with sepsis, severe sepsis, or septic shock showed significantly elevated C-reactive protein, S-100 $\beta$ , and cortisol in those patients with delirium compared with those without delirium.<sup>27</sup> These authors further found that cerebral autoregulation was disturbed and that inflammation may impede endothelial function of the cerebral vasculature, thus making the blood-brain barrier more permeable to inflammatory insults.<sup>27</sup>

### Large Neutral Amino Acids

Changes in large neutral amino acids (LNAAs), precursors of many of the neurotransmitters discussed previously, may cross the blood-brain barrier and affect cerebral neurotransmitters, leading to symptoms of delirium.<sup>28</sup> Two particular LNAAs, tryptophan (Trp) and phenylalanine (Phe), have been implicated in delirium.<sup>29</sup> Trp, a precursor to serotonin, competes with other LNAAs for transport across the blood-brain barrier, dictating uptake into the brain and subsequently the level of various neurotransmitters.<sup>30</sup> Levels of Trp have been shown to be lower in elderly postsurgical patients (mostly men), who subsequently developed delirium,<sup>31</sup> whereas both low and high levels of tryptophan have been associated with delirium in ICU patients (Pandharipande et al. Intensive Care Med (2009) 35:1886–1892).

### **RECOGNITION OF DELIRIUM**

Early recognition of delirium is important, if only to avoid lengthening its course through exacerbation by iatrogenic factors. However, delirium remains unrecognized in a large number of patients, reported in some studies as high as 46% to 76% in various settings.<sup>32,33</sup> The standard diagnosis of delirium requires fulfillment of the criteria set forth in *DSM-IV*.<sup>5</sup> However, the time and understanding required to achieve this on an individual basis is impractical. Clinicians must therefore use assessment tools that allow for timely, accurate assessment by a broad range of practitioners in a variety of settings.

Recognition becomes additionally difficult in patients in the ICU setting because patients may have a purposefully altered sensorium secondary to sedation administered for procedures, pain, or mechanical ventilation. Assessment of a patient for delirium therefore becomes a *two*-step process because it is important for the clinician first to establish the current level of sedation *before* assessing the patient for delirium. Examples of scales that can be used to assess sedation include the Ramsay Sedation Scale (RS),<sup>34</sup> the Riker Sedation-Agitation Scale (RAS).<sup>36,37</sup>

Once the level of sedation has been established and the patient is responsive to verbal stimulus, it is then appropriate for the clinician to assess for the presence of delirium. Although there have been multiple instruments validated for use in non-ICU patients, only two are validated for diagnosing delirium in mechanically ventilated patients: the Intensive Care Delirium Screening Checklist (ICDSC)<sup>38,39</sup> and the Confusion Assessment Method for the ICU (CAM-ICU). The CAM-ICU is a scale that is based on the Confusion Assessment Method<sup>40</sup> but amended to increase its applicability in the ICU setting. It takes a trained ICU nurse about 2 minutes to complete the CAM-ICU, and accuracy over a set of 471 paired observations in the ICU setting resulted in an accuracy rate of 98.4% with excellent inter-rater reliability.<sup>41</sup> It is the scale recommended by the

+4	Combative	Overtly combative or violent, immediate danger to staff	ך		
+3	Very agitated	Pulls on or removes tube(s) or catheter(s) or has aggressive behavior toward staff			
+2	Agitated	Frequent nonpurposeful movement or patient-ventilator dyssynchrony			
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous		-	Proceed to Step 2: Delirium
0	Alert and calm				Assessment
-1	Drowsy	Not fully alert, but sustained (>10 seconds) awakening to voice, with eye contact			
-2	Light sedation	Briefly (<10 seconds) awakens with eye contact to voice			
-3	Moderate sedation	Any movement (but no eye contact) to voice	] ]		
-4	Deep sedation	No response to voice, but any movement to physical stimulation	ך		Stop—Assess
-5	Unarousable	No response to voice or physical stimulation			later

STEP 1: Assess sedation (RASS)

**Figure 78-1.** Richmond Agitation-Sedation Scale (RASS),<sup>36,37</sup> used to determine the level of sedation.

Society of Critical Care Medicine (SCCM) in its clinical practice guidelines<sup>42</sup> and has been validated in multiple ICU settings.<sup>43,44</sup>

A combination of the RASS for assessment of sedation (Fig. 78-1) followed by the CAM-ICU (Fig. 78-2) or the ICDSC (Table 78-2) can be used for the establishment of delirium in ICU patients.

The diagnosis of delirium using the CAM-ICU (after establishing a RASS score of -3 or lighter) requires (1) acute change or fluctuation in mental status (feature 1),



**Figure 78-2.** Confusion Assessment Method for the Intensive Care Unit (CAM-ICU), used to determine the presence or absence of delirium after the level of sedation has been assessed. (Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: Validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). JAMA. 2001;286:2703–2710.)

*and* (2) inattention (feature 2), *and* (3) one of the following: (a) disorganized thinking (feature 3) *or* (b) altered level of consciousness (feature 4). Only those patients with a RASS score of -3 and higher (those alert enough to respond to the test) are assessed for delirium. For diagnosis of delirium using the ICDSC, patients who score at least 4 points are considered to have delirium.

### PRIMARY PREVENTION

The prevention of delirium in the ICU requires constant reassessment of patients' clinical courses and treatments. Outlined previously were several potential pathophysiologic contributors to delirium. All have end points associated with cellular mechanisms, suggesting that avoiding metabolic derangements, including electrolyte abnormalities, hypoglycemia, hypoxia, dehydration, and hyperthermia, are paramount in the prevention of delirium.

Medications have long been implicated in the development of delirium, either because of their side effects or their direct effects on the central nervous system. Both the number of medications administered<sup>11</sup> and their psychoactive effects<sup>45</sup> have been suggestive of precipitating delirium.

Patients in the ICU setting are frequently administered analgesics and sedatives in continuous drips. These have variable accumulation in individual patients and can predispose to a withdrawal syndrome on discontinuation.<sup>42,46</sup> Because substance-induced delirium is one of the etiologies recognized by the *DSM-IV*, it is no surprise that polypharmacy of analgesics and sedatives contributes significantly, and hence strategies to reduce exposure to psychoactive medications need to be implemented.

### Table 78-2 Intensive Care Delirium Screening Checklist

### PATIENT EVALUATION

#### Altered Level of Consciousness (A-E)\*

Inattention	Difficulty following a conversation or instructions. Easily distracted by external stimuli. Difficulty shifting focuses. Any of these scores 1 point.
Disorientation	Any obvious mistake in time, place, or person scores 1 point.
Hallucinations, delusion, psychosis	The unequivocal clinical manifestation of hallucination or of behavior probably due to hallucination or delusion. Gross impairment in reality testing. Any of these scores 1 point.
Psychomotor agitation or retardation	Hyperactivity requiring the use of additional sedative drugs or restraints to control potential danger to oneself or others. Hypoactivity or clinically noticeable psychomotor slowing.
Inappropriate speech or mood	Inappropriate, disorganized, or incoherent speech. Inappropriate display of emotion related to events or situation. Any of these scores 1 point.
Sleep-wake cycle disturbance	Sleeping less than 4 hr or waking frequently at night (do not consider wakefulness initiated by medical staff or loud environment). Sleeping during most of the day. Any of these scores 1 point.
Symptom fluctuation	Fluctuation of the manifestation of any item or symptom over 24 hr scores 1 point.
Total score (0-8)	

\*Level of consciousness: A, no response, score 0; B, response to intense and repeated stimulation (loud voice and pain), score 0; C, response to mild or moderate stimulation, score 1; D, normal wakefulness, score 0; E, exaggerated response to normal stimulation, score 1.

Adapted from Bergeron N, Dumont M, Dial S, et al. Intensive Care Delirium Screening Checklist: Evaluation of a new screening tool. *Intensive Care Med.* 2001;27:859-864.

A study evaluating daily interruptions of continuous sedative infusions in ICU patients showed that those managed with a cessation protocol had a significant reduction in the duration of mechanical ventilation and length of ICU stay, without adverse psychological outcomes from potential "undersedation."<sup>47,48</sup> The multicenter Awakening Breathing Controlled (ABC) trial linked both sedation and ventilator weaning protocols.<sup>49</sup> Both groups in the ABC trial had a targeted sedation strategy, but patients in the control group received only daily spontaneous breathing trials (SBTs), whereas those in the treatment group had mandatory spontaneous awakening trials (SATs) before each SBT. Patients who were managed with the "wake-up and breathe" intervention (SAT and SBT)

had reduced time on mechanical ventilation (despite the same targeted sedation), reduced time in the ICU and hospital, and a significant reduction in mortality.<sup>49</sup> Although neither of these studies showed a significant impact on delirium, they did show significant reduction in benzodiazepine and opiate use, and the ABC study did have reduction in delirium duration in the septic subgroup in the intervention arm (Dr. T. D. Girard, personal communication).

Another potential risk factor for delirium is the alteration of the sleep cycle. Often, disruption of the sleep-wake cycle in the ICU is necessary to continuously monitor the critically ill patient through blood samples, measurements, nursing interventions, patient bathing, and so forth. However, this disruption takes its toll on the patient because it has been shown to have detrimental effects on cognition and memory in multiple studies, even in the healthy, non-ICU patient.<sup>50,51</sup> Maintaining a sleep-wake cycle as best as possible through nonpharmacologic or pharmacologic means may help prevent delirium.

There has been some debate about whether the "protocolization" of patient care may reduce the incidence of delirium. In a study that included 852 general medical patients older than 70 years, standardized protocols were developed for six risk factors of delirium, including cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment, and dehydration. Using these protocols resulted in a 40% reduction in the initial development of delirium in the intervention patients.<sup>52</sup> However, when these patients were assessed after 6 months for 10 outcomes, including items such as functional status, cognitive status, delirium, and rehospitalization, only incontinence was slightly less common in the intervention group.<sup>53</sup> Unfortunately, these studies have yet to be performed in ICU patients.

We have included an empirical protocol (Fig. 78-3) that we use to treat delirium in ICU settings that is based on the current SCCM Clinical Practice Guidelines. It is merely an example of such a protocol, and the use of a similar protocol should be updated with current data and designed to be implemented specifically at an individual institution. The choice of particular antipsychotics is not described because there are limited data guiding such recommendations.

### PHARMACOLOGIC INTERVENTION

Although antidelirium medications in either the preventive or treatment stage are appealing, there are currently none available that have the ability to alter the outcome of delirium, and there are no U.S. Food and Drug Administration (FDA) approved medications designed specifically for the treatment of delirium. Before administering new psychotropic medications to the delirious patient, one must rule out all reversible causes that may be either the underlying etiology of the delirium or that may be exacerbating the current situation. Reversible causes that could precipitate or exacerbate delirium include hypoxia, hypercarbia, hypoglycemia, metabolic derangements, infection, or shock. Once a decision is



- Consider stopping or substituting for deliriogenic medications such as benzodiazepines, anticholinergic medications (metochlorpromide, H2 blockers, promethazine, diphenhydramine), steroids etc
- 2. See nonpharmacologic protocol at right
- Analgesia Adequate pain control may decrease delirium. Consider intermittent narcotics if feasible. Asses with objective tool.
- 4. Typical or atypical antipsychotics While tapering or discontinuing sedatives, consider haloperidol 2 to 5 mg IV initially (0.5–2 mg in elderly) and then q 6 hours. Guideline for max haloperidol dose is 20 mg/day due to ~60% D<sub>2</sub>-receptor saturation. May also consider using any of the atypicals (e.g. olanzapine, quetiapine, risperidone, ziprasidone, or abilifide). Discontinue if high fever, QTc prolongation, or drug-induced rigidity.
- Spontaneous Awakening Trial (SAT) Stop sedation or decrease infusion (especially benzodiazepines) to awaken patient as tolerated.
- 6. Spontaneous Breathing Trial (SBT) CPAP trial if on ≤50% and ≤8 PEEP and Sats 90%
- Sedatives and analgesics may include benzodiazepines, propofol, dexmedetomidine, fentanyl, or morphine

#### Nonpharmacologic protocol<sup>2</sup> Orientation

Provide visual and hearing aids Encourage communication and reorient

patient repetitively

Have familiar objects from patient's home in the room

Attempt consistency in nursing staff Allow television during day with daily news

Nonverbal music

Environment

Sleep hygiene: Lights off at night, on during day. Sleep aids (zolpidem, mirtazipine)? Control excess noise (staff, equipment, visitors) at night

Ambulate or mobilize patient early and often *Clinical parameters* 

Maintain systolic blood pressure >90 mm Hg Maintain oxygen saturations >90%

Treat underlying metabolic derangements and infections

**Figure 78-3.** An example of an empirical protocol used for the treatment of delirium in an intensive care unit setting. CAM-ICU, Confusion Assessment Method for the Intensive Care Unit; CHF, congestive heart failure; CPAP, continuous positive airway pressure; PEEP, positive end-expiratory pressure; RASS, Richmond Agitation-Sedation Scale. (*Courtesy of Dr. E. W. Ely, http://www.icudelirium.org*).

made to use antipsychotic medications (typical or atypical), these medications should be individualized (and minimized) to avoid associated adverse events.

### Haloperidol

Haloperidol is a medication frequently used in the ICU for delirium. The SCCM guidelines recommend the use of haloperidol but recognize that the recommendation is level C data secondary to lack of evidence.<sup>42</sup> Haloperidol can be used either intermittently or in a continuous infusion.<sup>42</sup> Kalisvaart and colleagues assigned 430 older hip surgery patients to haloperidol or placebo in the perioperative period.<sup>54</sup> No change in incidence of delirium was found, but a significant reduction in the severity and duration of delirium, as well as in postoperative stay, was found. Therefore, it was suggested that haloperidol may be better than placebo in decreasing duration of delirium. However, in a recent Cochrane database review studying the efficacy and incidence of adverse effects among haloperidol, risperidone, olanzapine, and quetiapine, essentially no differences in efficacy in the management of delirium in hospitalized patients were found.55 Despite the lack of strong evidence backing its recommendation, haloperidol is still the most widely used neuroleptic agent in the ICU.<sup>56</sup>

Haloperidol must be used with caution because it has a variety of adverse effects, including dystonias, neuroleptic malignant syndrome, extrapyramidal effects, and the most worrisome torsades de pointes. It should not be given to patients with electrocardiographic evidence of prolonged QT interval. QT interval daily measurements are recommended when haloperidol is initiated.

### **Atypical Antipsychotics**

There are a variety of newer "atypical" antipsychotic agents (e.g., risperidone, ziprasidone, quetiapine, and olanzapine) that affect neurotransmitters other than dopamine and may be more efficacious than haloperidol, with a lower side-effect profile.<sup>57–59</sup> Prakanrattana and colleagues<sup>60</sup> showed that a single dose of risperidone in 126 patients after cardiac surgery significantly reduced the incidence of delirium. However, Skrobik and colleagues<sup>59</sup> found that in an ICU population, haloperidol was as effective as the atypical antipsychotic olanzapine, although the atypical group had fewer side effects. Atypical antipsychotics are associated with the same concerns regarding QT prolongation as haloperidol and should also be used with caution.

### Dexmedetomidine

The relatively recent addition of dexmedetomidine, an  $\alpha_2$ -agonist, to medications available to the intensivist has opened alternatives to the GABA agonist pathway for sedation. In a recent double-blind randomized controlled trial comparing dexmedetomidine with lorazepam, sedation of mechanically ventilated patients with dexmedetomidine resulted in more days alive without delirium or coma and a greater achievement of target sedation.<sup>61</sup> A follow-up double-blind randomized controlled trial<sup>62</sup>

revealed improvements in the resolution of delirium in the dexmedetomidine group compared with midazolam. This suggests that dexmedetomidine may be useful if sedation is required and delirium is a concern.

### Benzodiazepines

Benzodiazepines present a particular dilemma for the clinician. In the patient who is suffering from alcohol withdrawal or seizures, benzodiazepines are the treatment of choice and can have life-threatening consequences if withheld. However, the use of benzodiazepines for delirium in most other cases is strongly *discouraged* because they can paradoxically exacerbate delirium or create a situation of oversedation and respiratory suppression, leading to hypoxia and hypercarbia, both of which are life-threatening and can contribute to the new onset or prolongation of delirium. Elderly patients are particularly susceptible.

### Opioids

ICU patients, especially postoperative patients, require appropriate analgesia, and pain itself can exacerbate delirium.<sup>63</sup> However, the choice of opioid may be important: Pandharipande and colleagues demonstrated that fentanyl was associated with delirium, but morphine was not.<sup>13</sup> Thus, clinicians must be careful to balance the risk for delirium associated with pain with the risk for delirium associated with opioids. These data suggest that a multimodal approach to postoperative analgesia and adjunct therapies to minimize opioid dosage in the ICU may be beneficial.

### AUTHORS' RECOMMENDATIONS

- Delirium is a disturbance of consciousness and cognition, occurring over a short period of time. It is associated with significantly increased morbidity and mortality.
- Subtypes of delirium include hyperactive, hypoactive, and mixed. The subtype may carry a prognostic implication, with hyperactive having a better prognosis.
- Many risk factors are associated with delirium, and some of these are modifiable or preventable by the clinician, such as hypoxia, metabolic, and electrolyte disturbances and infection, dehydration, hyperthermia, sepsis, psychoactive medications, and sleep deprivation.
- A variety of cellular and metabolic processes are proposed etiologies for delirium, all of which are likely interrelated.
- There are multiple validated assessment tools for delirium. Patients in the ICU must first be assessed for their level of sedation (using a scale such as the RASS), and then for the presence of delirium (using a scale such as the CAM-ICU or the ICDSC).
- Minimizing sedation by employing tactics such as daily interruptions for sedation helps reduce the exposure to deliriogenic psychoactive medications.
- Benzodiazepines should be avoided in the ICU, except for the treatment of specific conditions. Alternatives for sedation include haloperidol, atypical antipsychotics, dexmedetomidine, and remifentanil, although additional studies are required to determine the role of these medications in preventing and treating delirium.

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## Sleep Disturbances in the Intensive Care Unit: Do They Matter?

Avery Tung

Existing evidence clearly suggests that naturally occurring sleep is limited for patients in the intensive care unit (ICU). Both electroencephalographic (EEG) studies<sup>1</sup> and patient reports<sup>2</sup> testify that sleep loss and the perception of inadequate sleep are significant in critically ill patients. Considerable uncertainty exists, however, with respect to the outcome effect of that limited sleep, or even how the effect of such sleep loss on patients should be quantitated. The many methodologic challenges inherent in studying sleep in the ICU include the lack of meaningful clinical and EEG definitions of sleep in patients receiving sedation, a method for separating potential consequences of sleep loss from the normal course of ICU care, a lack of effective strategies to promote sleep in the ICU, and difficulty in measuring the degree of sleep "debt" in critically ill patients.<sup>3</sup> Nevertheless, recent progress in understanding the effects of acute or chronic sleep loss in healthy patients has begun to suggest how inadequate sleep may affect other aspects of critical illness.<sup>4</sup> This chapter briefly describes naturally occurring sleep and its alterations in the ICU, reviews the consequences of sleep loss in normal patients, examines potential mechanisms for inadequate sleep in the ICU setting, and suggests potential strategies for improving sleep in critically ill patients.

### NORMALLY OCCURRING SLEEP

One obstacle to accurately evaluating the effect of sleep loss in the ICU is the difficulty in defining sleep. Because the function of sleep is not known, it is generally described by its behavioral and physiological characteristics. Of these, the most commonly measured are brain EEG patterns, electromyographic (EMG) patterns, and alterations in respiratory behavior.<sup>5</sup> Normal sleep is characterized by a periodic progression through defined states of EEG and EMG behavior termed slow wave or non-rapid eye movement (NREM) and rapid eye movement (REM). NREM sleep is characterized by predominantly lowfrequency, high-amplitude EEG waveforms and muscle flaccidity. NREM sleep is divided into four stages: stages 3 and 4 are termed slow-wave sleep and have higher-amplitude and lower-frequency EEG elements than stages 1 and 2. REM sleep is distinctly different, with low-amplitude, high-frequency EEG waveforms similar to wakefulness, a greater degree of muscle flaccidity than NREM sleep, and characteristic rapid, fluttering eye motions. In normal individuals, about 80% of the total sleep period is NREM sleep, and 20% is spent in REM sleep. More importantly, normal sleep progresses predictably through the different stages, moving from REM to stage 2, deepening from stage 2 to stage 4, backtracking to stage 2, and then switching back to REM. These cycles take about 100 minutes and occur 4 to 5 times per night.<sup>5</sup>

One piece of evidence supporting a hypothesis of inadequate sleep in the ICU is that the normal sleep patterns described previously do not occur in critically ill patients. ICU sleep is fragmented, with frequent arousals. Slowwave (stages 3 and 4) sleep is reduced, as is REM sleep. These decreases are made up by increased time in NREM stage 1 and 2 sleep. The circadian rhythm of sleep is also altered. Whereas sleep in normal humans is clustered mostly at night, nearly half of sleep in ICU patients occurs in the daytime (and correspondingly less at night). Total sleep time is likely less, although difficulties in measuring sleep in critically ill patients limit the ability to quantitate that difference.<sup>6</sup>

On the surface, it is easy to imagine that these changes should dramatically affect patient welfare. Animal studies demonstrate that both total sleep and REM sleep deprivation are fatal to rats,<sup>7</sup> and in humans, both NREM and REM sleep deprivation are followed by a rebound increase in the sleep state in deficit.<sup>8</sup> EEG evidence of sleep, however, may not be the best marker for non-EEG consequences of sleep. As an example, although selective REM sleep deprivation by forced locomotion techniques is fatal in rats, patients taking tricyclic antidepressants experience a similar lack of REM sleep.<sup>9</sup> Additionally, animal studies suggest that propofol sedation allows sleep debt to discharge in a similar fashion to naturally occurring sleep, even though the EEG signatures of natural sleep and propofol-based sedation differ considerably.<sup>10</sup> Finally, benzodiazepine use may change the perception of adequate sleep considerably, even though REM sleep may be reduced.<sup>11</sup> Taken together, these factors indicate that sleep is an extremely complex state, with EEG, hormonal, restorative, and other poorly defined effects. Abnormalities in one aspect of sleep may not necessarily

predict or correlate with abnormalities in others. Existing animal evidence, for example, suggests that effects of sleep loss on adult neurogenesis persist even after sufficient recovery sleep to normalize EEG behavior.<sup>12</sup> Further work is likely required to evaluate whether normalizing EEG indices of sleep normalizes effects of sleep loss relevant to critical illness.

### POTENTIAL CONSEQUENCES OF SLEEP DISRUPTION IN THE INTENSIVE CARE UNIT

In normal humans, psychological and physiologic consequences of sleep loss have been described. Among the relevant psychological consequences for ICU patients are hyperalgesia, increased anxiety, mood changes (anger, depression, frustration), and difficulty concentrating.<sup>13</sup> Although intuitively plausible,<sup>14</sup> no documented relationship between sleep disruption and delirium has yet been demonstrated. Nevertheless, it is clear that anxiety, difficulty concentrating, and mood changes can interfere with ventilator weaning, physical therapy, rehabilitation, and other ICU care strategies requiring patient cooperation. Such strategies have the potential to alter ICU outcomes.

Among the physiologic effects of sleep deprivation are increases in vasomotor tone,<sup>15</sup> altered cellular and humoral immune system activity, and increases in cortisol, glucose tolerance, and insulin resistance.<sup>16</sup> Current evidence also hints at altered metabolism, with obesity and diabetes both potentially linked to sleep loss.<sup>4</sup>

Many of these consequences interact with the physiologic consequences of critical illness. The altered nutritional balance, increased glucose tolerance, and insulin resistance are also hallmarks of critical illness.<sup>17</sup> Increased levels of interleukin-6 (IL-6), tumor necrosis factor (TNF), and C-reactive protein are consistent with the increased inflammatory state seen in sepsis.<sup>18</sup> Although no demonstrated relationship between ICU delirium and sleep deprivation exists to date, psychological changes consistent with sleep deprivation are similar to those seen with ICU delirium,<sup>19</sup> and circadian changes in sleep periodicity can contribute to delirium in elderly patients. Taken together, it seems reasonable that sleep deprivation can at the least complicate the delivery of critical care and potentially perpetuate the inflammation, altered metabolic consequences, and mental status complications of critical care.

### THERAPEUTIC APPROACHES TO SLEEP IN THE INTENSIVE CARE UNIT

Although sleep is clearly altered in the ICU, and the consequences of those alterations have the potential to alter the patient's course, no data currently link therapies directed toward improving ICU sleep to improved outcome. Nevertheless, it seems reasonable to prioritize sleep to the degree that it does not interfere with other more important care priorities. Reducing light intensity at night when it is not needed, for example, or bunching nursing care procedures to avoid unnecessarily disturbing patient sleep are examples of such low-cost approaches.

Perhaps the least invasive of strategies to promote sleep is to control light and noise to create a sleep-conducive environment. In principle, a quiet, dark room should represent a considerable change from the usually bright, loud environment of the ICU and allow patients to sleep. Current evidence, however, is mixed regarding the effectiveness of controlling light and sound to facilitate sleep.<sup>20</sup> Studies of ICU factors perceived as disruptive to sleep, for example, identify several factors besides light and sound as disruptive.<sup>21</sup> Although light and noise modulation should facilitate appropriately timed melatonin secretion and improve sleep, existing literature shows limited success in ICU environments. In addition, although some studies suggest benefit from light and noise control, other studies of nursing home patients suggest little effect.<sup>22</sup>

Another strategy to facilitate sleep is by choice and dose of sedative. Although it is unclear whether a sedated patient is actually sleeping, animal data demonstrate that sleep debt (as defined by amount of subsequent rebound sleep) does not accumulate during prolonged sedation with propofol<sup>23</sup> and that sleep-deprived rats are able to discharge accumulated sleep debt during propofol anesthesia to the same degree as during a similar duration of naturally occurring sleep.<sup>10</sup> For short-term sleep facilitation, benzodiazepines significantly improve the perceived restfulness of sleep, although they rapidly induce tolerance and can be associated with withdrawal in ICU patients.<sup>24</sup>

The role of dexmedetomidine in facilitating sleep is intriguing, but unproved. By suppressing adrenergic output from the locus ceruleus, dexmedetomidine acts differently from GABA agonists such as propofol or benzodiazepines.<sup>25</sup> In vitro studies suggest that patterns of brain activity during sedation with dexmedetomidine are similar to those that occur during natural sleep.<sup>26</sup> Although no clinical relationship between dexmedetomidine sedation and sleep has yet been demonstrated, patients with persistent agitation and those who are resistant to more standard sedatives may reasonably be more likely to obtain sleep when given dexmedetomidine.

By reducing nonspecific agitation, directly treating delirium may also improve patient sleep. Although no specific treatment for ICU delirium exists, normalizing metabolic disturbances, limiting medications that promote confusion and altered consciousness, and periodically reorienting the patient are relatively simple steps to implement. Dexmedetomidine may also play a role in controlling sedation. In early clinical reports, sedation with dexmedetomidine reduced the incidence of delirium compared with lorazepam.<sup>27</sup> Further work is needed to clarify the relationships between dexmedetomidine, restorative sleep, and delirium.

### CONCLUSION

Measuring sleep and assessing its impact are difficult in critically ill patients. Most critical care physicians believe that patients do not get adequate sleep in the ICU. Existing data suggest that that total sleep time is reduced, that REM and slow-wave sleep are reduced (and replaced by stage 1 and 2 sleep), and that circadian patterns of sleep periodicity are also disrupted. The causes of these changes are incompletely understood but are likely multifactorial and range from intrinsic effects of critical illness to environmental disturbances and altered circadian patterns of light and activity.

The consequences of such disturbances, however, have not been well established. Behavioral consequences such as anxiety, mood changes, and difficulty concentrating are difficult to quantitate and even more difficult to attribute to a specific cause. Physiologic consequences such as immune suppression, inflammation, hormonal dysregulation, and vasomotor tone are even more difficult to assess against the background of critical illness. Finally, no study has yet demonstrated a reversal of these effects with interventions that improve sleep.

In the absence of definitive strategies to improve sleep and no conclusive data to demonstrate improved outcomes as a function of sleep, what should the clinician do? Perhaps the most reasoned approach would be to focus on sleep promotion when such efforts do not interfere with other aspects of critical care delivery. Controlling environmental disturbances at night, limiting noise and light pollution when unnecessary, limiting medications that promote confusion, and reorienting patients periodically are all reasonable strategies. Further work is required, however, to clarify the mechanisms relating sleep and outcome in critically ill patients.

### AUTHOR'S RECOMMENDATIONS

- Measuring sleep and assessing its impact are difficult in critically ill patients.
- Most critical care physicians believe that ICU patients do not get adequate sleep.
- It appears that total sleep time is reduced in critically ill patients.
- REM and slow-wave sleep are reduced (and replaced by stage 1 and 2 sleep) in critically ill patients.
- ICU care disrupts circadian patterns of sleep periodicity.
- The causes of these changes are likely multifactorial.
- Sleep disruption results in anxiety, mood changes, and difficulty concentrating.
- Physiologic consequences of sleep disruption include immune suppression, inflammation, hormonal dysregulation, and altered vasomotor tone.
- No study has demonstrated a benefit from interventions that improve sleep.
- The clinician should focus on sleep promotion when such efforts do not interfere with other aspects of critical care delivery. Approaches include controlling environmental disturbances at night, limiting noise and light pollution, limiting medications that promote confusion, and reorienting patients periodically.

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## 80 How Should Patients with Thoracic Trauma Be Managed in the Intensive Care Unit?

William P. Riordan, Jr., Bryan A. Cotton

Thoracic injury accounts for up to 25% of deaths due to trauma. Forty-five percent to 50% of unrestrained motor vehicle crash victims sustain thoracic injury, and 40% of patients with penetrating trauma have associated thoracic injury. Missed or mismanaged thoracic injuries are poorly tolerated; the well-described "deadly dozen" of thoracic injury includes multiple possibilities for rapid cardiovas-cular collapse and death (Table 80-1).

### **INJURY TO THE CHEST WALL**

Injuries to the chest wall include chest wall contusion, sternal fracture, rib fractures, and flail chest. Rib fractures are a source of considerable morbidity and mortality. In a review of 7147 trauma patients, Ziegler and Agarwal found that rib fractures are a marker of severe injury and are associated with a 12% mortality rate.<sup>1</sup> In addition, greater than 90% of patients with thoracic injuries have associated injuries, one half require operative and intensive care unit (ICU) care, one third develop pulmonary complications, and one third will require discharge to an extended care facility.<sup>1</sup> The elderly population is at particular risk for morbidity and mortality in the setting of multiple rib fractures.<sup>2,3</sup> Bulger and associates compared a cohort of 277 elderly patients  $(\geq 65$  years old) with a control group of 187 randomly selected patients (18 to 64 years old), and found that elderly patients have twice the mortality and thoracic morbidity rates of younger patients with similar injuries.<sup>4</sup>

Rib fractures are notoriously painful, and the resultant morbidity has been attributed to, among others, splinting and impaired coughing.<sup>1</sup> Treatment of rib fractures includes aggressive pulmonary toilet and an appropriate analgesia regimen. Options for analgesia include intravenous narcotics, intrapleural anesthesia, intercostal nerve block, and thoracic paravertebral block. There are an increasing number of studies that support the use of epidural analgesia in patients with blunt chest trauma as the optimal and preferred modality for pain relief in the setting of multiple rib fractures.<sup>3,4</sup> Bulger and colleagues demonstrated that epidural analgesia (compared with intravenous narcotics) was associated with a shorter duration of mechanical ventilation and a decrease in the incidence of nosocomial pneumonia.<sup>4</sup>

### CHEST WALL STABILIZATION

Many questions remain to be answered regarding the management of patients with flail chest. Operative stabilization of the chest wall may be performed using a variety of techniques and has been reported by multiple authors.<sup>5</sup> However, controversy surrounds patient selection, indications for operative stabilization, and actual benefit (if any). Tanaka and colleagues<sup>6</sup> prospectively compared surgical stabilization with internal pneumatic stabilization (i.e., mechanical ventilation) in 37 consecutive patients with flail chest. In patients undergoing operative stabilization, they observed a decrease in requirement for mechanical ventilation (10.8  $\pm$  3.4 days versus 18.3  $\pm$  7.4 days; P < .05), shorter ICU stay (16.5  $\pm$  7.4 days versus 26.8  $\pm$ 13.2 days; P < .05), and lower incidence of pneumonia (24% versus 77%; P < .05). Percent forced vital capacity was higher in the surgical group at 1 month and thereafter (P < .05). The percentage of patients who had returned to full-time employment at 6 months was significantly higher in the surgical group (11 of 18 versus 1 of 19).

### THORACIC SPINAL CORD INJURY

Upper thoracic spine fractures are less common than those of the cervical or thoracolumbar junction.<sup>7</sup> This reflects the more stable biomechanical structure of this region of the vertebral column.<sup>8,9</sup> A significantly greater traumatic energy is necessary to fracture the thoracic spine in this area, and not surprisingly, these injuries are associated with a higher risk for spinal cord involvement and concomitant thoracic injuries.<sup>10</sup> Associated injuries such as pulmonary contusion, rib fractures, and hemopneumothorax add to the morbidity and mortality risk in this patient population. Pulmonary complications are the most common cause of death in patients with spinal cord injury.<sup>11,12</sup> Atelectasis, pneumonia, and ventilatordependent respiratory failure are the result of impairment of both inspiratory and expiratory muscle groups as well as the paradoxical chest wall movement seen in spinal cord injury patients.<sup>13</sup>

In addition to biomechanical disturbances of the chest wall, interruption of sympathetic innervation (T1 to T6),

Table 80-1 The Deadly Dozen					
Primary Survey	Secondary Survey				
Airway obstruction	Simple pneumothorax or hemothorax				
Tension pneumothorax	Traumatic aortic disruption				
Open pneumothorax	Tracheobronchial injury				
Massive hemothorax	Pulmonary contusion				
Flail chest	Blunt cardiac injury				
Cardiac tamponade	Diaphragmatic injury				

with unopposed parasympathetic stimulation, results in increased bronchial tone and upper airway vascular congestion.<sup>14</sup> Although respiratory complications result in a mortality rates of 20% to 50% after cervical spinal cord injury (especially above the C5 level),<sup>15,16</sup> few studies have examined respiratory complications in patients with thoracic level involvement. Cotton and colleagues reviewed a large series of such patients and observed respiratory complications in 51.1% of patients with T1 to T6 spinal cord injury (versus 34.5% in T7 to T12 spinal cord injury and 27.5% in thoracic fractures).<sup>17</sup> The need for intubation, the risk for pneumonia, and the risk for death were significantly greater for patients with T1 to T6 level spinal cord injury. In patients with an Injury Severity Score of less than 17 (n = 6427), the relative mortality risk was 26.7 times higher with the development of respiratory complications (9.9% versus 0.4%).<sup>T</sup>

Screening for injury to the thoracolumbar spine has evolved during the past decade as computed tomography (CT) scan technology has improved. Historically, plain films were the standard of care for evaluation of the thoracolumbar spine in the setting of trauma. The Eastern Association for the Surgery of Trauma (EAST) practice management guidelines committee issued evidence-based recommendations on screening for injury to the thoracolumbar spine. Although no prospective randomized trials of available imaging modalities have been published, recommendations were made by the authors based on a comprehensive review of relevant studies. The group recommended the use of multidetector CT scan with reformatted axial collimation (because it was demonstrated to be superior to plain films) in the evaluation of the thoracolumbar spine for bony injury. However, the group supported clinical clearance by qualified physicians (without imaging studies) for patients who are awake, not intoxicated, and without distracting injuries. Radiographic screening is recommended in the setting of known cervical spine fracture or a high-energy mechanism of injury (e.g., falls from significant height [>10 feet]; motor vehicle, motorcycle, bicycle, or all-terrain vehicle crash; pedestrians struck; assault; sport or crush injury). Ligamentous injury in the absence of thoracolumbar spine fracture is rare. However, magnetic resonance imaging (MRI) is indicated for patients with neurologic deficits, abnormal CT scans, or clinical suspicion despite normal radiographic evaluation.<sup>18</sup>

### CHEST TUBE MANAGEMENT

Pleural manifestations of thoracic trauma include pneumothorax and hemothorax. It has been estimated that 85% of penetrating chest injuries can be managed with simple tube thoracostomy. Indeed, fewer than 5% of patients with blunt chest trauma will require thoracotomy.<sup>19</sup> It follows that a thorough understanding of this therapeutic modality is important for the intensivist responsible for the management of patients with thoracic trauma.

Thoracostomy tubes may be removed safely if no air leak is present and if drainage is limited. Younes and associates conducted a prospective randomized study that compared uninfected drainage thresholds of 100, 150, and 200 mL per day in a population of 139 surgical patients.<sup>20</sup> This study demonstrated that chest tube removal was safe if drainage is less than 200 mL per day. A water seal chest radiograph is traditionally obtained before chest tube removal. Schulman and colleagues prospectively compared early and late timing of this study and concluded that a normal chest radiograph obtained 3 hours after placing a chest tube on water seal effectively excluded development of a clinically significant pneumothorax.<sup>21</sup>

The requirement of a water seal period before chest tube removal has been questioned by some. In a prospective randomized trial of thoracostomy removal algorithms performed by Martino and colleagues, 205 patients were randomized to either a group receiving a water seal or a group not receiving a water seal. Patients in the water seal group were disconnected from low wall suction, and a chest radiograph was obtained 6 to 8 hours later. Chest tubes in the no water seal group were disconnected from wall suction and pulled immediately. Recurrent pneumothorax was seen in 13 patients in the water seal group and in 9 patients in the no water seal group. However, 7 patients in the no water seal group required chest tube reinsertion, compared with 1 patient in the water seal group (P < .05). The authors concluded that a period of water seal allowed occult air leaks to become clinically apparent and reduced the need for repeat tube thoracostomy.<sup>22</sup> A previous study by Davis and colleagues randomized 80 patients to a continuous-suction group or a water seal group.<sup>23</sup> They observed a similar incidence of recurrent pneumothorax (2.5%) in both groups and noted that the suction algorithm could help reduce length of stay by reducing total chest tube time (72.2 hours versus 92.5 hours; P = .013) as well as removal time (25.2 hours versus 35.6 hours; P = .034).

Recurrent or "postpull" pneumothorax may occur after thoracostomy tube removal. A small apical pneumothorax may be seen after chest tube removal in up to 24% of patients; many of these resolve spontaneously and do not require repeat thoracostomy.<sup>24</sup> Bell and colleagues conducted a prospectively compared removal of 102 chest tubes in 69 trauma patients either at end inspiration or end expiration and found no significant difference in the incidence of recurrent pneumothorax.<sup>25</sup> Although unstudied, our practice is to return a previous water seal system to suction for a brief period before removal. This "might help, can't hurt" approach may remove residual air or fluid from the tubing and pleural space.

Typically, a chest radiograph is obtained after thoracostomy tube removal to evaluate for recurrent pneumothorax. Pizano and colleagues conducted a prospective study in a population of 75 mechanically ventilated patients to determine the appropriate timing of this study.<sup>26</sup> This study demonstrated that a chest radiograph obtained 1 to 3 hours after thoracostomy tube removal effectively identified recurrent pneumothorax. Retained hemothorax is a recognized sequel of chest wall injury that can lead to significant complications, including empyema and fibrothorax. Early evaluation for retained hemothorax can reduce morbidity.27,28 Screening may be initiated 48 hours after admission. If an upright chest radiograph demonstrates significant opacification, chest CT should be obtained to evaluate for retained hemothorax. Although chest radiography is a useful screening tool, it does not reliably predict the need for surgical evacuation of retained hemothorax.<sup>29,30</sup> Meyer and colleagues conducted a prospective randomized trial in 1997 and demonstrated that early thoracoscopy (versus additional tube thoracostomy) for retained hemothorax decreased duration of tube drainage, hospital length of stay, and hospital cost.<sup>28</sup>

The administration of antibiotics for prophylaxis in all clean-contaminated and many clean procedures has become accepted as the standard of care.<sup>31</sup> However, the use of antibiotics for prophylaxis or presumptive therapy in trauma patients remains controversial. Study of antibiotic prophylaxis for tube thoracostomy in trauma patients is complicated by the fact that wounding of the chest wall or lung and pleura most often occurs before antibiotic administration and thoracostomy tube placement. In 2004, Maxwell and colleagues published a multicenter prospective randomized double-blind trial that demonstrated a low incidence of empyema.<sup>32</sup> This study suggested that the use of presumptive antibiotics does not reduce the incidence of empyema or pneumonia. The authors noted that the low incidence of empyema in the study population (2.6% in 224 patients) may lead to a type II statistical error. A summary of meta-analyses is provided in Table 80-2, and a summary of class I studies is provided in Table 80-3. As noted in the tables, there is a varied approach to class of antibiotic, dosing regimen, and patient populations considered in the various studies. Based on available data, the EAST 2000 guidelines support administration of a first-generation cephalosporin (e.g., cefazolin) before thoracostomy tube placement when possible.<sup>33</sup> Antibiotic therapy should not be continued beyond 24 hours. This approach is based on level III data only.

### **OCCULT PNEUMOTHORAX**

One controversial situation that frequently arises in clinical practice is the management of occult pneumothorax. By definition, these are not identified with a chest radiograph but are visible on CT scan. Which ones require pleural drainage? Does positive-pressure ventilation matter? How should they be observed? When should interval imaging be performed, and is it even necessary? These questions remain to be answered by a large prospective randomized trial. Two smaller trials (with differing conclusions) have been published and are summarized in Table 80-4.<sup>34,35</sup> Other authors have studied occult pneumothorax in a nonrandomized or retrospective fashion, but these studies also have small numbers and conflicting results.<sup>36–39</sup>

### NONINVASIVE POSITIVE-PRESSURE VENTILATION

Trauma-related acute lung injury (ALI) is a clinically and biologically different process than ALI from other causes.<sup>40–42</sup> Although multiple controlled trials support the use of noninvasive positive-pressure ventilation in acute respiratory failure secondary to chronic obstructive pulmonary disease,<sup>43</sup> there are no prospective trials in a large population of trauma patients. Gunduz and colleagues conducted a prospective randomized study of 53 flail chest patients comparing intermittent positive-

<u>.</u>	N (T)		<b>D</b> II	<b>0</b>
Study	No. of Trials	No. of Subjects (Antibiotic/Control)	Results	Conclusion
Sanabria et al, 2006 <sup>45</sup>	5	351/263	Empyema (RR, 0.19) Pneumonia (RR, 0.44)	Antibiotics decrease incidence of empyema and pneumonia.
Evans et al, 1995 <sup>46</sup>	6	44/46 30/28 40/40 39/46 60/60 38/37	Summarized as a table for each of the six studies; includes uncorrected and corrected chi square with two-sided <i>P</i> value, Fisher's one and two-sided values	Studies reframed to evaluate any infectious chest process, including pneumonia, wound infection, empyema, tracheitis. Antibiotics should be used and target <i>Staphylococcus aureus</i> .
Fallon & Wears, 1992 <sup>47</sup>	6 (4)	Not specified Analysis done for cephalosporin use (4/6 studies)	Empyema (7.1% difference ± 3.3%) All infectious complications (13.4% difference ± 3.9%)	First-generation cephalosporin may be of value in reducing infectious complications; results may not be applicable to the multiply injured patient.

Table 80-2 Summary of Meta-Analyses: Antibiotic Prophylaxis for Tube Thoracostomy

Study	Study Population and No. of Subjects	Study Design*	Dosing and Duration	Resu	ılts
Maxwell et al, 2004 <sup>32</sup>	Blunt, penetrating trauma Cefazolin (duration), 77 Cefazolin (24 hr), 76 Placebo, 71	DB, P, R	1 g IV q 8 hr for 24 hr or one dose after chest tube removal	Pneumonia 7.8% 7.8% 2.8%	Empyema 0% 2.5% 5.6%
Gonzalez & Holevar, 1998 <sup>48</sup>	Blunt, penetrating trauma Cefazolin, 71 Placebo, 68	DB, P, R	1 g IV q 8 hr until chest tube removal	Pneumonia 0% 3%	Empyema 0% 3%
Nichols et al, 1994 <sup>49</sup>	Blunt, penetrating trauma Cefonicid, 63 Placebo, 56	DB, P, R	1 g IV q 24 hr, stopped within 24 hr of chest tube removal	Pneumonia 0% 5%	Empyema 0% 7%
Cant et al, 1993 <sup>50</sup>	Stab wounds Cefazolin, 57 Placebo, 56	DB, P, R	500 mg IV q 8 hr for 24 hr	Pneumonia 12% 34%	Empyema 0% 9%
Stone et al, 1981 <sup>51</sup>	Mixed population Cefamandole, 60 Placebo, 60	DB, P, R	1 g IV q 6 hr until second day after tube removal	Infection 1.7% 13.3%	
Grover et al, 1977 <sup>52</sup>	Penetrating Clindamycin, 38 Placebo, 37	DB, P, R	300 mg IV q 6 hr until 1 day after chest tube removal or 5 days	Pneumonia 10.5% 35%	Empyema 2.6% 16.2%

Table 80-3 Summary of Randomized Controlled Trials: Antibiotic Prophylaxis for Tube Thoracostomy

\*DB, double-blind; P, prospective; R, randomized.

Table 80-4 Summary of Randomized Controlled Trials: Occult Pneumothorax						
Study	No. of Subjects (Intervention/No Intervention)	Study Design*	Intervention	Outcome Measure; Results	Conclusions	
Enderson et al, 1993 <sup>35</sup>	40 (19/21)	PRCT	Chest tube vs. observation	Pneumothorax progression; 8/21 (3 tension)	Tube thoracostomy if patient is on positive- pressure ventilation	
Brasel et al, 1999 <sup>34</sup>	39 (18/21)	PRCT	Chest tube vs. observation	Respiratory distress Pneumothorax progression; 3/21 (2 required tube thoracostomy)	Occult pneumothorax can be safely observed, even with positive-pressure ventilation	

\*PRCT, prospective randomized controlled trial.

pressure ventilation (IPPV) through endotracheal intubation with continuous positive airway pressure (CPAP) by facemask.<sup>44</sup> They observed a lower infection rate (4 of 22 versus 10 of 21; P = .001) and higher survival rate (20 of 22 versus 14 of 21; P < .01) in the CPAP group. There were no significant differences in ICU length of stay between the two groups. Mean Po<sub>2</sub> was significantly higher in the endotracheal intubation group in the first 2 days (P < .05). The authors concluded that the use of CPAP resulted in lower mortality and nosocomial infection rate but similar oxygenation and ICU length of stay. The study is limited by the fact that 9 of the original 52 patients were excluded from the study owing to hemodynamic instability or severe respiratory distress requiring endotracheal intubation.

### **AUTHORS' RECOMMENDATIONS**

- Epidural analgesia in patients with blunt chest trauma as the optimal and preferred modality for pain relief in the setting of multiple rib fractures.
- Pulmonary complications are the most common cause of death in patients with spinal cord injury.
- A chest radiograph obtained 1 to 3 hours after thoracostomy tube removal effectively identified recurrent pneumothorax.
- The use of presumptive antibiotics does not reduce the incidence of empyema or pneumonia.
- There are no clear guidelines for the management of occult pneumothorax.
- Noninvasive ventilation may be of benefit in chest trauma, but data are currently lacking.

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# 81

## What Is Abdominal Compartment Syndrome and How Should It Be Managed?

Benjamin Braslow, S. Peter Stawicki

Abdominal compartment syndrome (ACS) can be defined as the development of physiologic dysfunction in both intra-abdominal and extra-abdominal organs as the result of increased intra-abdominal pressure (IAP).<sup>1</sup> ACS constitutes an extreme along a spectrum of disorders involving increased IAP or intra-abdominal hypertension (IAH).<sup>2</sup>

Broadly speaking, abdominal compartment syndrome can be defined as primary, secondary, or recurrent. *Primary* ACS can be defined as an organ-threatening increase in IAP that develops as a result of an abdominal injury or other surgical abdominal emergency (i.e., bowel perforation or bowel ischemia). *Secondary* ACS is defined as the development of ACS in the absence of abdominal injury (i.e., following massive volume resuscitation). *Recurrent* ACS has been defined as ACS that develops in a patient with an open abdomen following initial successful surgical or medical treatment of either primary or secondary ACS.

The classically described therapy for the ACS involves a "damage-control"–abbreviated laparotomy.<sup>3,4</sup> This operative intervention allows for decompression of the abdominal contents, assessment of bowel and other intra-abdominal organs for ischemia or other pathologic changes, and delay of definitive operative repair of injuries until physiologic restoration and hemodynamic stability return.<sup>5</sup>

This chapter discusses clinical strategies used when approaching IAH or ACS from the intensivist's point of view, focusing on the essential physiologic rationale and practical aspects of clinical management of ACS.

### PATHOPHYSIOLOGY AND MECHANISM OF ACTION

The pathophysiology of ACS is complex. Development of overt ACS depends on whether the equilibrium between abdominal arterial inflow and venous outflow is maintained. In a way, one can conceptualize ACS as one would any other compartment syndrome (i.e., lower extremity compartment syndrome, increased intracranial pressure [ICP]). In this context, it becomes understandable how a patient can develop ACS even in the setting of an open abdomen. Such a scenario may occur when the damagecontrol abdominal dressing is placed too tightly, leading to a decrease in abdominal perfusion pressure.<sup>6</sup> In terms of absolute numbers, IAH can be graded according to the classification noted in Table 81-1.

For comparison, a normal adult will have an IAP in the range of 0 to 5 mm Hg, although this may be higher in morbidly obese and elderly patients. A recent study showed an increase of between 0.14 and 0.23 mm Hg for each body mass index (BMI) unit and 0.20 mm Hg for each year increase in age.<sup>2</sup> A typical intensive care unit (ICU) patient has an IAP in the range of 5 to 7 mm Hg. A postlaparotomy patient will exhibit an IAP range of 10 to 15 mm Hg. Patients who are in septic shock usually have an IAP of about 15 to 25 mm Hg, and those with acute abdomen (e.g., peritonitis, ACS) have an IAP in the range of 25 to 40 mm Hg.<sup>2</sup>

The abdominal perfusion pressure (APP) is equal to the difference between the mean arterial pressure (MAP) and the abdominal compartment pressure (ACP). ACP most often is estimated by the urinary bladder pressure measurement.<sup>7</sup> An increasing body of evidence supports the value of measuring the APP when assessing IAH and ACS.<sup>7</sup> Risk factors for the development of ACS are detailed in Table 81-2.

Increased IAP results in dysfunction of the respiratory, cardiovascular, and renal systems.<sup>5</sup> Elevated ICP and depressed cerebral perfusion pressure (CPP) also may result from increased IAP. ACS may therefore lead to congestive failure of all organs that depend on the maintenance of an adequate pressure differential between systemic arterial and venous systems. The following sections discuss the effects of ACS on individual organ systems.

### Respiratory System and Intra-Abdominal Hypertension and Abdominal Compartment Syndrome

Intra-abdominal hypertension may cause progressive cephalad elevation of the hemidiaphragms. The resultant decreases in thoracic volume (primarily the functional residual capacity) and compliance lead to increased peak inspiratory pressures and pulmonary vascular resistance. Higher pressures will be required to deliver a predetermined tidal volume, and ventilation-perfusion abnormalities develop. Escalations of positive end-expiratory

Table 81-1 IAH (	Grading Classification
Grade	Intra-Abdominal Pressure (mm Hg)
I	12-15
П	16-20
III	21-25
IV	>25

From Harman PK, Kron IL, McLaachlan HD, et al. Elevated intraabdominal pressure and renal function. Ann Surg. 1982;196:594–597.

Table 81-2 <b>Risk Factor</b> of ACS	s for the Development
Acidosis (pH < 7.2)	Hypothermia (Core Temperature < 33°C)
Massive transfusion (>10 U of packed red blood cells) or resuscitation (>5 L of colloid or crystalloid per 24 hr)	Coagulopathy (platelets < 55,000 or activated partial thromboplastin greater than 2 times normal or international normalized ratio > 1.5
Sepsis (AECC definitions)	Bacteremia
Intra-abdominal infection and/or abscess	Peritonitis
Hepatic dysfunction or cirrhosis with ascites	Mechanical ventilation
Use of PEEP or the presence of auto-PEEP	Pneumonia
Abdominal surgery (especially with tight fascial closures or massive incisional hernia repair)	Gastroparesis, gastric distention, ileus
Bowel volvulus	Hemoperitoneum or pneumoperitoneum
Major burn injury	Major traumatic injury
Body mass index > 30	Intra-abdominal or retroperitoneal tumors
Prone patient positioning	Acute pancreatitis
Damage control laparotomy	Laparoscopy with excessive inflation pressures
Peritoneal dialysis	

AECC, American-European Consensus Conference; PEEP, positive endexpiratory pressure.

Data from references 2-4.

pressure (PEEP) become necessary to maintain adequate patient oxygenation and lung recruitment. However, high levels of PEEP can further impair abdominal arterial inflow and venous outflow. This creates a cycle: continued impairments in ventilation and oxygenation lead to hypercarbia, acidosis, and progressive hypoxemia.<sup>8</sup>

### Effects of Intra-Abdominal Hypertension and Abdominal Compartment Syndrome on the Cardiovascular System

Increases in IAP lead to elevations in central venous pressure (CVP), pulmonary artery wedge pressure (PAWP), and systemic vascular resistance.<sup>8</sup> The measured CVP and PAWP reflect both the actual filling pressure and increased pleural pressure. Therefore, they may be elevated spuriously.<sup>9</sup>

Cardiac output (CO) decreases progressively as the IAP increases, likely as a result of decreased venous return and impaired pulmonary and perhaps systemic outflow.<sup>8</sup> The magnitude of the decline in CO may depend on the patient's intravascular volume. One experimental study demonstrated a 53% decrease in CO in hypovolemic animals but only a 17% decrease in the presence of euvolemia. Interestingly, hypervolemic animals actually demonstrated a 50% increase in CO.<sup>10</sup> Hypovolemia exacerbates all the cardiovascular effects of ACS. Although intravenous volume expansion may enhance CO and central filling pressures, it will not correct depressed renal function and reduced splanchnic blood flow (see later).

### Effects of Intra-Abdominal Hypertension and Abdominal Compartment Syndrome on the Renal System

Renal vascular resistance increases several-fold in ACS. The renal vein and inferior vena cava are compressed. Direct compression of the renal parenchyma also contributes to the renal dysfunction. Oliguria may develop despite normal or mildly elevated CVP and PAWP. Oliguria may be associated with IAP greater than 15 mm Hg, and anuria is seen more frequently with IAP greater than 30 mm Hg. Renal blood flow and the glomerular filtration rate are diminished. In an animal model, an IAP of 20 mm Hg decreased renal blood flow and glomerular filtration rate to 25% of normal. The decrease was even more profound (7% of normal) at an IAP of 40 mm Hg.<sup>11</sup> Oliguria often is the earliest sign of ACS, and anuria follows if the IAP is not reduced.<sup>8</sup> In a swine model, elevated IAP was associated with decreased urine output and upregulation of the renin-angiotensinaldosterone system. Abdominal decompression and intravascular volume expansion were able to reverse these deleterious effects.

An inadequate renal filtration gradient (FG) and renal perfusion pressure (RPP) may be important in the development of IAH-induced renal failure.<sup>13</sup> The renal FG is the mechanical force across the glomerulus and equals the difference between the glomerular filtration pressure (GFP) and the proximal tubular pressure (PTP). In the presence of IAH and ACS, PTP may be assumed to be equal to the IAP. GFP is estimated by the difference between MAP and IAP. Thus, GFP = MAP – 2(IAP). Consequently, changes in IAP are more likely to have an impact on renal function and urinary output than changes in MAP.<sup>14</sup>

### Abdominal and Visceral Effects of Intra-Abdominal Hypertension and Abdominal Compartment Syndrome

Clinically, increases in IAP are associated with increased abdominal girth and abdominal distention. Splanchnic blood flow decreases as ACS develops. Animal models indicate that increases in IAP decrease ileal and gastric mucosal blood flow and the organ blood flow index (organ blood flow/cardiac output) in most major abdominal organs; alter hepatic arterial, portal venous, and hepatic microcirculatory blood flow; impair hepatic energy production and small bowel tissue oxygen levels; reduce the hepatic energy level; and enhance bacterial translocation.<sup>15–22</sup>

### Effects of Intra-Abdominal Hypertension and Abdominal Compartment Syndrome on the Central Nervous System

Animal studies indicate that elevated IAP increased ICP and decreased CPP.<sup>23–25</sup> The proposed mechanism is functional obstruction of jugular venous drainage due to the elevated pleural pressures and CVP. Abdominal decompression resulted in a return toward baseline for ICP and an improvement in CPP.<sup>24</sup> With the common association of abdominal injury and closed head injury, this observation (confirmed clinically) is important.

### Effect of Intra-Abdominal Hypertension and Abdominal Compartment Syndrome on the Eyes

Increased IAP has been associated with the rupture of retinal capillaries, resulting in the sudden onset of decreased central vision (Valsalva retinopathy). Retinal hemorrhage usually resolves within days to months, and no specific treatment is necessary.<sup>26</sup> The diagnosis should be considered in any patient with ACS who develops visual changes.

### TREATMENT OF INTRA-ABDOMINAL HYPERTENSION AND ABDOMINAL COMPARTMENT SYNDROME

The appropriate treatment for confirmed or suspected ACS is decompressive laparotomy. During decompression, several actions are needed to prevent hemodynamic decompensation. These include restoration of the intravascular volume, correction of hypothermia, and correction of coagulopathy.<sup>8</sup> The abdomen may be opened in the surgical intensive care unit (SICU); however, the operating room is preferable. If the abdomen is opened in the SICU, the operating room must be prepared to accept the patient if surgically correctable bleeding is identified at the time of decompressive laparotomy.<sup>27</sup>

Decompression often is followed by diuresis and polyuria may develop. Peak airway pressure decreases as the abdomen is opened, and adjustments of the ventilator are likely to be needed.<sup>27</sup> Opening the abdomen may precipitate abrupt hypotension. Two possible etiologies have been proposed for this phenomenon. Decompression of the abdomen results in an acute, dramatic decrease in systemic vascular resistance and an increase in cardiac output; an acute drop in blood pressure results.<sup>28</sup> The second mechanism proposes that reperfusion of ischemic tissues may release acid and toxic metabolites that have deleterious vasoactive properties.<sup>8,27</sup> Judicious volume resuscitation and pressor use are warranted here as the goal is to limit further bowel edema and splanchnic ischemia. Resuscitative fluids containing bicarbonate-based buffers and free radical scavengers have been suggested empirically to help ameliorate the effects of reperfusion injury, but this is not widely supported by level I or II evidence.

After decompressive laparotomy, a temporary abdominal closure is performed. Formal fascial closure is postponed to prevent the development of recurrent ACS.<sup>29</sup> The simplest option for temporary closure includes skinonly closure using towel clips or a running nonabsorbable suture. This allows for considerable abdominal expansion while maintaining an insulating, protective shield. If bowel edema prevents skin approximation, a temporary silo device is an option. The vacuum dressing has evolved as the approach of choice. This device can be placed quickly and allows for considerable increase in abdominal volume while maintaining some inward traction on the fascia. Controlled egress of fluid from the abdomen is permitted while maintaining a sterile, secure barrier. Commercially available vacuum dressing devices are now available.

A vacuum pack closure does not eliminate the possibility of recurrent ACS.<sup>6</sup> Occasionally, adequate re-decompression can be achieved without extensive reoperative intervention simply by incising the external vacuum pack drape. Failure to treat recurrent ACS immediately is associated with extreme mortality.

There are isolated reports of percutaneous decompression for acute ACS. In that paradigm, percutaneous decompression through a peritoneal lavage catheter has been described to temporize the IAH and halt its progression to ACS in burn patients.<sup>30</sup> However, this approach should be used with extreme caution until there is more clinical evidence to support its more widespread use.

### **AUTHORS' RECOMMENDATIONS**

- Early recognition and treatment are of utmost importance when approaching patients with IAH and ACS.
- Abdominal compartment syndrome affects every major endorgan system in the body, effectively resulting in congestive failure and relative ischemia secondary to loss of arterialvenous pressure gradient in each one of those end organs.
- It is important to measure bladder pressure in the correct fashion. Instilling too much irrigant may cause falsely elevated IAP readings and lead to overly aggressive treatment.
- Although aspiration of peritoneal fluid may be an acceptable temporizing measure in selected cases, decompressive laparotomy is the only proven therapy for IAH and ACS.
- Operative treatment of IAH and ACS in nontrauma patients has many similarities to the damage-control approach used for trauma patients.
- ACS may occur even after decompressive laparotomy was performed, requiring loosening of the temporary abdominal dressings or another operation to perform further decompressive maneuvers.

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## 82

## How Should Pelvic Fractures Be Managed in the Intensive Care Unit?

Tracey Dechert, Patrick M. Reilly

Pelvic fractures are a common injury, with an estimated incidence of greater than 100,000 per year in the United States. Pelvic fractures represent a spectrum of injuries, from low-energy minimally displaced fractures seen in elderly patients after falls to highly displaced fractures seen in severe blunt trauma as indicators of high-energy transfer. The most common mechanisms of injury are motor vehicle collision, motorcycle crash, auto-pedestrian collision, and fall. Despite recent advances in surgical and intensive care unit (ICU) care that have improved survival, the morbidity and mortality of pelvic fractures remain high.<sup>1</sup> Although hemorrhage is a common cause of death in pelvic fracture patients, mortality is often determined by associated injuries in the blunt trauma patient.<sup>2</sup>

As with many areas of injury management, evidencebased literature regarding pelvic fracture management in the ICU is scarce. Still, available literature and expert opinion lend themselves to some recommendations. This chapter focuses on a number of important issues that the intensivist may manage, including hemodynamic instability and thromboembolic prophylaxis. Other issues, such as concomitant pelvic organ injury (e.g., rectum or urethra) and non-pelvic organ injury (e.g. spleen, aorta), are beyond the scope of this chapter.

### **PELVIC STABILIZATION**

Provisional mechanical stabilization of pelvic injuries is an important component in the resuscitation of hemodynamically labile patients (Table 82-1). Various noninvasive modalities can be used in the emergency room and ICU to stabilize the pelvis and help control venous hemorrhage. The simplest noninvasive maneuver is wrapping a sheet around the greater trochanters to apply pressure as manual reduction of the pelvic fracture is performed. More recently, commercial devices have been specifically designed to stabilize the pelvis during initial resuscitation. These devices are time-effective and technically simple, and their use has been associated with decreased transfusion requirements and even reduced mortality.<sup>3</sup> They effectively bridge the gap from injury to definitive stabilization.<sup>4</sup>

Another temporary measure that helps stabilize pelvic fractures and decreases blood loss from venous and soft tissue sources and fracture sites is application of an external fixating device. Two basic types of external fixation are currently used: anterior frames and pelvic clamps. Application of these devices can be performed in the emergency room, the operating room, or the ICU. However, expert orthopedic surgery support is usually required.

External binders traditionally should be left in place for a limited time (24 to 48 hours) because longer use raises concerns regarding skin breakdown. If left in place longer, regular examination of pressure points on the pelvis should be performed. Care should be taken to continue pelvic stabilization during laparotomy. Lower abdominal incisions may increase pelvic volume significantly and negatively affect attempts at tamponade of bleeding sources in the pelvis. Definitive internal stabilization (or long-term external fixation) should be considered as the patient's hemodynamics stabilize.

### **HEMORRHAGE CONTROL**

Resuscitation from hypovolemic shock is essential while hemorrhage control proceeds. Guidelines for resuscitation and transfusion of the bleeding trauma patient are discussed elsewhere. Care must be taken to monitor patients for abdominal compartment syndrome (ACS) during resuscitation. The combination of a large volume resuscitation and retroperitoneal hematoma from pelvic bleeding may lead to abdominal hypertension and ultimately the physiologic derangements seen in ACS. Although an element of tamponade may be useful in controlling bleeding from pelvic fractures, excessively high bladder pressures may make it necessary to open the upper abdomen. This allows abdominal visceral perfusion and improved ventilation and oxygenation by enhancing diaphragmatic motion.

### Interventional Radiology

After initial stabilization of the pelvic fracture and exclusion of other sources of hemorrhage, definitive management of pelvic bleeding must be addressed. Although

Table 82-1 Summary of Pelvic Stabilization Literature							
Study	No. of Subjects	Study Design	Intervention	Control	Outcomes		
Ghanayem et al, 1995 <sup>34</sup>	5 cadavers	Case series	Laparotomy	External fixator	Increase in pelvic volume during laparotomy without external fixation		
Bottlang et al, 2002 <sup>35</sup>	7 cadavers	Case series	Circumferential compression	No therapy	Decreased diastasis		
Krieg et al, 2005 <sup>36</sup>	16 patients	Case series	Circumferential compression	N/A	10% decrease in pelvic width		
Croce et al, 2007 <sup>3</sup>	186 patients	Retrospective	Pelvic orthotic device	External fixator	Decreased transfusion requirement and mortality vs. external fixation		
Nunn et al, 2007 <sup>37</sup>	7 patients	Case series	Pelvic orthotic device	N/A	Improved hemodynamics		
Jowett & Bower, 2007 <sup>38</sup>	10 patients	Case series	Pelvic orthotic device	No therapy	Increased pressure over bony prominences of pelvis		

veins and bony surfaces may be a major source of pelvic fracture bleeding that may be provisionally controlled by fracture stabilization, many patients with pelvic injury have arterial hemorrhage. Arterial hemorrhage from pelvic fracture should be suspected in patients with recurrent hypotension after a response to initial resuscitation efforts and in those patients with contrast extravasation seen on computed tomography (CT) scan. It is important to identify these patients early to prevent the development of hypothermia, coagulopathy, and multiple-organ dysfunction.

Since first reported in 1972, angiography in the management of hemorrhage associated with pelvic fracture has been a fundamental part of the management of these complicated injuries. A recent review of hemodynamically unstable pelvic fracture patients in Australia and New Zealand revealed that angiographic embolization is the preferred method to control pelvic arterial hemorrhage at the 11 trauma centers included in the study.<sup>5</sup> Various studies have shown angiography to have tremendous sensitivity and specificity (Table 82-2).

Transfemoral arteriography offers the opportunity to identify bleeding points and stop bleeding using selective embolization. This selective embolization often controls bleeding arteries that external fixation cannot tamponade. In some patients with severe hemodynamic instability and multiple bleeding points, scatter embolization of the bilateral internal iliac arteries provides effective control of retroperitoneal bleeding. The success of transarterial embolization of arterial bleeding from pelvic fractures is 85% to 100%.<sup>6</sup> However, even in the face of hemodynamic instability, no bleeding source is identified angiographically in 24% to 46% of patients with abdominal or pelvic trauma.<sup>7,8</sup> Studies have found that elderly patients are more likely to have arterial bleeding in conjunction with pelvic fractures.<sup>9,10</sup> The demonstration of bleeding sites may be more common in these patients owing to aging of vessels and atherosclerosis. Other independent

Table 82-2 Summary of Hemorrhage Control Literature					
Study	No. of Subjects	Study Design	Intervention	Control	Outcomes
Panetta et al, 1985 <sup>39</sup>	31 patients	Case series	Embolization	N/A	87% bleeding control
Stephen et al, 1999 <sup>40</sup>	111 patients	Case series	Computed tomography scan with intravenous contrast	N/A	Blush 80% positive predictive value and 98% negative predictive value for need for angiographic embolization
Velmahos et al, 2002 <sup>41</sup>	65 patients	Prospective	Angiography	N/A	95% success rate Rebleeding controlled by repeat angiography
Gourlay et al, 2005 <sup>42</sup>	556 patients	Retrospective	Angiography	N/A	7.5% required repeat embolization for additional bleeding
Cothren et al, 2007 <sup>43</sup>	28 patients	Prospective	Preperitoneal packing	N/A	Decreased transfusion requirement after procedure Decreased need for embolization
Tötterman et al, 2007 <sup>12</sup>	18 patients	Retrospective	Preperitoneal packing	N/A	Improved hemodynamics after procedure 80% need for embolization

predictors of active bleeding at time of angiography include need for emergent angiography and absence of long bone fracture.<sup>7</sup>

A number of complications of angiographic embolization have been reported. These include failure to control bleeding and the need for repeat angiographic embolization or pelvic packing.<sup>7</sup> Coagulopathic patients are at risk for ineffective embolization. It is possible that clot may not easily form in contact with Gelfoam slurry. This may allow vessels to recanalize before effective bleeding control is achieved. Gluteal necrosis, seen with bilateral internal iliac artery embolization, may be found in up to 5% of patients.<sup>11</sup> However, initial traumatic contusion may also contribute to the development of gluteal necrosis. The incidence of long-term sequelae, such as sexual dysfunction in males, is still unknown and is currently being studied.

### Other Options

Although the present dominant paradigm for unstable pelvic fracture patients is interventional radiologic management, definitive management also may be achieved with operative packing. Limited studies comparing angiographic embolization and pelvic packing have been performed. The resources available at each hospital must be considered, and if angiography is not immediately available, pelvic packing may be preferable in hemodynamically unstable patients.

In patients with no intraperitoneal hemorrhage, preperitoneal or extraperitoneal pelvic packing can be performed (see Table 82-2). This technique, widely used in Europe, is valuable when the origin of bleeding is known to be in the pelvic region. A lower midline incision is made, and the presacral and paravesical space is packed. These packs can remain in place for 24 to 48 hours as the patient continues to be resuscitated in the ICU. Advantages of this technique are that it is quick and easy to perform, and the pelvic packing cannot dislocate to the abdomen.

In patients with possible abdominal *and* pelvic sources, a laparotomy is required. These patients should be assessed for an expanding pelvic hematoma. If the hematoma is expanding or has ruptured, the pelvis can be packed and the wound closed over the packs. As with preperitoneal packing, these packs can remain in place for 24 to 48 hours, with a planned second procedure. This technique seems particularly applicable in patients who require a laparotomy for their intra-abdominal injuries.

The rationale behind pelvic packing derives from the fact that a major source of bleeding from the pelvis is venous. Whether traditional laparotomy or preperitoneal packing is performed, both should be followed by angiographic embolization. Of patients undergoing preperitoneal packing, up to 80% have arterial injury that requires embolization.<sup>12</sup>

### OTHER ISSUES

### **Open Pelvic Fractures**

Open pelvic fractures occur when there is communication between a fracture fragment and the skin, rectum, or vagina. Open fractures are seen in 4% to 5% of patients with pelvic fractures<sup>13</sup> and have a mortality rate of 30% to 50%.<sup>14</sup> Patients with open pelvic fractures are at risk for continued bleeding due to the disruption of the pelvic floor and subsequent loss of tamponade. These patients also are at risk for pelvic soft tissue infection and osteomyelitis. Pelvic fracture patients noted to have skin lacerations in the groin or perineum should be carefully evaluated for possible urinary tract, vaginal, or rectal injury. Often, rectal lacerations cannot be palpated, but blood will be found in the rectal lumen.

Historically, patients with open pelvic fractures underwent colostomy to prevent further perineal wound contamination. More recent studies have shown that the colostomy can be done selectively in open pelvic fracture patients based on the actual location of the laceration.<sup>15</sup> Patients with a perineal cutaneous wound and damage to the anal sphincter may need fecal diversion. Colostomy should be performed within the first 6 to 8 hours after injury to reduce the incidence of sepsis and death.<sup>16</sup>

Patients with open pelvic fracture in the ICU require meticulous wound care. These patients often require serial and radical debridement and repeated dressing changes, often requiring general anesthesia. Vacuum-assisted wound closure is an option for management of these complex wounds. Antibiotic treatment, whether systemic or by irrigation, has not been shown to reduce the incidence of infection or osteomyelitis.

### **Thromboembolic Prophylaxis**

Deep venous thrombosis (DVT) has been recognized as a major cause of morbidity and mortality after major blunt trauma.<sup>17,18</sup> A prevalence of 61% has been noted in patients with pelvic fractures that did not receive prophylaxis.<sup>19</sup> With prophylaxis, the prevalence of DVT ranges from 2% to 33% depending on patient population, screening method, and type of prophylaxis.<sup>20,21</sup> Most thrombi in pelvic fracture patients are intrapelvic.<sup>22</sup> In addition to causing pain, edema, and possibly postphlebitic syndrome, DVT may lead to pulmonary embolus, the most common cause of death occurring more than 7 days after traumatic injury.<sup>23</sup>

The American College of Chest Physicians conference on antithrombotic and thrombolytic therapy recommends prophylaxis for all major trauma patients.<sup>24</sup> Mechanical prophylaxis provides protection without increasing risk for blood loss and is available as low-pressure sequential compression devices or high-pressure pulsatile compression devices. Neither device has been found to be superior.<sup>25</sup> Patient compliance with mechanical prophylaxis usually is not a factor in the ICU. In addition to mechanical prophylaxis, pharmacologic prophylaxis also should be considered (Table 82-3). Enoxaparin, a low-molecularweight heparin, has been found to be more efficacious than low-dose heparin in preventing DVT in patients recovering from major trauma.26 The efficacy of enoxaparin is greater for proximal thrombi than for calf vein thrombi. In most patients, prophylaxis can safely be started within 36 hours of injury because bleeding has not been found to be a major complication.<sup>26</sup> Prophylactic inferior vena cava (IVC) filter placement has been described to prevent pulmonary emboli in patients with

Table 82-3 Summary of Thromboembolic Prophylaxis in Pelvic Fracture Literature

Study	No. of Subjects	Study Design	Intervention	Control	Outcomes
Dennis et al, 1993 <sup>44</sup>	395 patients	Prospective randomized	Heparin or SCD	No prophylaxis	SCDs comparable to heparin in lowering DVT incidence vs. control
Geerts et al, 1994 <sup>19</sup>	716 patients	Prospective	N/A	N/A	58% DVT rate without prophylaxis after major trauma
Geerts et al, 1996 <sup>26</sup>	344 patients	Prospective randomized	Enoxaparin	Heparin	Enoxaparin more effective in preventing venous thromboembolism
Velmahos et al, 2000 <sup>45</sup>		Meta-analysis	Heparin, enoxaparin, or SCD	No prophylaxis	No method of prophylaxis is superior to the other methods or to no prophylaxis
Velmahos et al, 2000 <sup>46</sup>		Meta-analysis	Vena caval filter	N/A	Suggestion that vena caval filter decreases risk for pulmonary embolus

DVT, deep venous thrombosis; SCD, sequential compression device.

complex pelvic fractures. The literature to support this practice is weak, and current guidelines do not recommend routine prophylactic IVC filter placement.

Duplex scanning has shown acceptable rates of sensitivity and specificity for diagnosing DVT in symptomatic patients. Venography remains the gold standard. However, there are risks associated with this study that relate to contrast and injection. Regarding surveillance, there currently are no standardized prophylactic programs. Although some data indicate that routine screening of asymptomatic high-risk patients may have benefit,<sup>27–29</sup> other studies suggest that routine screening is cost-prohibitive.<sup>30–32</sup> In patients with pelvic fractures, screening of leg veins actually may give a false sense of security as the pelvic veins may still contain a clot.

### CONTROVERSIES

The lack of class I evidence regarding pelvic fracture management ensures that controversies persist. Pelvic stabilization with a noninvasive binder has gained widespread support owing to its limited downside. Currently, controversy centers on the relative role and timing of radiographic embolization and preperitoneal packing in the treatment of hemodynamically unstable patients with pelvic fracture bleeding. Although the interventions may, in part, be complementary, the order in which they are performed varies greatly between trauma centers. Relative availability of resources may ultimately guide these decisions. If interventional radiologists are immediately available, the angiography suite may be the best place for the patient. If not, the operating room for preperitoneal packing may be indicated while the radiology team is mobilized. Regardless of procedure, ICU-level care needs to be delivered to continue and complete the resuscitation and rewarm the patient with complex pelvic trauma.

### GUIDELINES

Despite the lack of evidence, guidelines for the care of pelvic fracture bleeding are available. The Eastern Association for the Surgery of Trauma has evidence-based guidelines for "Hemorrhage in Pelvic Fracture" available on their website (http://www.east.org). These guidelines make level II recommendations regarding pelvic fracture stabilization, angiography, and embolization for hemorrhage control. The Western Trauma Association (WTA) has recently published a critical decision algorithm for the "Management of Pelvic Fracture with Hemodynamic Instability."<sup>33</sup> In addition to recommendations regarding stabilization and interventional radiology, the WTA algorithm also addresses the role of preperitoneal packing for hemorrhage control. Finally, the American College of Chest Physicians published an evidence-based review of the "Prevention of Venous Thromboembolism" in a 2008 supplement.<sup>24</sup> Specific attention to prophylaxis in the trauma patient is made with an extensive bibliography on the topic.

### **AUTHORS' RECOMMENDATIONS**

- Patients with pelvic fractures and hemodynamic instability represent a challenging patient population.
- Early noninvasive pelvic stabilization is beneficial in patients who have a mechanically unstable pelvis. This may limit venous bleeding (especially during transports) and provide an element of tamponade.
- Once other sources of hemorrhage are excluded, attention to direct control of pelvic bleeding may be indicated.
- If arterial pelvic bleeding is identified, immediate angiographic control is warranted. In the absence of immediate access to interventional radiology, surgical control with preperitoneal packing may be indicated.
- Throughout the process, ICU-level resuscitation should be ongoing. This should include warm blood products (including adequate factor replacement) to minimize end-organ ischemia.
- Care to monitor for abdominal hypertension is necessary in this patient population.
- Attention to thromboembolic prophylaxis is paramount because even the coagulopathic injured patient becomes hypercoagulable over the first few days in the ICU.

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## How Should Patients with Burns Be Managed in the Intensive Care Unit?

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More than 500,000 burn injuries occur annually in the United States.<sup>1</sup> Although most are minor, about 40,000 to 60,000 burn patients require admission to a hospital or major burn center for appropriate treatment every year.<sup>2</sup> The devastating consequences of burns have resulted in the allocation of significant clinical and research resources. This has led to improved care. Indeed, recent reports reveal a 50% decline in burn-related deaths and hospital admissions in the United States during the past 20 years. This reflects effective prevention strategies, decreasing the number and severity of burns.<sup>3,4</sup> Advances in therapy strategies, based on improved understanding of resuscitation, enhanced wound coverage, better support of the hypermetabolic response to injury, more appropriate infection control, and improved treatment of inhalation injury, also have improved the clinical outcome of this unique patient population. It is important to recognize that successful management of burn patients requires a diversified and multidisciplinary approach. This chapter gives an overview of the evidenced-based management of severely burned patients in the intensive care unit (ICU).

## INITIAL ASSESSMENT AND EMERGENCY TREATMENT

All burned patients should be managed initially as trauma patients, following the guidelines of the American College of Surgeons Committee on Trauma and the Advanced Trauma Live Support Center.<sup>5</sup> The algorithms for trauma evaluation should be diligently applied to the burn patient. On occasion, a severely burned patient may arrive in the ICU unintubated. In such cases, frequent evaluation of the airway and respiratory system may be required to detect impending respiratory failure. Any wheezing, stridor, hoarseness, or tachypnea may be a sign of airway compromise. Tracheal tugging, carbonaceous sputum, soot around the patient's airway passages, and singed facial or nasal hair may suggest an impending problem and requires immediate attention. As in any trauma patient, progression to the next step in the primary survey is delayed until a proper airway is established and maintained.

Respiratory rate, respiratory effort, breath sounds, and skin color reflect oxygenation and provide objective measurements of breathing.<sup>6,7</sup> A respiratory rate of less than 10 or greater than 60 breaths per minute is a sign of impending respiratory failure.<sup>6</sup> Use of accessory muscles, manifested by supraclavicular, intercostal, subcostal, or sternal retractions, and the presence of grunting or nasal flaring are signs of increased work of breathing.<sup>7</sup> Auscultation of breath sounds provides a clinical determination of tidal volume. Skin color deteriorates from pink, to pale, to mottled, to blue as hypoxemia progresses.<sup>8</sup> These signs must be followed throughout the primary survey to avoid respiratory failure. Children with probable respiratory failure should receive rapid, aggressive, definitive airway management. Oral intubation is the preferred method for obtaining airway access and should be accomplished early if impending respiratory failure or ventilatory obstruction is anticipated.<sup>7</sup>

Cardiac performance may be may be especially difficult to evaluate in the burn victim. In particular, burned extremities may impede the ability to obtain a blood pressure reading. In these situations, arterial lines, particularly femoral lines, are useful to monitor continuous blood pressure readings. Invasive hemodynamic monitoring through a pulmonary artery catheter (PAC) permits the direct and continuous measurement of central venous pressure (CVP), pulmonary capillary wedge pressure, cardiac output (CO), systemic vascular resistance (SVR), oxygen delivery (Do<sub>2</sub>), and oxygen consumption (Vo<sub>2</sub>). PAC-guided therapy has been studied most extensively in trauma and critically ill surgical patients. Hemodynamic data derived from the PAC appeared to be beneficial in assessing cardiovascular performance in certain situations (e.g., inadequate noninvasive monitoring, difficult-to-define end points of resuscitation).<sup>9</sup> However, the general practicability, riskto-benefit ratio, and lack of mortality reduction when using PAC have been widely criticized. Currently, there are no studies in burn patients that provide evidence-based recommendations. To overcome the disadvantages of the PAC, less invasive techniques have been developed.<sup>10</sup> However, none of these is specific to burn patients.

Recently, a novel technology has been described for ICU patients, the PiCCO technology. An arterial inserted catheter utilizes thermodilution to determine cardiac performance. This technique has been studied in critically ill patients but only small descriptive studies are available for burn patients right now. we conducted a prospective feasability study in 69 severely burned pediatric patients and found that this technology is feasable and continously monitors cardiac performance being less invasive when comapred to an PAC (Branski et al. Crit Care in press 2010).

### FLUID RESUSCITATION

Severe burn causes significant hemodynamic changes. These must be managed carefully to optimize intravascular volume, maintain end-organ tissue perfusion, and maximize oxygen delivery to the tissues.<sup>11</sup> Massive fluid shifts after severe burn injury result in the sequestration of fluid in both burned and nonburned tissue.<sup>12</sup> Release of proinflammatory mediators such as histamine, bradykinin, and leukotrienes leads to increased microvascular permeability, generalized edema, and burn shock, a leading cause of mortality in severely burned patients.<sup>13–15</sup> Early and accurate fluid resuscitation of patients with major burns is therefore critical for survival.<sup>16</sup> Calculations of fluid requirements are based on the amount of body surface involved in second- or

third-degree burns (not first-degree burns). The "rule of nines" (Fig. 83-1A) has been used to estimate the area of burned body surface, but this rule has limitations in the children, in whom the head is proportionally larger than the body. A more accurate assessment can be made of the burn injury, especially in children, by using the Lund and Browder chart, which takes into account changes associated with growth (Fig. 83-1B). After 48 hours, most practitioners give enough fluid to maintain urine output at 0.5 to 1 mL/kg body weight per hour. Various resuscitation formulas have been used. These differ in the amount of crystalloid and colloid to be given and in fluid tonicity (Table 83-1).<sup>11</sup> The American Burn Association (ABA) recently published practice guidelines on burn shock resuscitation.<sup>17</sup> However, no formula will accurately predict the volume requirements of an individual patient. The modified Brooke and Parkland (Baxter) formulas are the most commonly used early resuscitation formulas.<sup>18</sup> They use 2 to 4 mL/kg per percentage of body surface area burned (%BSAB) of lactated Ringer solution over 24 hours.<sup>15</sup> In children, maintenance requirements must be added to the



FIGURE 83-1. A, Estimation of burn size using the "rule of nines." B, Estimation of burn size using the Lund and Browder method.

Colloid Formula	Electrolyte	Colloid	
Evans	Normal saline, 1.0 mL/kg/%burn	1.0 cc/kg/%burn	
Brooke	Lactated Ringer solution, 1.5 mL/kg/% burn	0.5 mL/kg	
Slater	Lactated Ringer solution, 2 L/24 hr	Fresh-frozen plasma, 75 mL/kg/24 hr	
Crystalloid formulas Parkland Modified	Lactated Ringer solution Lactated Ringer solution	4 mL/kg/%burn 2 mL/kg/%burn	
Hypertonic saline solutions Monafo Warden	Volume to maintain urine output at 30 mL/hr; fluid contains 250 mEq Na/L Lactated Ringer solution + 50 mEq NaHCO <sub>3</sub> (180 mEq Na/L) for 8 hr to maintain urine output at 30-50 mL/hr. Lactated Ringer solution to maintain urine output at 30-50 mL/hr beginning 8 hr postburn		
Dextran formula (Demling)	Dextran 40 in saline, 2 mL/kg/hr for 8 hr Lactated Ringer solution, volume to maintain urine output at 30 mL/hr Fresh-frozen plasma, 0.5 mL/kg/hr for 18 hr beginning 8 hr postburn		

### Table 83-1 Formulas for Estimating Adult Burn Patient Resuscitation Fluid Needs

From Warden GD. Burn shock resuscitation. World J Surg. 1992;16:16–23.

Table 83-2 Formulas for Estimating Pediatric Resuscitation Needs				
Cincinnati Shriners Burns Hospital	4 mL × kg × % total BSA burn + 1500 mL × m <sup>2</sup> BSA	1st 8 hr 2nd 8 hr 3rd 8 hr	Lactated Ringer solution + 50 mg NaHCO <sub>3</sub> Lactated Ringer solution Lactated Ringer solution + 12.5 g albumin	
Galveston Shriners Burns Hospital	5000 mL/m <sup>2</sup> BSA burn + 2000 mL/m <sup>2</sup> BSA	Lactated Ringer solution + 12.5 g albumin		

BSA, body surface area.

resuscitation formula. Therefore, we recommend the Galveston Shriners Burns Hospital formula. This calls for initial resuscitation with 5000 mL/m<sup>2</sup>/% body surface area burned  $+ 2000 \text{ mL/m}^2/\%$  body surface area per day of lactated Ringers solution<sup>19</sup> (Table 83-2). For both formulas, the first half is administered within the first 8 hours after the burn, and one fourth is given in each of the next 16 hours. Intravascular volume status must be re-evaluated frequently during the acute phase. Fluid balance during burn shock resuscitation is typically measured by hourly urine output through an indwelling urethral catheter. It has been recommended to maintain urine output of about 0.5 mL/kg per hour in adults<sup>20</sup> and 0.5 to 1.0 mL/kg per hour in patients weighing less than 30 kg.<sup>21</sup> However, no clinical studies have identified the optimal hourly urine output to maintain vital organ perfusion during burn shock resuscitation. Because large volumes of fluid and electrolytes are administered both initially and throughout the course of resuscitation, it is important to obtain baseline laboratory measurements.<sup>22</sup> Crystalloid, in particular lactated Ringer solution, is the most popular resuscitation fluid currently used for burn patients.<sup>19</sup> Proponents of the use of crystalloid solutions alone report that other solutions, specifically colloids, are not better and are more expensive.<sup>23</sup> Perel and Roberts identified 63 trials comparing colloid and

crystalloid fluid resuscitation across a wide variety of clinical conditions and found no difference in survival.<sup>24</sup> The Cochrane Central Register of Controlled Trials could not demonstrate that albumin reduces mortality in this particular patient population compared with cheaper alternatives.<sup>25</sup> Vincent and colleagues showed in a cohort, multicenter, observational study that albumin administration was associated with decreased survival in a population of acutely ill patients compared with those who did not receive any albumin at any time throughout their ICU stay.<sup>26</sup> It is noteworthy that in this study, patients who received albumin were more severely ill than patients who did not receive albumin. Nonetheless, most burn surgeons agree that patients with very low serum albumin during burn shock may benefit from albumin supplementation to maintain oncotic pressure.<sup>27</sup>

### INHALATION INJURY

Inhalation injury constitutes one of the most critical problems accompanying thermal insult, with mortality paralleling that for ARDS in patients requiring ventilator support for more than 1 week.<sup>28,29</sup> Early diagnosis of bronchopulmonary injury is initiated by a history of closed-space exposure, facial burns, or carbonaceous

debris in mouth, pharynx, or sputum.<sup>30</sup> However, there are few evidence-based data regarding inhalation injury. Chest radiographs are routinely normal until complications have developed. The standard diagnostic method therefore should be bronchoscopy of the upper and lower airway of every burn patient. Endorf and Gamelli established a grading system for inhalation injury (0, 1, 2, 3, and 4) derived from findings at initial bronchoscopy and based on Abbreviated Injury Score (AIS) criteria.<sup>31</sup> Bronchoscopic criteria that are consistent with inhalation injury included airway edema, inflammation, mucosal necrosis, presence of soot and charring in the airway, tissue sloughing, or carbonaceous material in the airway. However, at this time, there are neither uniform diagnosis criteria nor standardized treatment guidelines.

Advances in ventilator technology and treatment of inhalation injury have resulted in some improvement in mortality. Pruitt and colleagues showed that since the advent of high-frequency ventilation, mortality has decreased to 29%, from 41% reported in an earlier study using historical control (estimated blood loss [EBM] grade C).<sup>32</sup> Management of inhalation injury consists of ventilatory support, aggressive pulmonary toilet, bronchoscopic removal of casts, and nebulization therapy.<sup>11</sup> Permissive hypercapnia may be required. According to the ABA guidelines, prophylactic antibiotics are not indicated.

### SEPSIS

Sepsis is one of the leading causes of morbidity and mortality in critically ill patients.<sup>33</sup> Severely burned patients are susceptible to a variety of infectious complications.<sup>34</sup> The standard criteria for infection and sepsis do not apply to burn patients because these patients already suffer from a systemic inflammatory response.<sup>35</sup> Consequently, 23 experts in the field of burn care or research established definitions and guidelines for the diagnosis and treatments of wound infection and sepsis in burns (Table 83-3).

### **BURN WOUND EXCISION**

Methods for handling burn wounds have changed in recent decades. Increasingly, aggressive early tangential excision of the burn tissue and early wound closure primarily by skin grafts have led to significant improvement of mortality rates and substantially lower costs in this particular patient population.<sup>11,36–39</sup> Éarly wound closure also has been associated with decreased severity of hypertrophic scarring, joint contractures and stiffness, and quicker rehabilitation.<sup>11,36</sup> Techniques of burn wound excision have evolved substantially over the past decade. Published estimates of bleeding associated with these operations range between 3.5% and 5% of the blood volume for every 1% of the body surface excised.<sup>40,41</sup> Blood loss during excision should be minimized through the use of extremity tourniquets and dilute epinephrine injection.<sup>42</sup> Burn wound excision should occur in the operating room soon after the patient is admitted; however, sometimes excision may be necessary in the ICU.

Various biologic and synthetic substrates have been employed to replace the injured postburn skin. Autografts

### Table 83-3 Definition of Burn Sepsis

### AMERICAN BURN ASSOCIATION CONSENSUS DEFINITION ON BURN SEPSIS

At least 3 of the following parameters:

- $T > 38.5 \text{ or} < 36.5^{\circ}C$
- Progressive tachycardia > 90 bpm in adults or > 2 SD above age-specific norms in children
- Progressive tachypnea > 30 bpm in adults or > 2 SD above age-specific norms in children
- WBC >12,000 or < 4000 in adults or > 2 SD above age-specific norms in children
- Refractory hypotension: SBP < 90 mm Hg, MAP < 70, or an SBP decrease > 40 mm Hg in adults or < 2SD below normal for age in children
- Thrombocytopenia: platelet count < 100,000/μL in adults,</li>
  < 2 SD below norms in children</li>
- Hyperglycemia: plasma glucose > 110 mg/dL or 7.7 mM/L in the absence of diabetes
- Enteral feeding intolerance (residual > 150 mL/hr in children or 2 times feeding rate in adults; diarrhea > 2500 mL/day for adults or > 400 mL/day in children)

### AND

Pathologic tissue source identified: >105 bacteria on quantitative wound tissue biopsy or microbial invasion on biopsy Bacteremia or fungemia

Documented infection as defined by CDC

From Greenhalgh DG, Saffle JR, Holmes JH, et al. American Burn Association consensus conference to define sepsis and infection in burns. J Burn Care Res. 2007;28:776–790.

from uninjured skin remain the mainstay of treatment for many patients. Because early wound closure using autograft may be difficult when full-thickness burns exceed 40% total body surface area, allografts (cadaver skin) may serve as a skin substitute in severely burned patients.<sup>43</sup> Although xenografts provide a biologically active dermal matrix, immunologic disparities prevent engraftment and predetermine rejection over time.<sup>44</sup> However, both xenografts and allografts are only a means of temporary burn wound cover. True closure can only be achieved with living autografts or isografts. Autologous epithelial cells grown from a single full-thickness skin biopsy decreased mortality in massively burned patients in a prospective, controlled trial.<sup>45</sup> Barret and others found that cultured epithelial autografts, in combination with wide mesh autograft and allograft overlay, in a pediatric patient population with burns covering 90% or more of their total body surface area were associated with improved cosmetic results.<sup>46</sup> Widespread use of cultured autografts has been primarily hampered by poor longterm clinical results, exorbitant costs, and fragility and difficult handling of these grafts.<sup>44,47,48</sup> Alternatively, dermal analogs have been approved by the U.S. Food and Drug Administration and have been associated with reduction in length of hospital stay, favorable cosmetics, and improved functional outcome in a prospective and controlled clinical study.<sup>49–52</sup> Use of analogs in children has been associated with attenuated hepatic dysfunction, improved resting energy expenditure, and improved

postburn aesthetic outcome.<sup>53</sup> AlloDerm, an acellular human dermal allograft, may be useful in the treatment of acute burns.<sup>54–57</sup> Tissue engineering technology is advancing rapidly. Fetal constructs have recently undergone successfully trials by Hohlfeld and colleagues,<sup>58</sup> and the bilaminar skin substitute of Supp and Boyce<sup>59</sup> is now routine in clinical use and promise spectacular results.<sup>60</sup> Advances in stem cell culture technology are expected to deliver full cosmetic restoration for burn patients.

### METABOLIC RESPONSE AND NUTRITIONAL SUPPORT

The metabolic consequences of severe burn injury are profound, and their modulation constitutes an ongoing challenge for successful treatment.<sup>61</sup> Metabolic rates of burn victims dramatically exceed those of most other critically ill patients and cause marked wasting of lean body mass within days of injury.<sup>62</sup> Failure to meet the subsequent large energy and protein requirements may result in impaired wound healing, organ dysfunction, increased susceptibility to infection, and death.<sup>63</sup> Thus, adequate nutrition is imperative. Because of the significant increase in postburn energy expenditure, high-calorie nutritional support was thought to decrease muscle metabolism.<sup>64</sup> However, a randomized, double-blind, prospective study found that aggressive high-calorie feeding with a combination of enteral and parenteral nutrition was associated with increased mortality.65 Most authors therefore recommend adequate calorie intake through early enteral feeding and avoidance of overfeeding.<sup>11,62</sup> Different formulas have been developed to address the specific energy requirements of burned adult and pediatric patients<sup>66</sup> (Tables 83-4 and 83-5). The caloric requirements in adult burn patients most often are calculated using the Curreri formula. This calls for 25 kcal/kg per day plus 40 kcal/% BSAB per day.<sup>69</sup> This formula provides for maintenance needs plus the additional caloric needs of the burn wounds. Normally, significant alterations in the metabolism of lipids, carbohydrates, and proteins determine the caloric distribution of the dietary needs of the critically ill patient. The optimal dietary composition contains 1 to 2 g/kg per day of protein, providing for the synthetic needs of the patient.<sup>63</sup> Because of glucose intolerance

and futile cycling in critical illness, most ICUs provide a significant amount of caloric requirements as fat.<sup>63,70</sup> However, burn patients require a different approach. Several studies indicated that increased fat administration may lead to increased complications, including hyperlipidemia, hypoxemia, fatty liver infiltration, higher incidence of infection, and higher postoperative mortality rates in the burned patient population.<sup>71–73</sup> Livers of burn patients secrete less very-low-density lipoprotein, and this

Table	83-5	Form	ulas fo	or Esti	imati	ng Ca	aloric
Requi	remei	nts in	Pediat	tric B	urn P	atien	its

Formula	Sex/Age	Equation (Daily Requirement in kcal)
WHO <sup>109</sup>	Males 0-3 yr 3-10 yr 10-18 yr Females 0-3 yr 3-10 yr 10-18 yr	$(60.9 \times W) - 54$ $(22.7 \times W) + 495$ $(17.5 \times W) + 651$ $(61.0 \times W) - 51$ $(22.5 \times W) + 499$ $(12.2 \times W) + 746$
RDA <sup>110</sup>	0-6 mo 6 mo to 1 yr 1-3 yr 4-10 yr 11-14 yr	$\begin{array}{l} 108 \times W \\ 98 \times W \\ 102 \times W \\ 90 \times W \\ 55 \times W \end{array}$
Curreri junior <sup>111</sup>	<1 yr 1-3 yr 4-15 yr	$\begin{array}{l} \text{RDA} + (15 \times \%\text{BSAB}) \\ \text{RDA} + (25 \times \%\text{BSAB}) \\ \text{RDA} + (40 \times \%\text{BSAB}) \end{array}$
Galveston infant <sup>112</sup>	0-1 yr	2100 kcal/m <sup>2</sup> BSA + 1000 kcal/m <sup>2</sup> BSAB
Galveston revised <sup>68</sup>	1-11 yr	1800 kcal/m <sup>2</sup> BSA + 1300 kcal/m <sup>2</sup> BSAB
Galveston adolescent <sup>113</sup>	12+	1500 kcal/m <sup>2</sup> BSA + 1500 kcal/m <sup>2</sup> BSAB

%BSAB, percentage of total body surface area burned; BSA, body surface area; BSAB, body surface area burned; RDA, Recommended Dietary Allowance (U.S.); WHO = World Health Organization.

Table 83-4 Formulas for Estimating Caloric Requirements in Adult Burn Patients				
Formula	Age/Sex	Equation		
Harris-Benedict <sup>108</sup>	Men	BEE (kcal/day) = $66.5 + (13.75 \times W) + (5.03 \times H) - (6.76 \times A)$		
	Women	BEE (kcal/day) = 655 + (9.56 $\times$ W) + (1.85 $\times$ H) - (4.68 $\times$ A)		
Comment: Multiply BEE by stress factor of 1.2-2.0 (1.2-1.5 sufficient for most burns) to estimate caloric requirement.				
Curreri <sup>66</sup>	Age: 16-59 yr	Calories (kcal/day) = $(25 \times W) + (40 \times \text{\%BSAB})$		
	Age: >60 yr	Calories = $(20 \times W) + (65 \times \text{\%BSAB})$		
Comment: Specific for burns, may significantly overestimate energy requirements, maximum 50% BSAB.				
%BSAB, percentage of total body surface area burned; A, age (yr); H, height (cm); BEE, basal energy expenditure; W, weight (kg).				

contributes to hepatic triglyceride accumulation.<sup>74</sup> Thus, the extent to which exogenous lipid can be used as an energy source is limited.<sup>61,70,75</sup> Consistent with the previous observations, studies in a large cohort of severely burned children demonstrated that patients receiving a low-fat, high-carbohydrate diet had a significantly lower incidence of fatty liver on autopsy. Relative to historical controls, these patients had a significantly lower incidence of sepsis, prolonged survival, and significantly shorter stays in the ICU (grade C data). Based on these findings, we recommend that nutritional regimes for treatment of burn patients include a significantly reduced proportion of fat as the source of total caloric intake.

Diminished gastrointestinal absorption, increased urinary losses, altered distribution, and altered carrier protein concentrations following severe burns may lead to micronutrient deficiency. These deficiencies in trace elements and vitamins (Cu, Fe, Se, Zn, vitamins C and E) have been repeatedly described in major burns.<sup>76–78</sup> This may lead to infectious complications, delayed wound healing, and stunting in children.<sup>79</sup> Thus, supplementation would seem appropriate. However, evidence-based practice guidelines are not currently available for the assessment and provision of micronutrients in burn patients. Enhancing trace element status and antioxidant defenses by supplementing selenium, zinc, and copper was shown to decrease the incidence of nosocomial pneumonia in critically ill, severely burned patients in two consecutive, randomized doubleblind trials.<sup>80</sup> Caution should be used to avoid toxic side effects.

### MODULATION OF THE HORMONAL AND ENDOCRINE RESPONSE

Modification of adverse components of the hypermetabolic response to burn injury, particularly protein catabolism, would seem to be desirable. β-Adrenergic blockade, β-adrenergic supplementation, anabolic steroids, recombinant growth hormone, and insulin-like growth factor (IGF) are under active investigation. Various studies have demonstrated the potential beneficial effect of  $\beta$ -blockers in burn patients. In a single-center study, administration of propranolol in doses that decrease the heart rate by about 15% to 20% from baseline reduced the release of free fatty acids from adipose tissue, decreased hepatic triacylglycerol storage and fat accumulation, and reversed muscle protein catabolism.<sup>81-83</sup> In a retrospective study of adult burn patients, use of β-blockers was associated with decreased mortality, wound infection rate, and wound healing time.<sup>84</sup> Therefore, β-blockers appear to be a highly effective anticatabolic treatment in severely burned patients.

Treatment with anabolic agents, such as oxandrolone, a testosterone analog, improved muscle protein catabolism through enhanced protein synthesis efficiency,<sup>85</sup> reduced weight loss, and increased donor site wound healing.<sup>86</sup> In a prospective randomized study, Wolf and colleagues demonstrated that administration of 10 mg of oxandrolone every 12 hours decreased hospital stay.<sup>87</sup> In a large prospective, double-blind, randomized single-center study, oxandrolone given at a dose of 0.1 mg/kg every

12 hours shortened length of acute hospital stay, maintained lean body mass, and improved body composition and hepatic protein synthesis.<sup>88</sup>

The use of recombinant human growth hormone in daily subcutaneous doses has been reported to accelerate donor site healing and restore earlier positive nitrogen balance.<sup>89–91</sup> Indeed, administration of 0.05 mg/kg of recombinant human growth hormone given over a 12-month period after burn injury improved height, weight, lean body mass, bone mineral content, cardiac function, and muscle strength significantly.<sup>92</sup> These findings are in contrast to those of Takala and colleagues<sup>93</sup> and with studies showing that growth hormone treatment induced hyperglycemia and insulin resistance.<sup>91,94</sup> It is likely that the prolonged catabolic nature of burn injury and perhaps the dose account for these discrepant results. IGF-1 has been shown to decrease the metabolic rate after burn injury and to increase whole-body anabolic activity without hyperglycemia or insulin resistance.<sup>95</sup> However, studies by van den Berghe and colleagues (reviewed in Endocrinol Metab Clin North Am. 2006;35:793-805 or Crit Care Clin. 2006;22:17-28) indicate that the use of IGF-1 alone is not effective in critically ill patients without burns. Again, the prolonged catabolic nature of burn injury may explain the difference.

### **GLUCOSE CONTROL**

A prominent component of the hypermetabolic response after burn injury is hyperglycemia and insulin resistance.<sup>96</sup> These result from both an increase in hepatic gluconeogenesis and impaired insulin-mediated glucose transport into skeletal muscle cardiac muscle and adipose tissue.<sup>97–100</sup> Both hyperglycemia and elevations in circulating insulin concentrations are of serious clinical concern. Hyperglycemia has been linked to impaired wound healing, increased infectious complications, and increased mortality.<sup>101–103</sup> Thus, recent studies have focused on potential treatment options. These studies<sup>104–107</sup> are reviewed elsewhere. However, the available data supporting intensive insulin therapy are equivocal. Despite the presumed importance of glucose control in burn patients, there are few data.

### CONCLUSION

Burn injuries alter a number of physiologic functions and are associated with substantial morbidity and mortality. Appropriate early and continued fluid resuscitation likely improves tissue perfusion and limits organ system failure. Similarly, early excision of burn wounds and topical antimicrobial agents may limit sepsis. Patients who have sustained an inhalation injury also may require additional support. Enteral tube feeding is useful to control stress ulceration, maintain intestinal mucosal integrity, and provide fuel for the resulting hypermetabolic state.  $\beta$ -Adrenergic blockade is recommended by many burn units as an anticatabolic treatment. Centralized care in burn units has promoted a concentrated team approach that has promoted clinical studies to examine such issues
as fluid resuscitation, nutrition, wound excision, and temporary wound coverage. Further studies are required to address the primary determinants of death, inhalation injury complications, and pneumonia as well as to ameliorate pain and scar formation. Through the use of aggressive resuscitation, nutritional support, infection control, surgical therapy, and early rehabilitation, better psychological and physical results can be achieved for burn patients.

#### AUTHORS' RECOMMENDATIONS

- Burn patients should be managed initially as trauma patients. Algorithms for trauma evaluation should be diligently applied to the burn patient.
- Early and accurate fluid resuscitation of patients with major burns is critical for survival. However, overaggressive resuscitation should be avoided, particularly in small children younger than 4 years.
- Early diagnosis of bronchopulmonary injury is critical. Management of inhalation injury consists of ventilatory support, aggressive pulmonary toilet, bronchoscopic removal of casts, and nebulization therapy.
- Adequate nutritional intake through enteral tube feeding will aid in the control of stress ulceration, preserve intestinal mucosal integrity, and provide fuel for the resulting hypermetabolic state. Nutritional regimes for treatment of burn patients include a significantly reduced proportion of fat as the source of total caloric intake.
- Modulation of the hypermetabolic response improves outcomes.
- Hyperglycemia in burn patients is associated with increased complications. The benefit of tight euglycemic control is under investigation.

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84

### What Is the Best Approach to Fluid Management, Transfusion Therapy, and the End Points of Resuscitation in Trauma?

Samuel A. Tisherman

Exsanguinating hemorrhage is a major cause of death from trauma. Rapid fluid resuscitation accompanied by aggressive efforts at hemostasis is required to save lives. Many questions regarding fluid resuscitation remain. This chapter addresses the choice of fluid and indications for blood products, as well as the goals for fluid resuscitation, which are different before and after hemostasis is achieved.

#### CHOICE OF FLUID

The use of crystalloids for resuscitation from traumatic hemorrhagic shock (HS) was initially promoted by the work of Shires based on changes in fluid compartments during HS.<sup>1,2</sup> Administration of lactated Ringer (LR) solution quickly became a standard of the Advanced Trauma Life Support (ATLS) course of care in prehospital and emergency department (ED) resuscitation of trauma victims. The use of crystalloids for resuscitation of trauma patients has recently come into question. These solutions are not as innocuous as originally believed. Laboratory studies have demonstrated that crystalloids may exacerbate cellular injury. LR solution can cause an increase in oxidative burst and expression of adhesion molecules on neutrophils in human blood.<sup>3</sup> During HS in pigs, LR solution similarly increases neutrophil oxidative burst.<sup>4</sup> No clinical studies have yet compared different crystalloids.

Modifications of LR, for example, substituting the L-isomer of lactate or substituting pyruvate or ketone bodies ( $\beta$ -hydroxybutyrate) for racemic lactate can decrease the neutrophil activation and apoptosis.<sup>5,6</sup> Hypertonic saline (HTS) and fresh whole blood, in contrast, do not cause neutrophil activation.<sup>7</sup> HTS can attenuate immune-mediated cellular injury after trauma<sup>8</sup> through several mechanisms, including decreased neutrophil excitation,<sup>9</sup> neutrophil-endothelial binding,<sup>10</sup> and lung damage.<sup>11</sup> Rizoli and colleagues demonstrated that HTS promoted a more balanced inflammatory response to traumatic hemorrhagic shock.<sup>12</sup>

Several small clinical trials have suggested a benefit of hypertonic solutions for resuscitation of trauma patients (Table 84-1). These studies explored the use of HTS alone or hypertonic saline-dextran (HSD), a hypertonic fluid with a colloid added to prolong the intravascular volume expansion. Multiple studies<sup>13-22</sup> demonstrated that HTS or HSD increased blood pressure and volume expansion better than crystalloids but could not document improved survival. Mattox and colleagues<sup>16</sup> and Wade and coworkers<sup>20</sup> found that HSD improved survival in the subset of patients who required operation, presumably more severely injured patients. Similarly, Bulger and associates found that HSD, compared with LR, improved acute respiratory distress syndrome (ARDS)-free survival only in patients who required more than 10 U of packed red blood cells (PRBCs).<sup>2</sup>

Several meta-analyses of the studies comparing crystalloids, hypertonic fluids, and colloids have been performed (Table 84-2). Those regarding colloids were recently reviewed.<sup>24</sup> Both Velanovich<sup>25</sup> and Bisonni and coworkers<sup>26</sup> examined a relatively small number of studies that compared colloids and crystalloids. In the subsets of patients with hypovolemia, colloids appeared to increase mortality. Using more sophisticated methodology, Schierhout and Roberts included 37 studies and found only a trend toward worse outcomes with colloids.<sup>27</sup> This analysis was confounded, however, by the fact that they combined studies of HTS alone with studies of colloids. The Cochrane Injuries Group Albumin Reviewers similarly only found a trend toward worse mortality with colloids in hypovolemic patients.<sup>28</sup> Using a more rigorous approach, Choi and coworkers found a significant increase in mortality associated with the use of colloids in trauma patients.<sup>29</sup> The most recent analysis by Wilkes and Navickis found only a trend toward increased mortality with the use of albumin in surgery and trauma patients.<sup>30</sup> Regarding hypertonic fluids, Wade and associates reviewed 14 trials of HTS or HSD and found that neither conferred a statistically significant survival benefit but that HSD appeared more promising.<sup>31</sup>

Table 84-1 Summary of Randomized Controlled Trials						
Study	No. of Subjects (Intervention/ No Intervention)	Study Design	Intervention	Control	Outcomes	
HYPERTONIC SAL	INE FOR HEMORR	HAGIC SHOCK				
Bulger et al, 2007 <sup>8</sup>	36/26	Double-blind	HSD	LR	Inhibit CD11b Trend increase IL-1β, IL-10	
Bulger et al, 2007 <sup>23</sup>	110/99	Double-blind	HSD	LR	No difference ARDS-free survival. Improved ARDS-free survival if >10 U blood	
Rizoli et al, 2006 <sup>12</sup>	13/14	Double-blind	HSD	NS	Promotes a more balanced inflammatory response	
Wade et al, 2003 <sup>20</sup>	120/110	Double-blind	HSD	NS	Survival 83% vs. 76% overall (NS), 85% vs. 67% for patients requiring surgery (P = .01)	
Mauritz et al, 2002 <sup>19</sup>	100	Double-blind	HTS or HES		Increase BP, decrease HR. Five with side effects	
Vassar et al, 1993 <sup>18</sup>	85 HTS 89 HS 84 NS	Double-blind	HS or HSD	LR	HS improved survival compared with TRISS	
Younes et al, 1992 <sup>22</sup>	35/35/35	Double-blind	HS or HSD	NS	No difference in survival. Better blood pressure and volume expansion. Less fluid needed	
Vassar et al, 1991 <sup>13</sup>	83/83	Double-blind	HSD	LR	Improved BP. No change in survival	
Mattox et al, 1991 <sup>16</sup>	211/211	Double-blind	HSD	Crystalloid	No difference in survival, except patient who required operation. Improved blood pressure, fewer complications	
Vassar et al, 1990 <sup>17</sup>	32 HTS 23 HSD 51 LR	Double-blind	HSD HS	LR	No safety issues, except mild hyperchloremic acidosis	
Maningas et al, 1989 <sup>15</sup>	48		HSD	Plasmalyte A	Feasibility study	
Holcroft et al, 1989 <sup>21</sup>	32	Double-blind	HSD	Crystalloid	No difference in survival	
Holcroft et al, 1987 <sup>14</sup>		Double-blind	HSD	LR	Improved BP	
TRANSFUSION						
Phelan et al, 2007 <sup>45</sup>	240/439	Retrospective	Leukocyte- depleted packed red blood cells	Standard packed red blood cells	No difference in LOS or mortality	

	mmary of Randol	mizea Controllea	Trials—Cont <sup>r</sup> d		
Study	No. of Subjects (Intervention/ No Intervention)	Study Design	Intervention	Control	Outcomes
Nathens et al, 2006 <sup>44</sup>	286	Randomized	Leukocyte- depleted packed red blood cells	Standard packed red blood cells	No difference in infections, organ failures, mortality
Dunne et al, 2006 <sup>40</sup>	93/117	Prospective OIF	Transfused	Not transfused	Higher ISS, HR, lower hematocrit, increased infection rate, ICU, LOS
Silverboard et al, 2005 <sup>42</sup>	102	Prospective			The amount of transfused blood is independently associated with both the development of ARDS and hospital mortality
Dunne et al, 2004 <sup>39</sup>	954/8585	Prospective	Transfused	Not transfused	Older, higher ISS, lower Glasgow Coma Scale score, more SIRS, higher mortality
Malone et al, 2003 <sup>41</sup>	15,534	Prospective	Transfused	Not transfused	Increase mortality (odds ratio, 2.8), ICU, LOS
Offner et al, 2002 <sup>43</sup>	61	Prospective	Transfused		Older blood increased risk for infections
Hebert et al, 1999 <sup>37</sup>	418/420 ICU patients	Prospective	Hemoglobin 7-9 g/dL	Hemoglobin 10-12 g/dL	Improved survival to discharge, not long-term. Increase survival for APACHE <20 or <55 yr old
McIntye et al, 2004 <sup>38</sup>	100/103 trauma patients	Prospective	Hemoglobin 7-9 g/dL	Hemoglobin 10-12 g/dL	No differences
CLOTTING FACTO	OR REPLACEMENT				
Borgman et al, 2007 <sup>46</sup>	246		Plasma-to-red blood cell ratio		High plasma-to-red blood cell ratio 1:1.4 vs. 1:2.5 or 1:8 is correlated with improved survival
LIMITED FLUID R	ESUSCITATION FO	R UNCONTROLLED	HEMORRHAGE		
Dutton et al, 2002 <sup>55</sup>	55/55	Randomized	SBP > 70 mm Hg	SBP > 100 mm Hg	Survival 93% with no difference between groups
Hambly & Dutton, 1996 <sup>56</sup>	527	Retrospective	RIS used	Historical controls	Increases (4.8 times) risk for dying
Bickell et al, 1994 <sup>54</sup>	309/289	Randomized day of month	Delayed resuscitation		Improved survival: 70% vs. 62%. Decreased LOS
Kaweski et al, 1990 <sup>53</sup>	6855	Retrospective	Prehospital fluid	No prehospital fluid	No difference in mortality

### Table 84-1 Summary of Randomized Controlled Trials-Cont'd

Continued

#### Table 84-1 Summary of Randomized Controlled Trials-Cont'd

Study	No. of Subjects (Intervention/ No Intervention)	Study Design	Intervention	Control	Outcomes
END POINTS OF R	ESUSCITATION F	ROM TRAUMA			
McKinley et al, 2002 <sup>62</sup>	18/18	Prospective nonrandomized	Do <sub>2</sub> 500	Do <sub>2</sub> 600	Less fluid and blood needed, similar outcome
Velmahos et al, 2000 <sup>61</sup>	40/35	Prospective randomized	Supranormal Do <sub>2</sub>	Normal Do <sub>2</sub>	Patients who achieve supranormal values increased survival, but no difference between groups in mortality, organ failure, LOS
Bishop et al, 1995 <sup>59</sup>	50/75	Randomized	Supranormal Do <sub>2</sub>	Normal Do <sub>2</sub>	Improved survival (18% vs. 37%) and organ system failures
Fleming et al, 1992 <sup>60</sup>	33/34	Randomized	Supranormal Do <sub>2</sub>	Normal Do <sub>2</sub>	Decreased mortality, organ failure, LOS, ventilation days
Duane et al, 2006 <sup>71</sup>	50/176	Prospective	Blood sugar > 150	Blood sugar $\leq 150$	Blood sugar correlated with ISS and lactate
Fleming et al, 2006 <sup>60</sup>	5995	Retrospective			Lactate did not correlate with mortality
FitzSullivan, 2005 <sup>70</sup>	3102		Serum bicarbonate		Correlated with base deficit, survival
Cerovic et al, 2003 <sup>67</sup>	98	Prospective		Standard care	Admission lactate level correlates with ISS and 12-hr lactate with survival
Kincaid et al, 1998 <sup>66</sup>	100	Prospective	High base deficit	Low base deficit	Increased multiple- organ failure and mortality, low oxygen utilization
Davis et al, 1998 <sup>65</sup>	674	Observational			Base deficit worse in nonsurvivors. No difference in pH
Rutherford et al, 1992 <sup>63</sup>	3791	Retrospective			Base deficit, age, injury mechanism, and head injury were associated with mortality using logistic regression
Davis et al, 1988 <sup>64</sup>	209	Observational			Higher base deficit associated with lower BP and greater fluid resuscitation

APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; BP, blood pressure; Do<sub>2</sub>, oxygen delivery; HES, hydroxyethyl starch; HR, heart rate; HS, hemorrhagic shock; HSD, hypertonic saline-dextran; HTS, hypertonic saline; ICU, intensive care unit; IL, interleukin; ISS, Injury Severity Score; LOS, length of stay; LR, lactated Ringer solution; NS, normal saline; OIF, Operation Iraqi Freedom; RIS, Rapid Infusion System; SIRS, systemic inflammatory response syndrome; TRISS, trauma score-injury severity score.

The plasma substitutes discussed so far do not carry oxygen. Since the 1930s, there has been an interest in developing hemoglobin-based oxygen carriers (HBOCs) using hemoglobin from red blood cells to provide oxygen-carrying capacity. Unconjugated hemoglobin has severe renal and tissue toxicity. To decrease the nephrotoxicity and increase plasma half-life, researchers have developed a variety of techniques to stabilize the hemoglobin molecule. Some of these products may cause excessive vasoconstriction or oxidative damage. Diaspirin

Table 04-2 Summary of Meta-Analyses of Figure and Trauma					
Study	No. of Trials	No. of Subjects (Intervention/ No Intervention)	Intervention	Control	Outcomes
Choi et al, 1999 <sup>29</sup>	17	416/398	Colloid	Crystalloid	RR of death 2.6
Cochrane Injuries Group Albumin Reviewers, 1998 <sup>28</sup>	30	596/608	Albumin or plasma protein fraction	Crystalloid	RR of death 1.46 (CI 0.97-2.22)
Schierhout & Roberts, 1998 <sup>27</sup>	19	685/630	Colloid or HTS	Crystalloid	RR of death 1.3 (CI 0.95-1.77)
Wade et al, 1997 <sup>31</sup>	14	615/618	HTS or HSD	Crystalloid	No effect on survival. Possible greater trend for HSD
Bisonni et al, 1991 <sup>26</sup>	7	150/194	Colloid	Crystalloid	Mortality 17.8% vs. 7.3%
Velanovich, 1989 <sup>25</sup>	8	826	Colloid	Crystalloid	12.3% worse mortality with colloid

CI, confidence interval; HSD, hypertonic saline-dextran; HTS, hypertonic saline; RR, relative risk.

cross-linked hemoglobin (HemAssist, Baxter Healthcare, Round Lake, IL) was the first product to undergo a randomized clinical trial in trauma patients. Unfortunately, the trial had to be discontinued early because of increased mortality in the subjects exposed to the product.<sup>32</sup> More recently, polymerized hemoglobin derived from human blood (PolyHeme, Northfield Laboratories, Evanston, IL) was compared with PRBCs in a small randomized trial for trauma patients who required operations.<sup>33</sup> PolyHeme seemed safe and reduced the need for transfusion. In a subsequent series, PolyHeme was administered as the initial oxygen-carrying fluid replacement in trauma patients and patients undergoing urgent surgery.<sup>34</sup> Patients received up to 20 units (1000 g, 10 L) of PolyHeme. Total plasma hemoglobin was maintained at a mean of 6.8  $\pm$ 1.2 g/dL. The mortality rate in this population was 25.0%, compared with 64.5% in historical control patients who had refused blood transfusion. A pivotal, randomized trial of PolyHeme compared with LR has been completed, but the results have not been published. HBOC-201 (Biopure Corporation, Cambridge, MA) has been studied for perioperative use.<sup>35</sup> Questions related to its vasoreactivity have been raised, delaying approval for a trial in trauma patients.

#### TRANSFUSION

During the initial resuscitation of trauma victims, the ATLS course recommends that PRBCs be administered.<sup>36</sup> The goal is to acutely restore oxygen-carrying capacity.

After the initial resuscitation and achievement of normovolemia, the indication for blood transfusion is based primarily on hemoglobin level (see Table 84-1). In the general intensive care unit (ICU) population, a restrictive transfusion threshold (hemoglobin < 7 g/dL) was as good, and possibly better, than a more liberal threshold (<10 g/dL).<sup>37</sup> A subset analysis of trauma patients found no differences in outcomes between the two transfusion thresholds, suggesting that the more restrictive strategy was safe.<sup>38</sup> Dunne and colleagues,<sup>39,40</sup> Malone and coworkers,<sup>41</sup> and Silverboard and associates<sup>42</sup> found strong associations among the amount of blood transfused in trauma patients and Injury Severity Score (ISS), organ failure, length of stay (LOS), and mortality. Administration of blood stored for more prolonged periods of time may increase risk for infection.<sup>43</sup> Although some have postulated that complications of transfusions are related to leukocytes, leukocyte-depleted PRBCs appear to provide no benefit.<sup>44,45</sup>

Massive transfusions in trauma patients with hemorrhagic shock lead to coagulopathy. Traditionally, management of the coagulopathy has been reactionary, that is, administering fresh-frozen plasma, cryoprecipitate, platelets, and calcium once the patient is coagulopathic. Recent data from Operation Iraqi Freedom suggest that a more proactive approach may be beneficial.<sup>46</sup>

#### UNCONTROLLED HEMORRHAGIC SHOCK

In most circumstances, the goal for fluid resuscitation is to restore normal blood pressure. For patients with active, uncontrolled hemorrhage, however, aggressive resuscitation may lead to increased bleeding and worse outcomes. This has been demonstrated in a variety of animal models, including rat tail cut,<sup>47</sup> aortotomy,<sup>48</sup> and massive solid organ injury.<sup>49</sup> The optimal blood pressure goal during uncontrolled hemorrhagic shock (UHS) appears to vary with the injury. In some models, a mean arterial pressure (MAP) of 40 mm Hg appears best,<sup>50</sup> whereas MAP of 60 mm Hg is necessary in other models.<sup>51</sup> The safe duration of this limited, hypotensive fluid resuscitation has recently been questioned.<sup>52</sup>

Kaweski and workers retrospectively found that prehospital administration of fluids to trauma patients had no impact on mortality compared with no fluid administration<sup>53</sup> (see Table 84-1). Delayed resuscitation from HS was first tested in a randomized clinical trial by Bickell and associates.<sup>54</sup> Patients with hypotension following penetrating torso trauma either received no fluid resuscitation or standard fluid resuscitation until undergoing operative intervention. Survival was slightly better in the delayed resuscitation group (70% versus 62%). A more recent trial by Dutton and colleagues that included patients with both blunt and penetrating trauma did not demonstrate a difference in outcome, although survival was high in both groups.<sup>55</sup> In contrast, this group found that initial aggressive fluid resuscitation in severely injured trauma patients using the Rapid Infusion System increased the risk for dying almost fivefold.<sup>56</sup>

#### END POINTS OF RESUSCITATION

After hemostasis is achieved, the first goal of fluid resuscitation in hypotensive trauma patients is to restore normal blood pressure, heart rate, and urine output. In many patients, however, vital signs alone are inadequate. These patients have what has been termed *compensated shock*, in that some vascular beds remain inadequately perfused. Other clinical data are needed to identify this state and monitor further resuscitation.

Shoemaker and colleagues demonstrated that survivors of traumatic hemorrhagic shock had higher levels of cardiac output, oxygen delivery, and oxygen consumption than nonsurvivors.<sup>57,58</sup> In small randomized trials, they demonstrated that attempting to achieve these supranormal oxygen delivery values could improve survival.<sup>59,60</sup> Others have not been able to replicate these results.<sup>61</sup> Decreasing the oxygen delivery goals in the protocol produced similar outcomes with less fluid and blood product administration.<sup>62</sup>

Systemic evidence of inadequate tissue perfusion (i.e., compensated shock) can be identified by evidence of anaerobic metabolism. Lactate levels, base deficit, or serum bicarbonate correlates with survival.<sup>63–70</sup> Interestingly, admission serum blood glucose levels correlate with ISS and lactate levels.<sup>71</sup>

Use of gastric tonometry has also been explored as an end point, but no clear advantage for patient outcomes has been demonstrated.<sup>72</sup> Near-infrared spectroscopy holds promise for using tissue oxygenation as an end point for resuscitation.<sup>73</sup> So far, none of these strategies has proved better than standard clinical parameters (blood pressure, heart rate, urine output) and acid-base parameters (base deficit, lactate).

#### INTERPRETATION OF DATA

#### Choice of Fluid

The standard fluid for resuscitation of trauma patients remains crystalloids. Although hypertonic solutions have theoretical benefits in terms of rapidity of blood volume restoration and decreased inflammatory response, clinical trials to date have not been convincing. There appears to be even less clinical advantage to colloids, which may in fact be detrimental. Consensus conferences have recognized the deleterious effects of resuscitation with LR solution and the potential logistic benefits of hypertonic or colloid resuscitation in the military. One conference sponsored by the Institute of Medicine<sup>74</sup> recommended use of HTS. Another, sponsored by the Department of Defense,<sup>75</sup> recommended HSD. Data supporting these recommendations remain elusive. A large multicenter randomized trial comparing normal saline, HTS, and HSD in trauma victims suffering HS, under the auspices of the Resuscitation Outcomes Consortium (http://roc.uwctc.org), is in progress.

Use of HBOCs appears promising, particularly when blood is not readily available. No product is currently approved for use.

#### Transfusion

There is no question that blood transfusions in patients suffering HS can be life saving, but it is also clear that they can be detrimental. For patients in profound shock, initiation of PRBCs should begin as soon as possible. Once hemostasis has been achieved and volume status restored, however, administration of blood should be minimized because a higher number of transfused units appears to be an independent risk factor for mortality.

#### Uncontrolled Hemorrhagic Shock

Although trauma victims have active hemorrhage, attempting to restore normal hemodynamics is likely to increase bleeding and worsen outcome. Hemostasis should be achieved as rapidly as possible. In the meantime, limited (hypotensive) fluid resuscitation should be continued. Specifics of optimal blood pressure level and safe duration of this approach are yet to be determined.

#### **End Points of Resuscitation**

Currently, no ideal end point of resuscitation has been identified. A clinical practice guideline from the Eastern Association for the Surgery of Trauma recommended the use of lactate or base deficit as a readily measured and followed parameter to guide resuscitation.<sup>76</sup> Importantly, both of these parameters can be misleading (see Chapter 56). Nonetheless, if these values do not normalize rapidly, the patient may still be under-resuscitated or may have ongoing bleeding, and further investigation is necessary.

#### **AUTHOR'S RECOMMENDATIONS**

- HS causes tissue ischemia, which is followed by reperfusion injury and a systemic inflammatory response that can lead to multiple-organ dysfunction and death.
- Crystalloids remain the initial fluid of choice for resuscitation, although hypertonic fluids show promise.
- Transfusions should be limited to maintain hemoglobin higher than 7 g/dL.
- During active hemorrhage, fluid resuscitation should be limited to avoid exacerbating hemorrhage. Once hemostasis

has been achieved, fluid resuscitation should be aggressive to reverse tissue ischemia.

 To date, no optimal end point of resuscitation has been identified. Care must be taken to avoid under-resuscitation and over-resuscitation.

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# 85

### What Are the Critical Care Implications of Muscle and Long Bone Trauma?

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Severely injured patients often have multiple areas of injury that can leave them critically ill. The injuries frequently include muscle damage and long bone trauma. These injuries can lead to other complications. Of specific interest to the critical care practitioner are rhabdomyolysis, a disorder resulting from muscle trauma, and fat embolism syndrome (FES), a consequence of long bone trauma.

#### RHABDOMYOLYSIS

Muscle trauma can lead to rhabdomyolysis, a syndrome that is the direct result of the disintegration of striated muscle. This causes the release of myoglobin, other intracellular components, and electrolytes. Each may leak into the systemic circulation. Trauma or crush injury is the most common cause of rhabdomyolysis. Nontraumatic causes include alcohol abuse, seizures, muscle enzyme deficiencies, electrolyte abnormalities, infections, drugs and toxins, and endocrinopathies. Rhabdomyolysis has been implicated as a significant cause of acute kidney injury (AKI).<sup>1</sup> Alternative causes of AKI related to rhabdomyolysis include dehydration, sepsis, and drug nephrotoxicity.<sup>2</sup>

The association between rhabdomyolysis and acute renal failure was first established during World War II. After the bombing of London, crush victims developed AKI with pigmented casts in renal tubules at autopsy. However, the relationship between muscle injury and AKI remained unclear.<sup>3</sup>

#### **Clinical Manifestations**

The classic presentation of rhabdomyolysis includes myalgias, myoglobinuria (red to brown urine), and elevated serum muscle enzymes. The degree of muscle pain varies widely. Weakness occurs in those with severe muscle damage.

The hallmark of rhabdomyolysis is an elevation in serum creatinine kinase (CK). Rhabdomyolysis ranges from an asymptomatic illness with elevation in the CK level to a life-threatening condition associated with extreme elevations in CK, potassium, phosphate, and perhaps calcium; AKI; disseminated intravascular coagulation (DIC); and metabolic acidosis. Serum CK levels may be massively elevated, often approaching levels higher than 100,000 IU/L. The serum CK comes almost entirely from skeletal muscle fracture, although small amounts of the myocardial CK may be present.<sup>4</sup>

One major cause of rhabdomyolysis is crush syndrome. This is a systemic manifestation of muscle injury after traumatic compression of muscle followed by reperfusion. Indeed, the reperfusion injury also may result in significant damage. Signs and symptoms include tense, edematous, painful muscles, dark tea-colored urine, shock, and acidosis.

Compartment syndrome is a local manifestation of neuromuscular ischemia secondary to increased pressure within a closed anatomic space. This threatens the viability of the muscles and nerves within the compartment. Signs and symptoms include a tense, edematous compartment, pain with passive stretch, paresthesias or anesthesia, and weakness or paralysis of the affected extremity. Compartment syndrome secondary to severe rhabdomyolysis may develop after fluid resuscitation, with worsening edema of the limb and muscle.<sup>5</sup> Lower extremity compartment syndrome also can be caused by rhabdomyolysis, for example, after tibial fractures. Acute compartment syndrome is diagnosed clinically, and a fasciotomy should be performed if acute compartment syndrome is suspected.<sup>6</sup>

The most significant sequela of rhabdomyolysis is AKI with subsequent renal failure. Posttraumatic AKI resulting from rhabdomyolysis requires dialysis in up to 28% of cases.<sup>7</sup> The incidence of acute renal insufficiency, defined as serum creatinine level of 2.0 mg/dL or greater, in patients with rhabdomyolysis ranges from 17% to 33%.<sup>8</sup> There is disagreement about how to define AKI. Studies have defined AKI as serum creatinine greater than 1.5 mg/dL, greater than 2.0 mg/dL, or greater than 0.5 mg/dL above baseline, or as an acute decrease in kidney function requiring dialysis.<sup>9</sup>

Abnormalities in serum electrolytes and uric acid are common in patients with rhabdomyolysis. Hyperkalemia and hyperphosphatemia result from the release of potassium and phosphorus from damaged muscle cells. Hypocalcemia, which can be extreme, occurs in the first few days following injury because of both deposition of calcium salts in damaged muscle and decreased bone responsiveness to parathyroid hormone.<sup>10,11</sup> Severe hyperuricemia may result from the release of purines from damaged muscle cells and, if acute renal failure occurs, reduced urinary excretion.

#### Pathophysiology

Rhabdomyolysis can be defined as "an injury to the sarcolemma of skeletal muscle, resulting in leakage of its components into the blood or urine."<sup>12</sup> Injury to the sarcolemma may be caused by hypoxia, reperfusion injury, direct injury to the membrane integrity, or metabolic functions. Skeletal muscle hypoxia results in conversion to anaerobic metabolism, eventual inability to generate adenosine triphosphate (ATP), and subsequent loss of membrane integrity and ion gradients. Loss of the Na<sup>+</sup> gradient results in increases in intracellular calcium and activation of mitochondrial enzymes, initiating cell destruction with leakage of intracellular protein into the extracellular environment.<sup>9</sup>

Reperfusion injury results in the generation of oxygen free radicals that destroy tissues in several ways. These include induction of a no-reflow phenomenon by the vasoconstriction of precapillary arterioles, lipid peroxidation of cell membranes, and the formation of peroxynitrite when the oxygen free radicals react with endothelialgenerated nitric oxide. The net result is a self-perpetuating secondary injury. This secondary injury may result in a volume of tissue necrosis much larger than and remote from the primary zone of tissue injury.<sup>9</sup>

One major muscle component, myoglobin, is released from damaged muscle cells and eventually enters the blood and the urine. Myoglobin is a dark-red protein that is filtered by the glomerulus, but will not appear in the urine until a renal threshold is met. Serum myoglobin levels rise within hours of muscle damage. The classic finding of reddish-brown (tea-colored) urine found in rhabdomyolysis is not seen until serum levels of myoglobin reach 100 mg/dL.<sup>13</sup> The biochemical properties of myoglobin in the presence of acidic urine may cause precipitation of casts that occlude the renal tubules and block urine flow. When massive amounts of myoglobin are released, the protein binding capacity is exceeded, and myoglobin is then filtered at the level of the glomerulus. This also may obstruct the renal tubules. This is a proposed mechanism of acute renal failure in patients with rhabdomyolysis.9,13

A second proposed mechanism is that myoglobin, an iron-containing heme molecule, can react to produce oxygen free radicals and directly induce peroxidation of lipids within cellular membranes.<sup>14</sup> Vasoactive agents, such as platelet-activating factor, endothelin, and prostaglandin  $F_{2\alpha}$ , may also be increased in rhabdomyolysis, resulting in constriction of renal arterioles and decrease in glomerular filtration rate (GFR).<sup>14</sup>

#### Causes

The cause of rhabdomyolysis is usually evident from the history or from immediate preceding circumstances. The most common causes are crush injury, comatose or postictal state, postoperative surgical trauma, and extraordinary physical exertion. In some cases, however, the precipitant is not obvious. Possible causes include heritable muscle enzyme deficiencies, electrolyte abnormalities, infections, drugs and toxins, and endocrinopathies<sup>15</sup> (Table 85-1).

Trauma and muscle compression leading to crush syndrome, immobilization, and vascular occlusion are common causes of rhabdomyolysis. Crush syndrome may occur in multitrauma victims, particularly individuals trapped in motor vehicles after crashes or in collapsed buildings.<sup>16,17</sup> Rhabdomyolysis can arise from immobilization due to coma of any cause, in conscious individuals forced to lie in one position for hours, or when there is prolonged muscle compression resulting from positioning during a long surgical procedure. Thrombosis, embolism, clamping of vessels, or tourniquet use during orthopedic or vascular reconstruction procedures also may result in muscle cell necrosis if prolonged.<sup>14,18–20</sup>

Strenuous muscular exercise may cause myolysis, especially in untrained subjects and in individuals exercising under extremely hot, humid conditions. Potassium is essential for vasodilation of the microvasculature of the muscles; thus, exercise will cause more rapid muscle

Table 05 1 Courses of Dhahda

Muscle Injury	Medications and Illicit Drugs	Increased Muscular Activity
Trauma	Alcohol	Overexertion
Burns	Cocaine	Seizures, status epilepticus
Electrocution	Amphetamines	Status
Prolonged	РСР	Delirium
immobilization	(phencyclidine)	tremens
Compartment	HMG-CoA	Infections
syndrome	reductase inhibitors	(sepsis)
Metabolic disorders	Other antilipemic agents	Viral
Diabetes ketoacidosis	Neuroleptics	Bacterial
Hyponatremia	Sedative- hypnotics	Falciparum malaria
Hypokalemia	Amphotericin B	
Hypophosphatemia	1	Hereditary metabolic myopathies
Hyperaldosteronism	Toxins	5 1
Ischemia	Isopropyl alcohol	Hyperthermia
Compression	Ethylene glycol	Malignant hyperthermia
Vascular injury	Tetanus toxin	Neuroleptic malignant syndrome
Sickle cell disease	Venom (insect or snake)	Autoimmune diseases
	Quail	Polymyositis Dermatomyositis Idiopathic

Data from references 2, 13, and 15.

ischemia in hypokalemic subjects. This in turn may result from potassium loss in sweat. During exercise, muscle perfusion increases to meet enhanced energy demand. This vasodilation is mediated by the release of potassium from skeletal muscle cells. When potassium depletion occurs, there may be a decrease in blood flow. This in turn may lead to cramps, ischemic necrosis, and rhabdomyolysis.<sup>21–23</sup> In individuals with normal muscles, pathologically high energy states, including seizures, delirium tremens, psychotic agitation, and amphetamine overdose, may also lead to rhabdomyolysis.<sup>24,25</sup>

Rhabdomyolysis may develop in patients with abnormal muscles. Inherited childhood disorders of glycogenolysis, glycolysis, or lipid or purine metabolism should be suspected if muscular weakness or myoglobinuria recurs frequently or occurs in association with events during which it should not occur in healthy subjects. The precise mechanism of muscle necrosis in muscle myopathies has not been determined, but depletion of ATP secondary to insufficient energy production in exercising muscles is suspected.<sup>26</sup> Viral infection, exertion, or fasting may also aggravate these disorders.

High-voltage electrical injury, including lightning strikes, cause rhabdomyolysis in 10% of the subjects surviving the primary accident, even if the entry wounds are small. Muscle damage is attributable to thermal injury or electrical disruption of sarcolemma membranes, resulting in pore formation, loss of barrier function, and massive calcium influx.<sup>2</sup>

Excessive body temperature may result in muscle damage. Two causes of hyperthermia-associated rhabdomyolysis are neuroleptic malignant syndrome and malignant hyperthermia. Neuroleptic malignant syndrome is a disorder with high fever with or without muscle contraction or tremor that develops after exposure to neuroleptic and antiparkinsonian drugs (phenothiazides or haloperidol).<sup>27</sup> Malignant hyperthermia is an inheritable syndrome characterized by fever, generalized muscle contraction and rigidity, metabolic acidosis, and rhabdomyolysis. It most commonly occurs after the use of inhalational anesthetic agents in susceptible individuals.<sup>2</sup>

Nonexertional and nontraumatic causes of rhabdomyolysis include drugs and toxins, infections, and electrolyte abnormalities. Prescribed and illicit drugs as well as toxins can cause rhabdomyolysis by several different mechanisms. Coma induced by alcohol, opioid overdose, or other central nervous system depressants leads to immobilization and ischemic compression of muscle. Some drugs, such as statins and colchicine, are direct myotoxins. The most frequent cause of drug-induced rhabdomyolysis is the administration of HMG-CoA reductase inhibitors (statins). In addition, statins may increase the risk for rhabdomyolysis in patients with predisposing conditions such as hypothyroidism or inflammatory myopathy. Drug-drug interactions such as those involving macrolide antibiotics, cyclosporine, and other drugs metabolized by the cytochrome P-450 3A isoenzyme alter drug clearance. This leads to elevated plasma levels that may be responsible for rhabdomyolysis.<sup>2</sup>

Rhabdomyolysis has been associated with a variety of bacterial and viral infections<sup>30</sup> (see Table 85-1). Patients affected by viruses usually present with typical prodromal

symptoms 1 to 14 days before the onset of severe myalgias and pigmenturia. Patients may have elevated serum CK levels, and viral myositis should be suspected on clinical grounds. Although often delayed, serologic evidence of a recent viral infection provides additional support for the diagnosis. The mechanism of muscle damage due to viral infections has not been elucidated.

Bacterial pyomyositis is diagnosed by localized signs of muscle infection, including erythema, swelling, tenderness, fluctuation, and lymphangitis. Septicemia may result from muscle damage caused by toxins or from associated fever, rigors, and dehydration without direct muscle infection. In falciparum malaria, infected patients present with fever, chills, nausea, vomiting, and acute renal failure with or without signs and symptoms of muscle damage.<sup>31</sup>

Rhabdomyolysis has been associated with a variety of electrolyte disorders. These include hypokalemia,<sup>32</sup> hypophosphatemia,<sup>33</sup> and hyperosmolality due to diabetic keto-acidosis or nonketotic hyperglycemia<sup>34</sup> (see Table 85-1). As previously stated, decreased potassium release due to profound hypokalemia (serum K<sup>+</sup> < 2.5 mEq/L) may promote the development of rhabdomyolysis by decreasing blood flow to muscles in response to exertion. Clinically significant rhabdomyolysis associated with hypophosphatemia has been described almost exclusively in alcoholic patients and in patients receiving total parenteral nutrition.<sup>34</sup>

#### Management

The treatment of rhabdomyolysis includes initial stabilization and resuscitation of the patient while concomitantly attempting to preserve renal function. Retrospective analysis demonstrates that early aggressive fluid replacement with saline is beneficial in minimizing the occurrence of renal failure.35-37 Saline has been used as the fluid of choice for resuscitation in patients with rhabdomyolysis. However, a recent prospective randomized single-blind study compared using saline or lactated Ringer (LR) solution for initial resuscitation of patients with rhabdomyolysis induced by doxylamine. In addition, all patients were treated with bicarbonate and diuretics. The study found that less bicarbonate and diuretics were needed for the patients receiving LR.<sup>38</sup> Furthermore, the longer the time to initiation of rehydration, the more likely it is that renal failure will develop. Forced diuresis, when started within 6 to 12 hours of admission, has been reported to minimize the risk for AKI<sup>2,39</sup> (Table 85-2).

Mannitol is commonly employed following initial resuscitation with volume. Alkalinization of the urine with sodium bicarbonate has been suggested to minimize renal damage after rhabdomyolysis.<sup>13</sup> Although mannitol and sodium bicarbonate are frequently considered the standard of care in preventing AKI in patients with rhabdomyolysis, little clinical evidence exists to support the use of these agents. In a retrospective study of 24 patients, volume expansion with saline alone prevented progression to renal failure, and the addition of mannitol and bicarbonate had no additional benefit.<sup>36</sup> In another study reviewing 1771 trauma patients with increased CK levels, results showed that 217 patients (12%)

lable 85-2 Overview of Studies for Fluid Management of Rhabdomyolysis					
Study	Design	No. of Patients	Treatment	Conclusion	Level of Evidence
Brown et al, 2004 <sup>37</sup>	Retrospective	1771	Bicarbonate, mannitol, and saline vs. saline	No improvement over saline alone	III
Homsi et al, 1997 <sup>36</sup>	Retrospective	24	Bicarbonate, mannitol, and saline vs. saline	No improvement over saline alone	III
Cho et al, 2007 <sup>38</sup>	Prospective randomized	28	Lactated Ringer solution vs. saline	Decreased amount of bicarbonate and diuretics given with lactated Ringer solution	Π
Knottenbelt, 1994 <sup>39</sup>	Prospective	200	Balanced salt solution	Patients not receiving treatment in 12 hr have increased rate of acute kidney injury and death	III

developed renal failure and 97 (5.5%) patients required dialysis. Peak CK levels of more than 5000 U/L were found in 382 patients and were associated with increased risk for developing renal failure. Of these patients with elevated CK levels, 154 patients (40%) received mannitol and bicarbonate, whereas 228 patients did not. The rates of renal failure (22% versus 18%), dialysis (7% versus 6%), and mortality (15% versus 18%) showed no significant differences between the two groups, supporting the statement that mannitol and bicarbonate have little additional benefit over aggressive volume replacement alone<sup>37</sup> (see Table 85-2).

Additionally, the diuretic effect of mannitol in an acutely injured patient may further exacerbate hypovolemia, metabolic acidosis, and prerenal AKI.<sup>2</sup> Similarly, large doses of bicarbonate may worsen the degree of hypocalcemia and can cause more harm than benefit to the patient, especially if hypovolemia is corrected.<sup>38,40</sup>

The use of carbonic anhydrase inhibitors for urine alkalinization has been suggested when the arterial pH rises above 7.45 after sodium bicarbonate therapy or if there is continued aciduria despite alkalemia. There are case reports that demonstrate favorable outcomes with the use of acetazolamide; however, the use of acetazolamide as a means of alkalinizing the urine has not been shown to be consistently beneficial.<sup>41</sup>

Reactive oxygen metabolites may worsen the extent of acute renal failure seen in rhabdomyolysis. The administration of free radical scavengers reduces the magnitude of AKI in experimental models.<sup>42</sup> Pentoxyphylline is a xanthine derivative that has shown nephroprotective effects by decreasing intratubular cast formation, leukocyte infiltration, and vascular congestion in rat models.<sup>43</sup> In a study examining muscle necrosis of isolated gracilis muscle, controlled oxygen delivery and free radical scavengers reduced skeletal muscle necrosis by 25% after prolonged normothermic ischemia.<sup>44</sup> The extent of tissue damage reflects the balance between the free radicals generated and the antioxidant protective defense system.

Hyperbaric oxygen (HBO) therapy also has been advocated for the treatment of crush injuries because of its effects to increase peripheral oxygen transport. Data have shown that the distance that oxygen traverses in peripheral capillaries is increased fourfold.45 A randomized, double-blind study examined the effect of HBO on wound healing for crush injuries compared with conventional treatment. Thirty-six patients with crush injuries were studied, with 18 patients in each group. HBO treatment included 100% O<sub>2</sub> at 2.5 atmospheres, 90 minutes, twice daily for 6 days; placebo control included 21% O<sub>2</sub> at 1.1 atmospheres, 90 minutes, twice daily for 6 days. Complete healing was achieved for 17 patients in the HBO group versus 10 patients in the placebo group (P <.01). Subgroup analysis of patients matched for age and severity of injury showed that for those patients older than 40 years with extensive soft tissue injury, wound healing was obtained in 87.5% receiving HBO therapy compared with 30% of controls (P < .05). The transcutaneous oxygen pressure values of the traumatized tissue rose significantly over the 12 sessions after HBO treatment. There was no significant difference in length of hospital stay and number of wound dressings between the groups. This study demonstrated the effectiveness of HBO therapy in the treatment of crush injury.<sup>46</sup>

Regardless of optimal treatment, patients may still develop AKI, frequently with severe acidosis and hyperkalemia. Renal replacement therapy (daily hemodialysis or continuous hemofiltration) to correct fluid, electrolyte, and acid-base abnormalities may be required. This allows gradual removal of solutes and slow correction of fluid overload. Life-threatening hyperkalemia must be addressed quickly and effectively. The increase in serum potassium is most severe in the first 12 to 36 hours after muscle injury. Normalization of potassium is a priority because hyperkalemic cardiac arrest is a life-threatening early complication.<sup>2,40</sup>

Electrocardiogram (ECG) findings should guide the decision to begin emergent administration of serum potassium lowering agents. First-line treatment for severe hyperkalemia with ECG changes is calcium administration to stabilize cardiac membranes. However, if hyperphosphatemia (seen in rhabdomyolysis) is present, intravenous calcium may be less effective owing to its binding to extracellular phosphate leading to metastatic calcification. Temporary potassium-reducing agents include intravenous insulin with glucose, intravenous sodium bicarbonate, and inhaled  $\beta_2$ -agonists, all of which drive

extracellular potassium into intracellular compartments. Kayexalate given orally or rectally will remove potassium from circulation. Emergent dialysis is necessary if hyperkalemia persists despite these treatments.<sup>13</sup>

Factors that appear to be involved in the development of AKI in patients with rhabdomyolysis include GFR, acidemia, quantity of injured muscle protein, and myoglobinuria.<sup>9</sup> Small increases in serum creatinine can represent substantial decreases in GFR. For example, a healthy 27-year-old 85-kg male with a baseline serum creatinine (sCr) of 0.9 mg/dL presenting with an sCr of 1.5 mg/dL has a 60% reduction in GFR. Acidemia may allow the precipitation of myoglobin in the renal tubules. All that is required is a slight acidosis with a base deficit (BD) of -4 or less. Serum CK levels of 5000 U/L or greater reflect the amount of skeletal muscle damage and released myoglobin and may represent a threshold above which there is a substantial risk for the development of AKI in critically injured patients.<sup>8</sup>

Patients who do not develop significant acidosis (BD < -4) during the first 24 hours and have normal creatinine levels are at low risk for developing AKI secondary to rhabdomyolysis.<sup>9</sup> These patients can be adequately resuscitated, receive definitive treatment, and return to near-normal physiology within the first 24 hours after injury. Unless these patients have a change in clinical status, no further testing or specific treatment for rhabdomyolysis is necessary.<sup>8</sup>

Patients with normal creatinine levels and a metabolic acidosis (BD > -4) are at intermediate risk for AKI requiring dialysis. These patients may benefit the most from early intervention. The goal in this group should be aggressive resuscitation and correction of the acidosis. Patients at highest risk are those who are under-resuscitated, who have treatment-resistant shock, or in whom treatment is delayed. In a large multicenter retrospective study, under-resuscitation contributed to one third of the patients developing AKI requiring dialysis.<sup>7</sup>

Myoglobinuria, an inconsistent finding affected by timing of sampling, is not predictive of AKL.<sup>9</sup> The inconsistency of myoglobinuria also may reflect the short halflife of myoglobin in serum (1 to 3 hours). Quantitative urine or serum myoglobin levels, however, are predictive of acute renal failure. A low myoglobin clearance has been associated with an increased risk for acute renal insufficiency in one report. The removal of myoglobin by plasma exchange has not demonstrated any benefit.<sup>47</sup>

The administration of calcium should be avoided during the renal failure phase, unless the patient has symptomatic hypocalcemia or severe hyperkalemia because hypercalcemia is a unique management issue in rhabdomyolysis-induced AKI.<sup>2</sup>

#### **AUTHORS' RECOMMENDATIONS**

Rhabdomyolysis is a potentially life-threatening condition that must be suspected in all patients with a history of injury resulting in skeletal muscle damage. When treated early and aggressively, the prognosis is excellent. With adequate treatment, full recovery of renal function for most cases of rhabdomyolysis is expected. Irrespective of the cause of rhabdomyolysis, the mortality rate may still be as high as 8%. The following suggestions have been derived from the aforementioned studies:

- Management includes aggressive fluid resuscitation, correction of metabolic acidosis, and early identification and treatment of compartment syndrome.
- Alkalinization of the urine with sodium bicarbonate or acetazolamide has little benefit over aggressive volume replacement alone and thus is not recommended.
- Diuresis in an acutely injured patient may further exacerbate hypovolemia, metabolic acidosis, and prerenal AKI.
- Hyperbaric oxygen therapy is recommended for the treatment of crush injuries. Although the data are limited, HBO improved wound healing and transcutaneous oxygen pressure values in the patients who sustained crush injuries.
- Other treatments for consideration include free radical scavengers and therapies used routinely to treat severe electrolyte abnormalities, especially hyperkalemia.

#### FAT EMBOLI SYNDROME

FES is a diagnostic challenge for physicians. FES may complicate widely disparate clinical conditions and may vary greatly in severity. The reported mortality ranges from 5% to 15% in multiple studies.<sup>48</sup>

FES is commonly associated with long bone and pelvic fractures and is seen more frequently in closed, rather than open, fractures. Patients with a single long bone fracture have a 1% to 3% chance of developing the syndrome, and this rate increases in correlation with the number and severity of fractures. FES has been observed in up to 33% of patients with bilateral femoral fractures. FES can occur in a variety of other clinical settings, but the risk is lower than with closed long bone fractures.<sup>49</sup>

#### **Clinical Manifestations**

FES typically presents 24 to 72 hours after the initial insult. Rarely, cases occur as early as 12 hours or as late as 2 weeks after the inciting event. Affected patients present with a classic triad: hypoxemia, mental status changes, and petechial rash.

Dyspnea, tachypnea, and hypoxemia are the most common early findings. Patients often progress to a syndrome that is indistinguishable from acute respiratory distress syndrome (ARDS). About half of patients with FES caused by long bone fractures develop severe hypoxemia and require mechanical ventilation.

Neurologic abnormalities are noted in most patients with FES. Symptoms vary from confusion to encephalopathy with coma and seizures. Diffuse encephalopathy, petechial hemorrhages, localized cerebral edema, and white matter changes on computed tomography (CT) scan have also been described. The neurologic findings are usually transient and completely reversible in most cases.<sup>50</sup>

The characteristic petechial rash may be the last component of the triad to develop. The rash is found most often on the head, neck, trunk, conjunctiva, and axillae. Petechiae result from the occlusion of dermal capillaries by fat globules, leading to extravasation of erythrocytes. The rash resolves in 5 to 7 days.<sup>51</sup> Other minor manifestations of FES may be present. Some, such as scotoma (Purtscher retinopathy) and lipiduria, are attributed directly to systemic embolization of fat. Other findings, such as fever, coagulation abnormalities (mimicking DIC), and myocardial depression, appear to result from the release of toxic mediators secondary to either the inciting injury or dysfunctional lipid metabolism.<sup>52,53</sup>

#### Pathogenesis

Two theories to explain the pathogenesis of FES have been advanced. The first suggests that fat emboli may occur by direct entry of fat globules from disrupted tissue, usually bone marrow or adipose tissue, into the bloodstream. The second theory postulates that abnormalities arise from the production of toxic intermediaries of plasmaderived fat such as chylomicrons or lipids.

Fractures of marrow-containing bone may have the highest incidence of FES and cause the largest volume of fat emboli. The marrow contents enter the venous circulation through disrupted venules. These remain open within the osseous structure.

Echogenic material passing into the right heart is common during orthopedic and spinal surgery.<sup>54,55</sup> It has been hypothesized that with continued embolization, pulmonary artery and right heart pressures rise, and material can pass through a patent foramen ovale into the systemic circulation.<sup>54</sup>

Embolized material also may appear in the systemic circulation. How this occurs in the absence of a patent foramen ovale is difficult to explain. However, these emboli may explain the neurologic changes and petechiae.<sup>56</sup> Small emboli may gain access to the systemic circulation through pulmonary capillaries. This theory, however, does not sufficiently explain the 24- to 72-hour symptom-free interval following the acute insult.

A second theory proposes that FES-embolized fat does not directly cause acute lung injury. Rather, fat is hydrolyzed over time to several toxic products, including free fatty acids (FFAs), that injure the capillary endothelium. FFAs have been shown to cause ARDS in animal models and have also been associated with cardiac contractile dysfunction.<sup>57</sup>

The production of toxic intermediaries may explain the delay from the inciting event to the clinical appearance of

FES. Levels of circulating FFA are elevated in patients with fractures.<sup>58,59</sup> Large increases in circulating lipoprotein lipase and FFA have been seen in nontraumatic animal models of FES.<sup>60</sup> Nevertheless, there is no evidence to support the occurrence of these mechanisms in humans.

#### Diagnosis

The diagnosis of FES is clinical. The rash is considered pathognomonic, although it is only present in 20% to 50% of cases.  $^{61}$ 

Chest radiographs are normal in most patients, whereas a minority of radiographs have diffuse or patchy airspace consolidation consistent with edema or alveolar hemorrhage.<sup>62,63</sup> Ventilation-perfusion scans may demonstrate a mottled pattern of subsegmental perfusion defects with a normal ventilatory pattern. Focal areas of ground-glass opacification with interlobar septal thickening may be seen on chest CT scan.<sup>64,65</sup> Magnetic resonance imaging of the brain may reveal high-intensity T2 signal that correlates with the degree of neurologic impairment.<sup>66</sup>

The presence of fat globules in the sputum, urine, or wedged pulmonary artery catheter is not necessary to confirm the diagnosis of FES. Indeed, the recovery of fat globules is of unclear significance. In one study, fat globules were present in the serum of more than 50% of asymptomatic patients with fractures.<sup>67</sup> No laboratory test is sufficiently sensitive or specific to be diagnostically useful. Bronchoalveolar lavage to detect fat droplets in alveolar macrophages may be of value.<sup>68–70</sup>

#### Management

Early immobilization of fractures reduces the incidence of FES. The risk is further reduced by operative correction.<sup>71</sup> Supportive care is the mainstay of therapy for FES. Mortality has been estimated between 5% and 15% overall, but most patients fully recover.<sup>48,72</sup>

The use of corticosteroid in the treatment of FES is controversial. A number of studies report decreased incidence and severity of FES when corticosteroids are given prophylactically (Table 85-3).<sup>73–76</sup> In a double-blind study, 62 consecutive patients with lower-extremity long bone fractures received either placebo or methylprednisolone,

Study	Design	No. of Patients	Treatment	Conclusion	Level of Evidence	
Alho et al, 1978 <sup>74</sup>	Randomized	60	Methylprednisolone, $10 \text{ mg/kg} \times 3 \text{ doses}$	2/30 patients treated vs. 15/30 controls developed fat emboli syndrome	II	
Lindeque et al, 1987 <sup>77</sup>	Double-blind randomized	55	Methylprednisolone, $30 \text{ mg/kg} \times 2 \text{ doses}$	Reduction in development of fat emboli syndrome	II	
Kallenbach et al, 1987 <sup>75</sup>	Prospective	82	Methylprednisolone, $1.5 \text{ mg/kg} \times 6 \text{ doses}$	1/40 patients treated vs. 10/42 controls developed fat emboli syndrome	III	
Schonfeld et al, 1983 <sup>76</sup>	Double-blind randomized controlled	62	Methylprednisolone, 7.5 mg/kg × 12 doses	0/21 patients treated vs. 9/41 controls developed fat emboli syndrome	Π	

Table 85-3 Overview of Studies Using Corticosteroids for Treatment in Fat Emboli Syndrom

7.5 mg/kg every 6 hours for 12 doses. FES was diagnosed in 9 of 41 placebo-treated patients and in 0 of 21 steroid-treated patients (P < .05). No steroid-related complications were observed.<sup>75</sup>

Limiting elevations in intraosseous pressure during orthopedic procedures to reduce the entry of intramedullary fat and other debris into the bloodstream has been shown to prevent FES.<sup>77–81</sup> One study randomized 40 patients undergoing cemented total hip arthroplasty to either conventional technique or limiting the rise in intraosseous pressure through placement of a venting hole between the greater and lesser trochanters.<sup>74</sup> Significantly fewer major embolic events occurred in the vented group (20% versus 85%). Other operative procedures to limit intraosseous pressure include the use of cementless fixation of hip prostheses and unreamed intramedullary femoral shaft stabilization.<sup>77,78</sup>

Respiratory failure from FES and neurologic symptoms and complications are managed in the same way as acute lung injury and ARDS from any cause. Neurologic changes and petechial rash usually resolve spontaneously.

#### **AUTHORS' RECOMMENDATIONS**

- FES is commonly associated with closed long bone and pelvic fractures.
- Affected patients present with a classic triad: hypoxemia, mental status changes, and petechial rash. The rash is pathognomonic.
- Patients may develop ARDS.
- Early immobilization of fractures reduces the incidence of FES.
- Therapy is supportive.

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### 86 How Should the Critically III Pregnant Patient Be Managed?

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The critically ill pregnant woman presents many challenges to the intensivist who must consider the physiologic needs of both the mother and fetus in clinical decision making. Fortunately, it is unusual for obstetric patients to need critical care services. About 0.1% to 0.8% of obstetric admissions are admitted to an intensive care unit (ICU).<sup>1,2</sup> Another 1% to 2% of critically ill women are treated in a labor and delivery unit or a specialized obstetric care unit.<sup>3,4</sup> Based on the nearly 4.3 million births in the United States during 2006, about 42,000 to 128,000 women may require these services annually.<sup>5</sup> The first U.S. population-based attempt to quantify severe maternal morbidity at the time of hospitalization for delivery, including conditions which would typically be treated in an ICU, estimated the rate to be 5.1 per 1000 maternities.<sup>6</sup>

Further complicating clinical decision making is the paucity of research that has focused specifically on the critically ill pregnant patient. What follows is information, such as it exists, to assist the clinician caring for the septic pregnant woman, the pregnant woman who needs ventilator support, and the woman with refractory postpartum hemorrhage.

#### DO THE SURVIVING SEPSIS CAMPAIGN GUIDELINES FOR THE MANAGEMENT OF SEPSIS AND SEPTIC SHOCK APPLY IN THE CASE OF THE PREGNANT OR POSTPARTUM PATIENT?

There are no data specific to this population. In most trials, pregnant patients are explicitly barred from enrollment. Because severe sepsis and septic shock (aside from unsafe abortion) are not common in pregnancy, the epidemiology of sepsis in this population is not as well described as in a general medical-surgical population. The World Health Organization recently estimated 77,000 deaths worldwide per year from maternal sepsis, with 0.1% to 10% of all live births being complicated by some degree of maternal infection.<sup>7</sup> Criteria for sepsis or severe sepsis have been met in 0.03% to 0.09% of deliveries in Europe.<sup>8,9</sup> Comparable figures for North America are not available at this time. The case-fatality rate for sepsis in this population is not known with any degree of certainty, but the case-fatality rate for septic abortion specifically, however, is as high as 20%.<sup>10</sup> Sepsis

may be obstetric or nonobstetric. Causes of obstetric sepsis include uterine infection (chorioamnionitis if undelivered, endomyometritis postpartum), septic abortion, and wound infection (cesarean or episiotomy wound). In addition, sepsis may follow invasive procedures such as amniocentesis, chorionic villus sampling, cervical cerclage, or percutaneous umbilical blood sampling. One of the few case series in the American literature on septic shock in pregnancy<sup>11</sup> reported that half the cases have an obstetric cause whereas most cases of nonobstetric etiology were urinary in origin.

The Surviving Sepsis Campaign<sup>12</sup> is a multiorganizational effort to improve outcomes in sepsis and septic shock based on the best available evidence. It proposes a number of goals. These appear below with commentary specifically relating to obstetric patients. There is no evidence base for these guidelines in a pregnant or postpartum patient, but no evidence against them either.

- 1. Early goal-directed resuscitation during the first 6 hours after admission. Despite a paucity of evidence, this recommendation seems logical and appropriate to follow in the pregnant patient.
- 2. Blood cultures before antibiotic therapy. In theory, this should be appropriate. A Finnish study reported on this specific policy for obstetric patients and demonstrated that 2% (of more than 40,000) of patients were cultured for fever and had broad-spectrum antibiotics instituted immediately. Bacter-emia was confirmed in 5% of cases, but only 1 of the 798 patients cultured developed septic shock, an incidence of 0.1%.<sup>13</sup>
- 3. Imaging studies performed promptly to ascertain source of infection. Despite long-held dogma, pregnant women can be imaged, although there are some issues related to ionizing radiation. The American College of Obstetricians and Gynecologists suggests limiting total radiation dose during pregnancy to 5 cGy because no fetal effects are known to occur when exposure is this low. Substitute nonionizing modality if feasible. If ionizing radiation is to be used, shield the abdomen if possible. If ionizing radiation is required and the abdomen-pelvis is to be included in the field, modify the technique to minimize dose delivered to the fetus and use dosimetry to tally fetal dose. Gadolinium has been used in pregnancy without evident fetal compromise.

- 4. Initiation of broad-spectrum antibiotic therapy within 1 hour of diagnosis. This should be feasible. However, the hemodynamic picture that characterizes normal pregnancy may result in the overdiagnosis of sepsis. The central hemodynamics of normal pregnancy include increased cardiac output, increased heart rate, decreased systemic vascular resistance, and a somewhat lower blood pressure.<sup>14</sup> Most antibiotics can be used in pregnancy, although dose adjustments may be needed because of changes in pharmacokinetics.<sup>15</sup> Broadspectrum coverage is reasonable in obstetric patients. In a recent Finnish study of peripartum sepsis, more than 40 organisms were cultured. These included aerobic gram-positive and gramnegative, as well as anaerobic, bacteria.<sup>13</sup>
- 5. Reassessment of antibiotic therapy with clinical and microbiologic data to narrow antibiotic coverage when appropriate. There are no data specific to pregnancy. When narrowing coverage, consideration should be given as to whether transplacental coverage is appropriate. Some drugs do not cross the placenta well and may result in inadequate fetal treatment. Examples include erythromycin or azi-thromycin in the treatment of syphilis.<sup>16</sup>
- 6. Seven to 10 days of antibiotic therapy. There is no evidence base specific to pregnancy, but there also is no reason to recommend alteration of this goal.
- 7. Source control. There are no data specific to pregnancy. About half of cases of sepsis in pregnant and postpartum women localize to the uterus<sup>11</sup> and would therefore require that the uterus be emptied. Fetuses younger than 23-24 weeks' gestational age are unlikely to survive outside the uterus; although data from a large neonatal research network in the US suggest that survival at 23 weeks may reach 20% among the largest infants in the cohort, at least in selected centers, the rate of survival to hospital discharge in Europe is still under 10% for 24-weekers.<sup>18</sup> There are no data on antibiotics without delivery for women diagnosed with clinical sepsis attributed to intraamniotic infection. Women with a diagnosis of subclinical intra-amniotic infection who were treated with antibiotics alone, in the hope of delaying delivery to a more favorable gestational age, have been observed to have a prolongation of pregnancy by days to weeks, with the only maternal morbidity recorded being a 3% rate of postpartum endometritis.<sup>19</sup> However, the infant death rate is 33%, and major infant morbidity exceeds 75%. It should be emphasized that patients with subclinical chorioamnionitis, who typically present only with preterm labor or membrane rupture, are unlikely to come to the ICU. If these patients cannot reasonably be managed without delivery, however, ICU admission logically is indicated. There appears to be no place for deferring source control in pregnancy.
- 8. Crystalloid or colloid fluid resuscitation. There is no evidence to recommend one versus the other in pregnancy.

- 9. Fluid challenge to restore circulating filling pressure. There are no data specific to pregnancy. However, the gradient between colloid oncotic pressure and pulmonary artery occlusion pressure is lower in pregnancy,<sup>14</sup> so there may be a greater risk for pulmonary edema.
- 10. If filling pressures rise and tissue perfusion does not improve, reduction of rate of fluid administration. Again, this appears reasonable, but there are no specific data in this population.
- 11. Norepinephrine or dopamine to target initial mean arterial pressure higher than 65 mm Hg. No data exist to recommend a lower limit of mean arterial pressure (MAP) in pregnancy. However, MAP is normally lower in pregnancy than in healthy nonpregnant controls.<sup>20</sup> Thus, MAP > 65 mm Hg may be too stringent. Although the MAP difference is only 4 to 5 mm Hg, one cannot extrapolate and recommend a target of 60 mm Hg instead. The uteroplacental circulation does not autoregulate, and compromised placental perfusion may be apparent by examination of the electronic fetal heart rate tracing. Indeed, the tracing may allow individualization of target MAP. Although both dopamine and norepinephrine have been used clinically without adverse outcome, there are limited experimental data on safety or efficacy of either in pregnancy.
- 12. Dobutamine when cardiac output remains low despite fluid and vasopressor therapy. Adoption of this recommendation is complicated by lack of clarity regarding what "low" means in pregnancy. The normal cardiac output in pregnancy is increased and the systemic vascular resistance decreased. Indeed, central hemodynamics in normal pregnancy look very much like those of sepsis in the nonpregnant patient. Thus, surrogate markers of adequate maternal cardiac output must be used in this patient population to ensure adequate maternal oxygenation and end-organ perfusion. Examination of the electronic fetal heart rate tracing, when feasible, may be an indication of adequacy of uterine perfusion.
- 13. Stress dose steroid therapy only if blood pressure remains unresponsive to fluid and vasopressors. Again, there are no data for or against the use of steroids to support hemodynamics in pregnancy. Steroids are often given in pregnancy. There are specific fetal benefits to a brief course of dexamethasone or betamethasone, which cross the placenta and stimulate earlier lung maturation, but no data on the use of hydrocortisone.<sup>21</sup> Once again, the issue is complicated by a lack of consensus on appropriate hemodynamic parameters in pregnancy.
- 14. Recombinant activated protein C in severe sepsis if clinical assessment of high risk for death. Pregnant patients specifically were excluded from drotrecogin- $\alpha$  trials. Efficacy, side effects, and risks in this population are unknown. One case of placental abruption and hemorrhage with fetal death was reported to Lilly in 2005. Three case reports<sup>22,23,24</sup> exist in which drotrecogin- $\alpha$  was used in pregnancy and a live infant was delivered.

#### WHAT IS THE OPTIMAL STRATEGY FOR MECHANICAL VENTILATION WHEN THE PATIENT IS PREGNANT? DO ARDSNET GUIDELINES APPLY EQUALLY IN THIS PATIENT POPULATION?

Acute respiratory distress syndrome (ARDS) is an uncommon disorder in pregnancy, with an incidence estimated between 0.016% and 0.035% of deliveries or roughly 1 in 3000 to 6000.<sup>25,26</sup> The incidence of acute lung injury (including ARDS) is estimated at 80 per 100,000 patientyears in the general U.S. population.<sup>27</sup> Converting the number of deliveries to person-years and assuming each delivery to correspond to 0.75 person-years, the incidence of ARDS in pregnancy would be roughly 21 to 46 per 100,000 person-years in the obstetric population. This is lower than the rate in the general population (although not age adjusted). The mortality rate for ARDS among obstetric patients has been estimated to be 24% to 44% among older case series,<sup>25,26,28,29</sup> and about 33% in a more recent series.<sup>30</sup> Both are consistent with the general population case-fatality rate of 38%.<sup>27</sup> A national review of Canadian hospital admissions between 1991 and 2002, however, found that the case-fatality rate among obstetric patients with ARDS in the absence of any major preexisting condition (e.g., diabetes, heart disease) was only 6%.<sup>31</sup>

There are no randomized controlled trials of ventilator strategies in the obstetric population. Many authorities recommend maintaining maternal Spo2 more than 95%, or Pao<sub>2</sub> more than 60 mm Hg to preserve fetal well-being, but it is unclear what evidence supports this recommendation. Uteroplacental blood flow rather than maternal oxygenation per se is the major determinant of fetal oxygenation. The model for gas transport across the human placenta is thought to be that of a concurrent exchanger. The gradient between maternal and fetal oxygen content drives transfer. Because the oxygen content of fetal blood is quite low, the gradient is easily preserved. A normal fetal umbilical venous Po2 (the most highly oxygenated blood in the system) is only 31 to 42 mm Hg.<sup>32</sup> The nature of a concurrent exchanger is such that oxygen saturation at the most highly oxygenated end of the fetal side is still lower than the least oxygenated end of the maternal circulation, represented by the uterine vein and approximated by the Svo<sub>2</sub>. Only in the extreme case of a venous equilibrator could the two be equal, and under no circumstances can the fetal side be higher than the maternal venous side. Oxygen delivery to the fetus and to fetal organs, as to the adult, is calculated as the product of blood flow and oxygen content. Adaptive strategies in the fetus include higher affinity of fetal hemoglobin for oxygen and high cardiac output relative to size.

There is only one experimental trial of deliberate hypoxia in human pregnancy.<sup>33</sup> Ten women with normal pregnancies near term were exposed to a hypoxic gas mixture with an FIO<sub>2</sub> of about 0.1 (50% room air, 50% nitrogen) for 10 minutes, during which time Spo<sub>2</sub> decreased by 15%. Fetal parameters that are believed to represent fetal oxygenation (i.e., heart rate baseline and variability, fetal umbilical artery Doppler indices, and fetal middle cerebral artery Doppler indices) did not change during experimental maternal hypoxia. Direct sampling of fetal blood was not performed in this study.

After the publication of the Acute Respiratory Distress Syndrome Network (ARDSNet) trial, which showed a survival advantage in ARDS and acute lung injury when a strategy of low tidal volume ventilation was employed,<sup>34</sup> strategies for mechanical ventilation no longer were driven by a need to normalize arterial blood gases. Rather, the emphasis now is on limiting lung injury secondary to excess volume, pressure, stretch, or cyclic collapse and reexpansion. No similar trials have been performed in pregnant patients with ARDS. There are few publications that describe ventilator settings in cases of ARDS in pregnancy. In a case series from the era preceding low tidal volume ventilation for ARDS, barotrauma rates were 36% to 44% in obstetric patients who were mechanically ventilated.<sup>25,26</sup> This compares unfavorably with the background rate of 11% among nonobstetric patients ventilated with "traditional" tidal volumes in ARDS.34

When contemplating a low tidal volume ventilation strategy for pregnant women with ARDS, the maternal  $Paco_2$  is probably of more importance than the  $Pao_2$ .  $CO_2$  transfer across the placenta also requires a gradient. In this case, the higher  $Pco_2$  of fetal blood diffuses across the placental interface to the lower  $Pco_2$  of maternal blood. High maternal  $Pco_2$ , as in permissive hypercapnia, would be expected to impede transfer and allow fetal acidemia. In a small trial of  $CO_2$  rebreathing in 35 healthy pregnant women, a rise in the maternal end-tidal  $CO_2$  as high as 60 mm Hg was associated with a loss of fetal heart rate variability, a proxy for fetal acidemia, in 57% of fetuses monitored. Ninety percent of fetuses thus affected normalized the posttest tracing.<sup>35</sup>

Thus, it would appear that a pregnant woman ventilated with a low tidal volume strategy should have the fetal heart rate tracing continuously monitored. If the tracing shows signs of fetal acidemia or other compromise, interventions might include decreasing positive end-expiratory pressure (PEEP; improving uterine blood flow by improving cardiac output), or increasing tidal volume so as to increase maternal pH and decrease maternal Pco<sub>2</sub>. Others have recommended increasing maternal Pao<sub>2</sub>, albeit without obvious evidence to support the intervention. This would require increasing Fto2 rather than PEEP because of the effects of PEEP on cardiac output. Airway pressurerelease ventilation has been employed successfully in a single small case series of pregnant patients with ARDS, and may be considered as an alternative.<sup>36</sup>

Delivery in itself does not appear to improve maternal survival in ARDS.<sup>26,37,38</sup> Fetal survival, however, is tightly linked to gestational age at delivery. This would imply a fetal benefit to continuing rather than interrupting pregnancy, assuming maternal and fetal condition permits.

#### IS RECOMBINANT FACTOR VIIA INDICATED IN LIFE-THREATENING POSTPARTUM HEMORRHAGE?

Postpartum hemorrhage is a major cause of maternal morbidity and mortality worldwide. The prevalence of postpartum hemorrhage ( $\geq$ 500 mL blood loss) and of

severe postpartum hemorrhage ( $\geq$ 1000 mL blood loss) is estimated at 6% and 1.86%, respectively, of all deliveries.<sup>39</sup> According to a 2006 World Health Organization analysis, hemorrhage accounts for about 13.4% of maternal deaths occurring in developed countries.<sup>40</sup> Strategies to control postpartum hemorrhage include administration of uterotonics, placement of uterine hemostatic sutures, vessel ligation or embolization, intrauterine balloon tamponade, and support of hemostasis by infusion of appropriate blood replacement products. When these measures fail, hysterectomy may be required. The use of recombinant activated factor VII (rFVIIa) as an adjuvant therapy for postpartum hemorrhage is attractive. There are no randomized controlled trials assessing rFVIIa in obstetric hemorrhage.

The first case report of the successful use of rFVIIa to treat intractable obstetric hemorrhage in a nonhemophiliac patient was published in 2001.<sup>41</sup> Since that time, a number of case reports describing the use of rFVIIa have been published. In a compilation of many of these reports, totaling about 120 patients, the median dose was 71.6  $\mu$ g/kg (range, 10 to 170  $\mu$ g/kg), and patients received a median of 1.6 doses. Among these case reports, which likely reflect a reporting bias for positive outcomes, effectiveness in reducing or stopping bleeding was 90%.<sup>42</sup> Although administering rFVIIa before hysterectomy enabled some patients to avoid this intervention, this was not a universal outcome.

The Northern European Registry recently reported data collected from 108 women who received rFVIIa between 2000 and 2004 for postpartum hemorrhage. Ninety-two of these women were classified into a primary treatment group and the remaining into a secondary prophylaxis group. Women in the primary treatment group had a median blood loss of 5.8 L before rFVIIa and received red blood cell transfusion (median, 13 U), and 70% had clinical disseminated intravascular coagulopathy. Clinicians noted improvement after a single dose ( $\leq$ 90 µg/kg) in 80% of the women and in three additional patients after multiple doses. There appeared to be no effect from rFVIIa in 13.8% of cases.<sup>43</sup> Again, not all women avoided hysterectomy.

A main concern with the use of rFVIIa in the obstetric population is the risk for thromboembolic complication. Four women in the Northern European Registry developed thromboembolism. Two developed pulmonary embolism within 1 week of birth, one had bilateral ovarian vein thromboses 4 weeks postpartum, and one developed a subclavian vein thrombosis assessed as not related to the use of rFVIIa. One woman was diagnosed with myocardial infarction, but she experienced cardiac arrest before administration of rFVIIa. One patient developed a skin rash assessed as a possible allergic reaction.<sup>43</sup>

In summary, rFVIIa has shown some promise in stabilizing postpartum hemorrhage in nonrandomized case series. One author has suggested that this drug be administered not as a "last resort" and ideally before the decision to perform hysterectomy.<sup>42</sup> Given the relative infrequency of severe postpartum hemorrhage and the challenges of obtaining consent in an emergency situation, it is unlikely that results of a randomized trial will be available in the near future.

#### **AUTHORS' RECOMMENDATIONS**

- Care of the critically ill obstetric patient requires interpretation and adaptation of studies performed in the nonobstetric population.
- Although some data from nonpregnant patients can be generalized (e.g., guidelines for treatment of sepsis), other recommendations, such as ventilatory strategies in ARDS, may require modification for the pregnant woman and her fetus.
- In many clinical situations that complicate pregnancy, the likelihood of randomized trials being conducted is small. A multidisciplinary approach, should be adopted, since it is anticipated that it would lead to the best possible outcome for the mother and her fetus.

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## 87 Should One Prevent or Treat Hypothermia in the Intensive Care Unit?

**Dimitry Baranov** 

To a practicing intensivist, hypothermia in intensive care unit (ICU) patients might seem, to paraphrase Churchill, like a riddle, wrapped in a mystery, inside an enigma. Data in the literature on hypothermia in critically ill patients present a seemingly conflicting picture. Some believe that hypothermia is a sinister predictor or cause of mortality in many critically ill patients. Others view it as an important aid in preserving organ function that is particularly useful for neuroprotection. Who is correct? Is hypothermia in ICU patients an independent risk factor, and as such, does it need to be aggressively treated and prevented in every patient to improve outcomes? Or is it a consequence of the depletion of physiologic reserve associated with critical illness? Is there some beneficial protective or therapeutic effect in allowing or even inducing a certain degree of hypothermia in some ICU patients?

To resolve these conflicts, the reader must understand the pathophysiologic difference between unintentional and induced hypothermia. Familiarity with the history and use of induced hypothermia as a protective or therapeutic modality, covered elsewhere in this volume, also is crucial in dispelling many controversies.

Humans, like all homeothermic animals, maintain body core temperature within a very narrow range regardless of ambient temperature. This is of paramount importance for normal biochemical and cellular function. Thermal homeostasis is achieved by activation of multiple and complex thermoregulatory mechanisms that have been extensively described in the literature.<sup>1</sup> The decrease in physiologic reserve associated with critical illness may result in an inability to restore and maintain thermal homeostasis. Mild to moderate hypothermia is a routine finding when critically ill patients and severe trauma victims are admitted to the ICU. This usually results from environmental exposure, large volumes of unwarmed resuscitative fluids and blood products, anesthetic agents, or intoxication with alcohol or drugs. In addition, the patients' endogenous capacity to produce and retain heat may be severely limited by impairment of thermoregulatory mechanisms as well as a shock-induced reduction in blood flow. It is well established that accidental hypothermia from exposure, even in uninjured victims, is a significant independent risk factor for mortality.<sup>2</sup> Recent clinical trials demonstrated that even mild inadvertent

hypothermia in the perioperative setting is associated with increased rates of cardiac morbidity, surgical wound infection, higher blood loss, delayed anesthetic recovery, and prolonged hospitalization.<sup>3-6</sup> Therefore, maintenance of intraoperative normothermia is a routine practice. It would appear to be logical to actively restore and maintain body core temperature in all ICU patients. It turns out that this may not be correct. Multiple clinical retrospective studies have demonstrated an association between exposure hypothermia and poor outcome in trauma. Accordingly, the American College of Surgeons Advanced Trauma Life Support Program recommends prevention, prompt detection, and treatment of hypothermia in trauma patients. This is based on the hypothesis that prevention of hypothermia or of the need for rewarming will lead to improved outcomes. Conversely, numerous laboratory studies have indicated that the induction of mild hypothermia improves survival after hemorrhagic shock. How can such conflicting data can be reconciled? In part, this controversy highlights the dangers in drawing conclusions from epidemiologic as opposed to interventional data.

#### DEFINITIONS OF ACCIDENTAL AND INDUCED HYPOTHERMIA

Hypothermia in ICU patients may be accidental or induced. For example, major trauma often is associated with accidental, uncontrolled hypothermia. Conversely, induced hypothermia has been touted for preventive or therapeutic purposes and is implemented in a controlled and monitored fashion. Induced hypothermia can be protective-preservative (preinsult and intrainsult, as in cardiac surgical procedures requiring circulatory arrest<sup>-9</sup>) or resuscitative-therapeutic (postinsult, e.g., after sudden cardiac death<sup>7</sup>). The use of therapeutic hypothermia as an adjunct to resuscitation was first proposed in the 1950s but only recently has been validated for out-ofhospital cardiac arrest.<sup>10,11</sup>

Hypothermia also may be classified according to arbitrarily chosen ranges in body temperature as mild (33° to 36°C), moderate (30° to 33°C), or deep (<30°C). Therapeutically induced hypothermia characteristically is mild to moderate except in procedures in whom cardiopulmonary bypass is used. Deeper degrees of accidental hypothermia in major trauma victims usually result in poor outcomes.

#### HISTORICAL PERSPECTIVES

Our understanding of both accidental and induced hypothermia has undergone dramatic development since 1943, when Fay proposed the use of generalized refrigeration for the treatment of severe brain injury. Historically, the primary use of induced hypothermia has been for neuroprotection in a variety of clinical settings. In the 1950s, deep hypothermia was proposed and successfully introduced as a tool to improve outcomes in cardiac surgery and neurosurgery when prolonged episodes of brain ischemia were expected.<sup>12,13</sup> The neuroprotection afforded by profound hypothermia in surgical procedures in which circulatory arrest is planned is indisputable and remains a current standard of practice.<sup>7,9</sup> Early studies demonstrated that decreases in cerebral metabolism (CRMO<sub>2</sub>), cerebral blood flow (CBF), cerebral volume, and cerebrospinal fluid (CSF) pressure were associated with decreases in brain temperature.<sup>13</sup> This led to a widely held notion that hypothermia affords neuroprotection by slowing brain metabolism and prolonging tolerance for the metabolic substrate deprivation. Subsequent studies revealed slower adenosine triphosphate (ATP) depletion in the ischemic hypothermic brain.<sup>14</sup> By extrapolation, it was assumed that the more profound the hypothermia the greater the neuroprotection, and therefore clinical neuroprotection required a profound decrease in temperature. This limited the use of induced hypothermia to a few clinical situations because profound hypothermia led to a need for cardiopulmonary bypass and systemic anticoagulation. However, most clinical situations in which brain injuries occur do not lend themselves to preinsult or preventive therapeutic interventions, and the institution of both exogenous circulation and anticoagulation is contraindicated. Therefore, in the 1970s and 1980s, several investigators studied the use of moderate induced hypothermia with body surface cooling after insult in animal models of focal cerebral ischemia.<sup>15,16</sup> This approach was especially unconventional because the belief at the time was that the entire outcome following brain injury was determined at the time of the insult.7 However, some investigators hypothesized that the initial injury led to a cascade of secondary events that affected outcome in ischemic and traumatic brain injury victims. The existence of secondary brain *injury* opened a window of opportunity for therapeutic intervention after the initial insult. In a focal ischemia model of injury in monkeys, cats, and dogs, Michenfelder and associates found that prolonged moderate hypothermia significantly worsened outcome, with most hypothermic animals dying on rewarming and displaying massive brain edema.<sup>14-16</sup> This was attributed to the cardiotoxic effects of hypothermia. Human trials carried out during this period on patients after severe traumatic brain injury produced mortality rates between 43% and 72%, with most patients dying during rewarming or induced hypothermia.<sup>17</sup> Others reported life-threatening

side effects and uncertain benefits in hypothermic ICU patients.<sup>17-19</sup> As a result of this negative experience with prolonged moderate induced hypothermia, nearly a decade passed before new data led to a resurgence of interest in the use of post-insult-induced hypothermia. In the late 1980s, Busto and colleagues<sup>20</sup> demonstrated that even mild hypothermia (>33°C) could significantly improve outcomes after transient global brain ischemia in rats. This study called into question the notion that hypothermia afforded neuroprotection through an incremental reduction in the brain metabolism. Multiple laboratory studies demonstrated that mild induced hypothermia during or after an ischemic insult improved outcome in a wide variety of experimental models with relatively few side effects. However, subsequent clinical studies have failed to validate these results in humans. The first major breakthrough occurred in 2002 when two independent reports demonstrated improved outcomes in the victims of witnessed cardiac arrest treated with mild prolonged induced hypothermia.<sup>21,22</sup> Since these reports, the indications have expanded dramatically and are discussed elsewhere.

#### PHYSIOLOGY OF HYPOTHERMIA

The physiology of hypothermia is well described in the literature. For a more detail discussion of underlying mechanisms of hypothermia-mediated neuroprotection, the reader is referred to recent reviews on this subject.<sup>22–26</sup> We briefly describe only the most important physiologic effects of hypothermia in order of importance to the management of ICU patients.

#### **Thermoregulatory Mechanisms**

Body core temperature is maintained to a remarkably effective degree by thermoregulatory mechanisms. This occurs despite the need to respond to a wide range of ambient temperatures. In awake healthy individuals, a decrease of only a few tenths of a degree centigrade in core temperature triggers thermoregulatory vasoconstriction. This decreases cutaneous heat loss and restricts metabolic heat to the core thermal compartment.<sup>1</sup> A slightly lower temperature results in shivering to increase heat production. This increases metabolic rate and oxygen consumption by up to 100% and is accompanied by increases in the work of breathing, heart rate, and blood pressure. Administration of sedatives, opiates, and muscle relaxants may counteract thermoregulatory reactions. Counterwarming of hands, feet, and face helps to reduce shivering during hypothermia.<sup>25</sup> Thermoregulatory control is also impaired by surgery, advanced age, and critical illness.<sup>26</sup>

#### **Central Nervous System**

Hypothermia decreases CRMO<sub>2</sub>, CBF, and intracranial pressure (ICP). For each 1°C decrease in brain temperature, the CRMO<sub>2</sub> decreases by 6% to 7%, although this response is not linear. In normothermic patients, global brain ischemia exceeding 10 minutes invariably leads to catastrophic and permanent neurologic injury. In contrast,

profound (18°C) hypothermia during circulatory arrest appears to protect the brain for more than 50 minutes and typically is associated with complete gross neurologic recovery. Interestingly, even minor ( $2^{\circ}$  to  $4^{\circ}$ C) reductions in brain temperature in animal models of focal and global ischemia result in greater than predicted protection. This suggests that more than a reduction in brain metabolism is involved and points to the participation of other mechanisms. Multiple mechanisms by which hypothermia can affect processes taking place in the course of the secondary post-ischemia-reperfusion or traumatic brain injury have been proposed and studied in recent years. It has been reported that mild hypothermia decreases levels of excitatory amino acids, production of oxygen free radicals, and lactate concentration following ischemiareperfusion. The deleterious role of excessive concentrations of these substances in ischemia-reperfusion injury is well established. Hypothermia may modulate and inhibit caspase activation and reduce neural apoptosis. Hypothermia inhibits reperfusion-associated inflammatory and immunologic responses that may play a significant role in the secondary injury. The details regarding the effects of degree and duration of hypothermia have not been established.

#### Cardiovascular System

Cardiac arrhythmias are the most frequently cited side effect of hypothermia. They are quite common at temperatures below 30°C. Indeed, this is the main factor that makes the use of deep hypothermia impossible without cardiopulmonary bypass. Atrial fibrillation is typically observed initially, but ventricular fibrillation may follow as temperature drops below 28°C. In mild hypothermia, arrhythmias are uncommon. Mild to moderate induced hypothermia, when shivering is suppressed, is associated with 25% to 40% decrease in cardiac output, lower heart rate, and increased systemic vascular resistance with little change in mean arterial pressure. In contrast, shivering in accidental hypothermia significantly increases metabolic requirements. This leads to higher heart rates and raises a risk for myocardial ischemia in patients with ischemic heart disease. Cold diuresis may lead to hypovolemia.

#### **Respiratory System**

Shivering associated with accidental hypothermia increases the work of breathing. This may mandate intubation and controlled ventilation. During induced hypothermia, shivering is usually less pronounced or is inhibited. Hypothermia is associated with an increased risk for pneumonia.

#### Metabolic Changes

Hypothermia is associated with increased diuresis and hypokalemia. The latter generally needs to be corrected. Significant hyperkalemia may occur during rewarming. Insulin production by the pancreas is reduced during hypothermia. This may cause hyperglycemia. Exogenous insulin may be needed.

#### **Hematologic System**

Impairment of the coagulation cascade and platelet function occurs in deep accidental hypothermia, especially in the setting of major trauma. This is rare in mild induced hypothermia. During prolonged induced hypothermia, the function of white blood cells is adversely affected. This may lead to sepsis and poor surgical wound healing.

#### SHOULD MILD ACCIDENTAL HYPOTHERMIA BE CORRECTED?

Fay first proposed generalized refrigeration for the treatment of severe brain injury in 1943. Since that time, our understanding of both accidental and induced hypothermia has undergone dramatic development. In the 1950s, deep hypothermia was proposed and successfully introduced as a tool to improve outcomes in cardiac and neurologic surgery, in which prolonged episodes of brain ischemia were expected.<sup>12,13</sup> The neuroprotection afforded by profound hypothermia in surgical procedures in which circulatory arrest is planned is indisputable and remains a current standard of practice.<sup>9</sup> There have been many attempts to use induced hypothermia for therapy in different categories of critically ill patients.<sup>17,18,27-47</sup> Most results were disappointing. However, in 2002, two independent reports demonstrated improved outcomes in the victims of witnessed cardiac arrest treated with mild prolonged induced hypothermia.<sup>21,22</sup> These results not only reinvigorated interest in induced hypothermia as a treatment modality but also led to a reassessment of the need to reverse mild accidental hypothermia such as may occur in the operating room or the ICU.

#### **Detrimental Effects of Mild Hypothermia**

The potential benefits-preserved function of organ systems, especially the cardiovascular and central nervous systems-are self-evident and were recounted previously in this volume. However, the therapeutic trials also have enhanced our understanding of the detrimental effects of mild prolonged hypothermia. Recent clinical trials have demonstrated that even mild inadvertent hypothermia in the perioperative setting is associated with increased rates of cardiac morbidity, surgical wound infection, and blood loss as well as delayed recovery from anesthesia-sedation and prolonged hospital length of stay.<sup>3-6</sup> In addition, patients in most human trials of induced hypothermia had a higher incidence of pneumonia relative to normothermic controls. For example, in a recent trial of mild induced hypothermia in patients undergoing surgery for aneurysm clipping following subarachnoid hemorrhage, hypothermia-related side effects occurred in 93% of treated patients. Eighty-three percent had severe infectious complications, mostly ventilator-associated pneumonia.48 It is logical to conclude that other perioperative patients may be at similar risk. However, a recent observational study of 650 cases entered in the registry of the European Resuscitation Council Hypothermia after Cardiac Arrest Registry Study Group (ERC HACA-R)<sup>49</sup> found a lower rate of adverse events than in published randomized clinical trials.

Much of the data regarding the detrimental effects of rewarming are derived from the trauma literature. The successful use of hypothermia for organ and brain protection against hypoperfusion-ischemic injuries in cardiac surgery and organ transplantation led to interest in the use of therapeutic hypothermia for victims of hemorrhagic shock.<sup>47</sup> The reduction in metabolic rate associated with hypothermia could potentially alleviate the degree of ischemia in hemorrhagic shock.<sup>50</sup> Mild hypothermia during hemorrhagic shock or fluid resuscitation improved survival when uncontrolled,<sup>51</sup> volumecontrolled,<sup>52,53</sup> pressure-controlled,<sup>54</sup> and prolonged hemorrhagic shock, combined with significant tissue trauma<sup>55</sup> and hemorrhagic shock requiring intensive care environment similar to that found in clinical situations<sup>55</sup> in animals, was compared with normothermic resuscitation.

Conversely, other experimental and clinical studies of hemorrhagic shock indicated that hypothermia adversely affected vital organs and systems. This may explain why, despite the results of some animal studies, hypothermia is associated with mortality and morbidity in observational studies. That is, the adverse effects of hypothermia can be monitored and managed in the laboratory. For example, Mizushima demonstrated that hypothermia depressed cardiac function and hepatic blood flow in an animal model of hemorrhagic shock.<sup>56</sup> Active rewarming during resuscitation improved cardiac function and hepatic blood flow compared with animals that were allowed to remain hypothermic. Interestingly, the hypothermia-rewarming group of animals had improved parameters compared with the control group, in which normothermia was maintained during and after injury. None of the common complications associated with rewarming—especially coagulopathy<sup>57–61</sup> and immunosuppression<sup>62,63</sup>-were observed in the controlled laboratory environment.

Hypothermia-induced coagulopathy is a significant contributing factor to adverse outcomes in trauma. There is a strong association among hypothermia, blood loss, and impaired hemostasis in trauma patients.<sup>57</sup> Temperatures below 34° to 33°C directly impair the activity of enzymes in the coagulation cascade<sup>59–61</sup> as well as platelet function.<sup>60,61</sup> These may act synergistically with resuscitative hemodilution,<sup>58</sup> a finding that may explain the absence of coagulopathy in head injury, in which fluid administration was restricted.<sup>64</sup>

Another mechanism by which hypothermia may worsen outcomes in trauma patients is immunosuppression. Mild hypothermia may reduce the expression of heat shock proteins, impair granulocyte recruitment, and alter cytokine balance.<sup>62,63</sup>

Studies in brain-injured patients also indicate that hypothermia is associated with adverse outcomes. Clifton and colleagues<sup>17</sup> showed a greater complication rate in hypothermic patients compared with normothermic patients. A multicenter study of mild hypothermia in traumatic brain injury revealed infectious complications such as pneumonia and meningitis in the hypothermic group.<sup>43</sup> In addition, an association between fever and worsened neurologic deficit and mortality in stroke patients has been reported.<sup>27,28</sup>

#### **Detrimental Effects of Rewarming**

Gentilello and associates<sup>65</sup> studied the effect of rapid versus standard rewarming in moderately to severely injured patients with hypothermia. This study showed reduced fluid and blood product requirements, reduced length of ICU stay, and improved short-term, but not long-term, survival. This remains the only published prospective randomized controlled clinical trial of management of hypothermia in trauma patients. Nonetheless, rewarming is known to induce rebound cerebral edema and elevated ICP, shivering with an increased metabolic rate, arrhythmias, vasodilation with decreased blood pressure, pulmonary edema, hyperkalemia, hypermagnesemia, hyperphosphatemia, hypocalcemia, hypoglycemia, rhabdomyolysis, and alkalosis. Most can be easily managed in a critical care environment. However, the increase in metabolic rate and cardiac output associated with rewarming may precipitate myocardial ischemia.<sup>3</sup>

#### **AUTHOR'S RECOMMENDATIONS**

- Normal body temperature is maintained within a very narrow range. Extreme deviations are poorly tolerated.
- Hypothermia may deplete physiologic reserve. This may impair thermoregulatory mechanisms and predispose to complications.
- There are no widely accepted definitions of mild, moderate, and severe hypothermia. This has limited investigation.
- The presence of hypothermia, especially when severe, is associated with poor outcome from many other disorders.
- Because of impaired cardiac contractility and arrhythmias, management of severe hypothermia (below 30°C) may require cardiopulmonary bypass.
- Hypothermia impairs function in most organ systems.
- Rewarming is associated with an additional set of abnormalities. Most can be managed in an ICU environment.
- The benefits of hypothermia are proved only after cardiac arrest from a limited set of causes. Advantages are of questionable value in most other cases. Data on the value of unintentional hypothermia are anecdotal.
- Most hypothermia-associated abnormalities can be treated in an ICU. However, coagulation abnormalities and a predisposition to infection are problematic. Similarly, active rewarming may lead to complications, particularly in patients with coronary artery disease.
- At this time, it would seem prudent to actively treat unintentional hypothermia in a setting in which bleeding is likely or there is a predisposition to infection. This includes the perioperative period. It is unclear that mild hypothermia under other circumstances needs to be actively reversed.

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What Are the Special Considerations in the Management of Morbidly Obese Patients in the Intensive Care Unit?

Ali A. El Solh

Obesity is a chronic metabolic condition with important public health implications. It has been linked to increased morbidity and mortality from acute and chronic medical problems, including hypertension, cardiovascular diseases, dyslipidemia, diabetes mellitus, arthritis, sleep apnea, and certain forms of cancer.

Critically ill obese patients present the intensive care physician with unique challenges. Only a thorough knowledge of the peculiar pathophysiologic changes that occur in this population will allow for anticipation of complications and effective delivery of care.

#### AIRWAY MANAGEMENT

Morbid obesity is considered one of the risk factors for difficult intubation. In the Australian Incident Monitoring Study, limited neck mobility and mouth opening accounted for most cases of difficult intubation in obese subjects.<sup>1</sup> Naguib and colleagues<sup>2</sup> added to the preceding list a short sternomental distance, a receding mandible, and prominent teeth as potential causes for difficult intubation. In a study of 100 morbidly obese patients, Brodsky and associates<sup>3</sup> identified increased neck circumference and a Mallampati score of 3 or greater as the sole predictors of difficult intubation. Although these multivariate predictive models have yet to be tested in an intensive care unit (ICU) setting, Gaszynski was unable to validate any of these characteristics in a group of 87 morbidly obese patients<sup>4</sup> undergoing elective surgery. In fact, all morbidly obese patients with a body mass index (BMI) greater than 50 kg/m<sup>2</sup> were intubated on the first attempt. Neither obesity nor BMI predicted problems with tracheal intubation.<sup>3</sup> One of the reasons for the observed differences among these studies is the lack of consensus on the definition of the term difficult intubation. Although there is no consensus on intubation, the increased bulk of soft tissues in the upper airway makes the morbidly obese, particularly those with obstructive sleep apnea,

prone to partial obstruction and thus difficult to ventilate. Hiremath and coworkers<sup>5</sup> found that 8 of 15 individuals with Cormack and Lehane grade 4 laryngoscopic views had apnea-hypopnea indices consistent with previously undiagnosed sleep apnea syndrome, whereas only two matched controls without a difficult laryngoscopic view had similar scores.

Emergent airway management of critically ill morbidly obese patients is frequently complicated by the patient's limited physiologic reserve. Morbidly obese patients are more prone to hypoxemia due to reductions in expiratory reserve volume, functional residual capacity, and maximum voluntary ventilation. Moreover, increased intraabdominal pressure is thought to place the obese patient at a higher risk for aspiration of gastric content. In a cross-sectional study by Vaughan and associates,6 42 of 56 of obese patients (75%) presented with both gastric secretion volume of more than 25 mL and pH of less than 2.5 compared with 0 of 50 normal weight controls. These levels are considered to place the adult obese patient at risk for aspiration pneumonitis. Given these physiologic changes, a rapid sequence induction (RSI) has been advocated. However, the use of RSI in fasted patients with no risk factors for aspiration other than obesity is subject to debate. Zacchi and colleagues<sup>7</sup> have shown that obese patients without symptoms of gastroesophageal reflux have a resistance gradient between the stomach and the gastroesophageal junction similar to that observed in nonobese subjects. This is important given that there are significant drawbacks for RSI that could prove deleterious in these patients. First, there is a distinct risk for the "cannot intubate and cannot ventilate" scenario because the ability to mask-ventilate is not tested before the administration of the muscle relaxant. Second, although cricoid pressure may or may not decrease the risk for aspiration, there is evidence that it may worsen the quality of laryngeal exposure.<sup>8</sup> Finally, the application of cricoid pressure can lead to a complete airway occlusion between 6% and 11% of the time.

In short, the degree of obesity or neck size that justifies advanced interventions for intubation remains unknown. The experience and ability of the laryngoscopist are probably the most important determinants for establishing an airway in the morbidly obese patient.

Morbidly obese patients present a unique surgical challenge when tracheostomy is required. This reflects increased submental and anterior cervical adipose tissue. The initial goal of securing a stable airway also can be compromised by the size discrepancy and curvature mismatch between a standard-size tracheostomy tube and the increased distance between skin and trachea. Standard tracheostomy tubes typically are too short and too curved. Consequently, they are more likely to be dislodged. In a prospective study of 89 morbidly obese patients requiring surgical tracheostomy, El Solh and Jaafar<sup>10</sup> reported an overall complication rate of 25%, most of which were minor. Life-threatening complications occurred in 10% and were related to tube obstruction and extratracheal tube placement. Some surgeons perform a Björk flap at the time of surgery<sup>11</sup> to prevent tube misplacement in the pretracheal fascia. Alternatively, Gross and colleagues<sup>12</sup> advocated a cervical lipectomy in combination with tracheostomy. There are no studies to our knowledge that provide a conclusive answer regarding the benefit of these techniques in reducing the rate of extratracheal placement.

Percutaneous dilational tracheostomy (PDT) remains controversial for these patients. Obese patients with large and thick necks traditionally were considered poor candidates for PDT; however, PDT has been performed in these patients with low rates of complications. Mansharamani and colleagues<sup>13</sup> reported no complications in 13 consecutive obese patients, but Byhahn and coworkers<sup>14</sup> described a 2.7-fold increased risk for perioperative complications in obese patients (95% confidence interval [CI], 1.8 to 4.1; P < .001). This included a 4.9-fold increased risk for serious complications (95% CI, 3.1 to 7.8; P < .001). In the absence of large randomized trials, no recommendation could be made regarding PDT in this population. However, it should be pointed out that the outcome of PDT depends largely on the skills and the experience of the operator.

#### RESPIRATORY

The most prominent pulmonary function test abnormalities associated with obesity consist of decreased expiratory reserve volume (ERV) and functional residual capacity (FRC), whereas the vital capacity and total lung capacity are essentially unchanged. Relative to nonobese subjects, the total respiratory system compliance is decreased because of the greater degree of chest wall compression and cephalad displacement of the diaphragm.<sup>15</sup> In the supine and Trendelenburg positions, FRC may fall below the closing capacity. This leads to small airway collapse, atelectasis, ventilation-perfusion mismatch, and hypoxemia.<sup>16</sup> These alterations in pulmonary function carry important implications for the treatment of obese patients requiring mechanical ventilation. As lung volumes are reduced and airway resistance is increased, a tidal volume based on a patient's actual body weight is likely to result in high airway pressures, alveolar overdistention, and barotrauma. The current consensus would favor that the initial tidal volume be calculated according to ideal body weight and then adjusted according to the desired plateau pressure and systemic arterial blood gases.

The role of positive end-expiratory pressure (PEEP) on respiratory mechanics and blood gases in postoperative mechanically ventilated morbidly obese subjects has been tested by a number of studies. Pelosi and associates<sup>17</sup> applied PEEP of 10 cm H<sub>2</sub>O to nine anesthetized and paralyzed morbidly obese subjects after abdominal surgery and found a significant reduction in respiratory system elastance and resistance. This reduction was attributed to alveolar recruitment or to the reopening of closed airways. The authors also found a small but significant improvement in arterial oxygenation that correlated with the amount of recruited volume. In a similar group of subjects, Koutsoukou and colleagues<sup>18</sup> found that the PEEP (4-16 cm) caused a significant reduction in elastance and resistance in the respiratory system. However, PEEP had no significant effect on gas exchange. In both studies, oxygenation remained markedly abnormal even after the application of PEEP. In fact, Rothen and colleagues<sup>19</sup> have found that the extent of atelectasis, which was correlated with the amount of venous admixture, was not reduced by inflation of the lungs with conventional tidal volume or even with a doubled tidal volume.

The rate of reintubation in severely obese patients has been reported as 8% to 14% among patients undergoing mechanical ventilation for more than 48 hours.<sup>20,21</sup> Earlier investigations suggested that the prophylactic use of noninvasive ventilation (NIV) in morbidly obese patients during the first 24 hours postoperatively reduced pulmonary dysfunction after gastroplasty and accelerated reestablishment of preoperative pulmonary function. Joris and colleagues<sup>22</sup> demonstrated that the application of bilevel positive airway pressure set at 12 and 4 cm H<sub>2</sub>O significantly improved the peak expiratory flow rate, the forced vital capacity, and the oxygen saturation on the first postoperative day. This improvement was attributed to a combined effect of improved lung inflation, prevention of alveolar collapse, and reduced inspiratory threshold load. Duarte and colleagues<sup>23</sup> retrospectively studied the outcome of 50 morbidly obese patients admitted to a medical ICU with acute respiratory failure requiring ventilatory assistance. A total of 33 patients were treated with NIV. Sixty-four percent avoided invasive mechanical ventilation. Patients successfully treated with NIV had a significantly lower BMI, demonstrated improvements in gas exchange, and had a shorter hospital stay and a lower mortality. In contrast, patients who failed a trial of NIV and those who required invasive mechanical ventilation demonstrated a longer ICU and hospital length of stay and higher mortality (31%). In a nonrandomized concurrent prospective study of 62 morbidly obese patients treated in a medical ICU, El Solh and associates<sup>24</sup> reported a 16% absolute risk reduction in the rate of respiratory failure when NIV was instituted immediately after extubation. Subgroup analysis of hypercapnic patients showed reduced hospital mortality in the NIV group compared with controls.

#### DEEP VENOUS THROMBOSIS PROPHYLAXIS

Morbid obesity carries a moderate-to-high risk category for venous thromboembolic disease (VTE). Increased venous stasis, decreased mobility, and a possible hypercoagulable state are among the predisposing risk factors for VTE in the ICU. Unfortunately, there are limited data on the effect of prophylactic anticoagulation regimens in critically ill morbidly obese patients. These patients are typically excluded from trials because of the equivocal results of the diagnostic tests used to confirm or exclude thromboembolic disease.

Studies evaluating the effectiveness of VTE prophylaxis in obese hospitalized patients are listed in Table 88-1.<sup>25–36</sup> Despite the absence of well-designed randomized controlled trials in critically ill morbidly obese patients, the use of prophylaxis is indicated. However, there is no universal consensus on the optimal regimens (mechanical or pharmacologic) and duration of VTE prophylaxis in these patients.

#### PHARMACOTHERAPY

A number of factors underlie alterations in the rate and extent of drug distribution in morbidly obese patients. These include degree of tissue perfusion, binding of drugs to plasma proteins, and permeability of tissue membranes. In general, the extent to which obesity influences the volume of distribution of a drug depends on its lipid solubility.<sup>37</sup> Early work with barbiturates clearly demonstrated the close correlation between lipid solubility and drug distribution.<sup>38</sup> In this instance, loading is based on total body weight (TBW). However, lipophilic compounds do not always have larger volumes of distribution. For example, the volumes of distribution of digoxin and procainamide are not significantly influenced by obesity despite their relatively high lipid partition coefficient. Conversely, the volume of distribution for some hydrophilic drugs in adipose tissue may be only a fraction of the volume of distribution in other tissues. This is because the water content in adipose tissue is 20% to 50% of that in other tissues. Hence, distribution

Table 88-1 Evidence of Efficacy of Venous Thromboembolism Prophylaxis in Hospitalized Obese Patients

Study	Study Design	Intervention	Outcome
Samama et al, 1999 <sup>25</sup>	Randomized controlled trial	738 hospitalized medical patients > 40 years old, including 20% of obese patients randomized to enoxaparin 40 mg/day or placebo	RR, 0.37 (97.6% CI, 0.22-0.63) with enoxaparin 40 mg/day. Major hemorrhage in 1.7% vs. 1.1 % in the placebo group.
Kalfarentzos et al, 2001 <sup>26</sup>	Randomized controlled trial	60 patients undergoing bariatric surgery, randomized to 5700 IU or 9500 IU of nadroparin	No incidence of DVT in both groups receiving nadroparin. Major hemorrhage reported in 6.7% in the group receiving higher dose of nadroparin.
Scholten et al, 2002 <sup>27</sup>	Prospective noncontrolled study	481 patients undergoing bariatric surgery receiving prophylaxis with 30 mg SC q 12 hr or 40 mg q 12 hr of enoxaparin	Incidence of symptomatic VTE of 5.4% with enoxaparin 30 mg q 12 hr, and of 0.6% with 40 mg q 12 hr. Major hemorrhage in 1.0% and 0.25% in the two groups of enoxaparin, respectively.
Gonzalez et al, 2004 <sup>28</sup>	Prospective noncontrolled study	380 patients undergoing bariatric surgery with SCD	Incidence of symptomatic DVT of 0.26%. No PE reported.
Alikhan et al, 2003 <sup>29</sup>	Randomized controlled trial	866 hospitalized obese medical patients > 40 years old randomized to enoxaparin 40 mg/day or placebo	RR, 0.49 (95% CI, 0.18-1.36) with enoxaparin 40 mg/day.
Shepherd et al, 2003 <sup>30</sup>	Prospective noncontrolled study	700 patients undergoing bariatric surgery receiving prophylaxis with continuous intravenous UH during the perioperative period	Incidence of DVT and symptomatic PE of 0% and 0.4%, respectively. Postoperative hemorrhage in 2.3%.
Miller & Rovito, 2004 <sup>31</sup>	Retrospective cohort	255 patients undergoing bariatric surgery receiving prophylaxis with LDUH 5000 IU or 7500 IU q 8 hr	Overall incidence of VTE of 1.2%. Prospective hemorrhage in 2.4%.
Shepherd et al, 2004 <sup>32</sup>	Prospective noncontrolled study	19 patients undergoing bariatric surgery receiving prophylaxis with continuous intravenous UH during the perioperative period	No symptomatic VTE confirmed. Major hemorrhage in 10.5%.
Leizorovicz et al, 2004 <sup>33</sup>	Randomized controlled trial	3706 hospitalized medical patients > 40 years old, including 30% of obese patients randomized to dalteparin 5000 IU/day or placebo	RR, 0.55 (95% CI, 0.38-0.80) with dalteparin 5000 IU/day. Major hemorrhage in 0.49% vs. 0.16% in the placebo group.

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Study	Study Design	Intervention	Outcome		
Kucher et al, 2005 <sup>34</sup>	Subgroup analysis of randomized controlled trial	1118 hospitalized obese medical patients > 40 years old, randomized to dalteparin 5000 IU/ day or placebo	VTE occurred in 2.8% of the dalteparin and 4.3% of the placebo group. RR 0.64 (95% CI, 0.32 to 1.28) with dalteparin 5000 IU/day.		
Hamad & Choban, 2005 <sup>35</sup>	Multicentric retrospective cohort	668 patients undergoing bariatric surgery receiving prophylaxis with enoxaparin 30mg (daily or q 12 hr) or 40 mg (daily or q 12 hr) or no prophylaxis	Overall incidence of objectively confirmed symptomatic PE of 0.9%, and DVT of 0.1%; highest incidence without prophylaxis. Major hemorrhage in 0.9%.		
Quebbemann et al, 2005 <sup>36</sup>	Prospective noncontrolled study	822 patients undergoing bariatric surgery receiving prophylaxis with continuous intravenous UH at 400 U/hr from the preoperative period until discharge	Overall incidence of objectively confirmed symptomatic VTE of 0.1%. Major hemorrhage in 1.3%.		

Table 88-1 Evidence of Efficacy of Venous Thromboembolism Prophylaxis in Hospitalized Obese Patients—Cont'd

CI, confidence interval; DVT, deep venous thrombosis; IU, International Unit; PE, pulmonary embolism; RR, relative risk; SCD, ; UH, unfractionated heparin; VTE, venous thromboembolism.

of these drugs may warrant adjusting the dose in proportion to the excess in body weight with the use of a dosing weight correction factor (DWCF).

In the case of the least lipid-soluble drugs (atracurium, H<sub>2</sub>-blockers) and of specific lipophilic drugs (methylprednisolone), distribution is restricted to lean mass, and loading is usually based on IBW.

The influence of pathophysiologic and histologic changes associated with obesity on hepatic and renal metabolism has yet to be fully elucidated. Previous evidence has suggested that hepatic oxidative metabolism in obese patients is not different from lean individuals, but more recent investigations point to an increased activity of cytochrome P-450 enzymes. Kotlyar and Carson<sup>39</sup> have provided strong evidence that obesity significantly increases hepatic CYP2E1 activity while decreasing hepatic CYP3A4 activity. On the same note, the use of the creatinine clearance equations to assess renal function in morbidly obese patients can be misleading. In a study involving 12 men and 31 women who weighed more than 195% of their IBW, creatinine clearance was overestimated by 51 to 61 mL/1.73 m<sup>2</sup> per minute when using TBW and underestimated by 36 to 40 mL/1.73 m<sup>2</sup> per minute when using IBW.<sup>40</sup> Salazar and Corcoran<sup>41</sup> proposed alternative formulas based on animal models for creatinine clearance in obese subjects. These equations, however, have not been validated in critically ill morbidly obese patients. A recent formula derived from the Modification of Diet in Renal Disease (MDRD) study group<sup>42</sup> has the advantage of predicting glomerular filtration rate (GFR) rather than creatinine clearance:

$$GFR = 170 \times (SCr)^{-0.999} \times (age in years)^{-0.176} \times 0.762 \text{ (if female)} \times 1.18 \text{ (if black)} \times (BUN)^{-0.17} \times (albumin)^{+0.318}$$

where SCr is the serum creatinine level and BUN is the blood urea nitrogen level. Data obtained in an ICU from a morbidly obese patient using iodine-51 Cr-ethylenediamine tetra-acetic acid clearance as the gold standard suggest close estimation of the MDRD formula to the actual GFR.<sup>43</sup>

#### **Sedatives and Analgesics**

There are no established guidelines for the appropriate choice for sedation in critically ill morbidly obese patients. Midazolam, lorazepam, and propofol are currently the three sedatives most commonly administered in the ICU. Propofol is a hypnotic agent with a rapid onset and offset. Both volume of distribution and clearance are increased in obese patients and correlate with ABW. Because propofol is emulsified in a soybean base, it may increase  $CO_2$  production.

The lipophilic benzodiazepines demonstrate increased volume of distribution and increased elimination half-life in obese patients. Midazolam has the shortest half-life among benzodiazepines, but its sedative effect might be prolonged in morbidly obese patients because of its accumulation in the adipose tissue.<sup>44</sup> When combined with propofol or fentanyl, its clearance might decrease because of competitive inhibition of CYP3A4.45 The combination of haloperidol and midazolam can decrease the dose required to produce sedation and minimize the risk for respiratory depression. Dose calculations for continuous benzodiazepine infusion in obese patients should follow IBW because clearance is not significantly different from that in nonobese patients. Nonetheless, daily discontinuation with retitration to a target sedation end point is advocated to reduce the duration of mechanical ventilation and ICU length of stay.<sup>46</sup>

The synthetic opioids (remifentanil, fentanyl, and alfentanil) are lipophilic compounds with a rapid onset of action and minimal histamine-related vasodilation. Their ability to blunt cardiovascular responses to endotracheal intubation are comparable in morbidly obese and nonobese patients. Fentanyl is significantly less expensive than the other synthetic opioids and is the preferred Table 88-2 Proposed Dosing of Commonly Used Drugs in Obese Patients

Drug	Initial	Maintenance
Lidocaine	TBW	IBW
Digoxin	IBW	IBW
β-Blockers	IBW	IBW
Aminoglycosides	AW	AW
Vancomycin	AW	AW
Atracurium	TBW	TBW
Vecuronium	IBW	IBW
Fentanyl	$52/(1 + [196.4 \times$	$e^{-0.025 TBW} - 53.66]/100)$
Phenytoin	TBW	IBW
Corticosteroids	IBW	IBW
Cyclosporine	IBW	IBW
Aminophylline	IBW	IBW
Heparin*	ABW	
Enoxaparin*	TBW	TBW
Drotrecogin alfa	ABW	ABW

\*Dosing for treatment of venous thromboembolism.

ABW, adjusted body weight; IBW, ideal body weight; TBW, total body weight. Male: IBW = 50 kg + 2.3 kg per inch of height > 5 ftFemale: IBW = 45.5 kg + 2.3 kg per inch of height > 5 ft

AW = IBW + 0.4 (TBW - IBW)

analgesic agent for critically ill patients with hemodynamic instability or morphine allergy. Bently and colleagues<sup>47</sup> found similar fentanyl pharmacokinetics in obese and nonobese patients, suggesting dosing based on IBW. A more recent investigation observed that the relationship between TBW and fentanyl doses required to achieve and to maintain postoperative analgesic end points had a nonlinear profile<sup>48</sup> (Table 88-2). In contrast, pharmacokinetic data suggest that remifentanil dosing should be based on IBW.<sup>49</sup> An unblinded prospective study involving 10 obese patients undergoing gastric bypass surgery found a tenfold variation in morphine dosing that was unrelated to age, gender, or body surface area.<sup>50</sup> Similar variability was noted in another trial of 55 obese patients undergoing jejunoileal bypass.<sup>51</sup>

#### Neuromuscular Blockade

Atracurium and vecuronium both have limited volumes of distribution. However, although vecuronium, rocuronium, and cisatracurium dosing is based on IBW, the hyposensitivity to atracurium observed in obese individuals necessitates calculation of the dose based on TBW. There are no studies demonstrating a reduction in neuromuscular complications when intermittent dosing techniques are used instead of continuous infusions. Periodic monitoring with the train of four should be conducted routinely to adjust the rate of infusion. The increased adiposity around the wrist may require higher milliamperage to produce the desired result.

#### Anticoagulants

Morbid obesity had little to no effect on the weight-based heparin dosing protocols that use TBW for systemic anticoagulation. Data evaluating the safety and efficacy of weight-based dosing of low-molecular-weight heparin (LMWH) for the treatment of venous thromboembolism in critically ill morbid obese patients are limited. Pharmacokinetic studies suggest that body mass does not have a significant effect on the response to LMWH in obese patients with normal renal function.<sup>52–54</sup> Nonetheless, monitoring of antifactor Xa activity should be considered. Although the timing of blood sampling in relation to dose and the optimal range of values have yet to be clearly defined, a peak anti-factor Xa level drawn 4 hours after a dosing is considered the most useful. For twice-daily administration, a target of anti-factor Xa level of 0.6 to 1.0 IU/mL has been recommended. The range at 4 hours for those treated with once-daily dose is less certain, but a level of 1.0 to 2.0 IU/mL is suggested.<sup>52</sup>

For severe sepsis, the PROWESS trial excluded patients weighing above 135 kg.<sup>56</sup> In a pharmacokinetic-pharmacodynamic analysis, Macias and associates<sup>57</sup> found that larger patients have a higher mean plasma clearance of drotrecogin than normal patients. This led them to advocate for a dosing strategy based on ABW. These findings were substantiated in a later open-label, phase IV trial of drotrecogin alfa in patients weighing more than 135 kg.<sup>58</sup> However, there have been no data to support the safety of such recommendations at this time.

#### NUTRITIONAL CARE

There is a paucity of data to argue for any specific feeding strategy in critically ill morbidly obese patients. Generally, the energy expenditure of morbidly obese patients is increased owing to an increase in lean body mass. Inadequate nutritional intake, combined with elevated basal insulin concentrations, suppresses lipid mobilization from body store. This causes accelerated proteolysis that in turn forces rapid loss of muscle mass and early deconditioning. Conversely, aggressively high caloric formulas have been associated with increased carbon dioxide production that increases the work of breathing and may prolong the need for mechanical ventilation. Hence, the need to accurately determine energy requirements in this patient population cannot be overemphasized. Several predictive equations have been developed to estimate energy requirements, but adapting these formulas for obese patients is problematic. Estimates of energy expenditure in the critically ill traditionally have been derived from the Harris-Benedict equation, but several studies have demonstrated inaccuracies regarding the use of ideal or actual body weight.<sup>59</sup> In the morbidly obese, indirect calorimetry is considered the method of choice to determine energy expenditure if the inspired oxygen is less than 60%.

To date, five studies evaluated the use of hypocaloric nutrition support in critically ill obese patients (Table 88-3).<sup>60–64</sup> Overall, these studies showed a preserved nitrogen balance and decreased morbidity, but they were limited by the small number of patients and lack of mortality benefit. Further, the hypocaloric high protein diet has not

Study	Study Design	Intervention	Outcome			
Burge et al, 1994 <sup>60</sup>	Prospective double-blind randomized trial	16 obese hospitalized patients requiring TPN randomized to either HC or C formulas	Hypocaloric TPN beneficial in reducing the stimulus for insulin secretion and the hepatic complications of parenteral nutrition.			
Choban et al, 1997 <sup>61</sup>	Prospective double-blind randomized trial	30 obese hospitalized patients randomly assigned to parental hypocaloric or control formulas	Weight change did not differ significantly and nitrogen balance comparable between groups.			
Dickerson et al, 1986 <sup>62</sup>	Prospective nonrandomized study	13 obese patients requiring TPN received hypocaloric, high- protein feeding	Nitrogen balance achieved in 8 subjects. All patients exhibited complete tissue healing of wounds and closure of fistulas.			
Dickerson et al, 2002 <sup>63</sup>	Prospective nonrandomized study	40 critically ill obese patients stratified according to a eucaloric or hypocaloric enteral regimen	The hypocaloric group had a shorter stay in the intensive care unit and decreased duration of antibiotic therapy.			
Liu et al, 2000 <sup>64</sup>	Retrospective study	30 obese patients requiring parenteral nutrition support	5 patients $\geq$ 60 years old but only one < 60 years old had negative nitrogen balance.			

Table 88-3 Hypocaloric Nutritional Support in Obese Patients

TPN, total parenteral nutrition.

been evaluated in patients with renal or liver disease, so the use of hypocaloric nutrition support in obese patients with these conditions is not advocated at present.

### OUTCOMES IN CRITICALLY ILL OBESE PATIENTS

Since 2001, there have been numerous reports trying to describe the relationship between BMI and critical care outcome (Table 88-4). The first study to evaluate

nonsurgical morbidly obese patients (BMI >  $40 \text{ kg/m}^2$ ) in the critical care setting reported a higher mean length of stay in the ICU and a longer duration of mechanical ventilation compared with nonobese patients (BMI <  $30 \text{ kg/m}^2$ ).<sup>65</sup> There also was a 13% absolute difference in in-hospital mortality between the obese and nonobese patients. The study was criticized for the heterogeneity of the study population in terms of requirement for mechanical ventilation and the burden of comorbidities between the obese and the nonobese group. An interesting question that the data raised is whether assessment of

Table 88-4 Outcome Studies of Critically III Morbidly Obese Patients					
Study	Study Design	Study Population	No. of Obese Patients/ Total Patients (%)	Relative Risk for Mortality (95% Confidence Interval)	
El Solh et al, 2001 <sup>65</sup>	Retrospective	MICU	117/249 (47)	1.79 (1.12-2.88)	
Bochicchio et al, 2006	Prospective	Trauma ICU	62/1167 (5)	1.40 (0.84-2.31)	
Nasraway et al, 2006 <sup>73</sup>	Retrospective	SICU	366/1373 (27)	0.77 (0.47-1.29)	
Brown et al, 2005 <sup>76</sup>	Retrospective	Trauma ICU	283/1153 (25)	1.29 (0.99-1.68)	
Bercault et al, 2004 <sup>66</sup>	Prospective	MICU/SICU	170/340 (50)	1.86 (1.25-2.77)	
Neville et al, 2004 <sup>77</sup>	Retrospective	Trauma ICU	63/242 (26)	1.96 (1.20-3.21)	
Aldawood et al, 2006 <sup>82</sup>	Prospective	Mixed ICU	540/1835 (29)	0.93 (0.74-1.17)	
Peake et al, 2006 <sup>83</sup>	Prospective	MICU/SICU	129/433 (30)	1.02 (0.63-1.66)	
Alban et al, 2006 <sup>84</sup>	Retrospective	Trauma ICU	135/918 (15)	0.74 (0.36-1.50)	
O'Brien et al, 2006 <sup>71</sup>	Retrospective	Mixed ICU	457/1488 (31)	0.71 (0.59-0.86)	
Garrouste-Orgeas et al, 2004 <sup>85</sup>	Prospective	Mixed ICU	227/1698 (13)	0.81 (0.61-1.09)	
Ray et al, 2005 <sup>68</sup>	Prospective	MICU	550/2148 (26)	0.66 (0.47-0.94)	
Morris et al, 2007 <sup>72</sup>	Prospective	MICU	237/825 (29)	0.77 (0.62-0.96)	
Marik et al, 2003 <sup>86</sup>	Retrospective	Mixed ICU	12,011/48,176 (25)	0.88 (0.82-0.93)	

ICU, intensive care unit; MICU, medical intensive care unit; SICU, surgical intensive care unit.
severity of illness by Acute Physiology and Health Evaluation (APACHE) II score might be inadequate for prediction of hospital mortality in obese patients.

These findings were duplicated by Bercault and associates<sup>66</sup> in a more robust matching design that demonstrated a higher mortality for morbidly obese patients  $(BMI > 30 \text{ kg/m}^2)$  compared with controls (odds ratio, 2.1). The increased mortality was attributed to more frequent ICU-acquired complications. An interesting finding in this study was that obesity had no effect on mortality in the less severely obese patients. Predicted Simplified Acute Physiology Score (SAPS) II mortality was less than 10% in this group, compared with greater than 50% in the more severely obese patients. Moreover, in an analysis stratified by age, obesity-related excess mortality was observed among the youngest obese patients, whereas the death rate among the older group (>65 years) was increased only for patients with a BMI of more than  $35 \text{ kg/m}^2$ . In a parallel study, Goulenok and colleagues<sup>67</sup> noted that a BMI of more than  $27 \text{ kg/m}^2$  was predictive of increased mortality and longer ICU stay, although the observed difference in frequency of nosocomial infection and duration of mechanical ventilation was not different between the obese and the nonobese patients.

These dire prognostications for critically obese patients have been challenged recently by parallel investigations. Using five BMI categories, Ray and colleagues<sup>68</sup> reported no differences in APACHE II score, mortality, ICU length of stay, ventilator days, or average total cost among the five groups. Other authors have demonstrated that the relation between BMI and mortality appears to reflect a U-shaped curve, with underweight and severely obese patients having significantly higher adjusted mortality across all age groups, whereas moderately overweight and less severely obese patients had a comparatively improved mortality.<sup>69</sup> A further understanding of the role of morbid obesity on critical outcomes was derived from the National Heart, Lung, and Blood Institute's multicenter randomized trials of the Acute Respiratory Distress Syndrome Network. This attempted to address the effect of obesity on the course of ventilated patients with acute lung injury (ALI). The secondary analysis of pooled data from three studies revealed that the unadjusted outcomes across BMI groups did not differ significantly for any of the dependent variables (28-day mortality rate, achievement of unassisted ventilation, 180-day mortality rate, or ventilator-free days).<sup>70</sup> The authors acknowledged that improved outcomes in the study population could have been the result of increased intensity of care and standardized weaning procedures. In addition, although the data did not reach statistical significance, a trend toward worse 28-day survival with increasing BMI was observed.

In a subsequent study including a larger cohort of participants, O'Brien and coworkers<sup>71</sup> found that BMI was independently associated with mortality in ventilated patients with ALI. Patients with the lowest BMIs had the highest mortality rate in the cohort, whereas the lowest odds of hospital mortality were found in those with higher BMIs. Notwithstanding, severe obesity has been associated consistently with increased use of hospital resources and higher hospitalization costs.<sup>72</sup>

Against this improved outlook of obesity outcome in predominantly medical ICUs, morbidly obese patients requiring admission to surgical or trauma units had more adverse events than their nonobese counterparts. Morbid obesity was reported to be an independent risk factor for death in surgical patients who required 4 days or more in the ICU. This indicates that complications of health care processes may be the key to improved outcomes in this cohort. The increased mortality was attributed to organ failures, need for more vasopressors, and failed extubation.<sup>73</sup> These complications were not higher in obese cardiac patients who required bypass graft surgery than they were in similar nonobese patients, although the risks for sternal wound infection were substantially increased in obese and severely obese patients.

In trauma patients, obesity appears to be associated with poorer outcomes.<sup>76–78</sup> In blunt trauma, obese patients sustain different types of injuries than lean patients, with a higher frequency of thoracoabdominal wounds and less traumatic brain injuries. Moreover, obese trauma patients had more than twofold increases in the risk for acquiring a blood-stream, urinary tract, or respiratory tract infection (including sepsis, ventilator-associated pneumonia, and catheter-associated bacteremia) after hospital admission.<sup>79,80</sup>

The impact of obesity on mortality has been summarized recently in a meta-analysis encompassing 14 studies and 15,347 critically ill obese patients.<sup>81</sup> The study revealed that obesity per se was not associated with an increased risk for ICU mortality. However, duration of mechanical ventilation and ICU length of stay were significantly longer in the obese group (by 1.48 days and 1.08 days, respectively) compared with the nonobese group. In a subgroup analysis, improved survival was observed in obese patients with a BMI ranging between 30 and 39.9 kg/m<sup>2</sup> compared with nonobese patients (relative risk, 0.86; 95% CI, 0.81 to 0.91).

### AUTHOR'S RECOMMENDATIONS

- The critical care aspects of the morbidly obese are multifaceted and require a true multidisciplinary approach for optimal outcomes.
- Life-threatening cases in morbidly obese airway management result not from failure of intubation but from failure of ventilation.
- The respiratory system is by far the most affected by the excess weight. Reduction in FRC and ERV predispose these patients to ventilation-perfusion mismatching leading to arterial hypoxemia, most notably in the supine position.
- Mechanical ventilation should be initiated with a tidal volume calculated according to the IBW to avoid alveolar overdistention and barotrauma. The addition of PEEP is highly recommended to facilitate alveolar recruitment and prevent atelectasis.
- Application of noninvasive ventilation immediately after extubation might reduce the rate of respiratory failure and decrease mortality in hypercarbic patients
- The most appropriate dosing regimens in critically ill morbidly obese patients are extrapolated from the limited number of pharmacokinetic and pharmacodynamic investigations conducted in patients with varying degrees of obesity.

- In assessing metabolic demand, indirect calorimetry is considered the method of choice to determine energy expenditure. Recommended nutritional support ranges from 3 to 36 kcal/kg and from 0.83 to 2.2 g/kg of protein per IBW per day. Calories should be supplied primarily as carbohydrates, with fats given to prevent essential fatty acid deficiency.
- Overall, the effect of morbid obesity on critical care outcome remains controversial, with the worst outcomes reported in obese trauma patients.

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# 9 How Do I Transport the Critically III Patient?

### John Chandler, John Bates

The provision of intensive care during transport to and from the intensive care unit (ICU) presents a major challenge. Available data<sup>1</sup> suggest that critical care transport is becoming increasingly common, driven by the centralization of specialties and an expanding number of diagnostic and therapeutic options outside of the ICU. The bulk of critical care transports happens within the hospital itself. Observational data<sup>1–3</sup> suggest that critical care transport is a high-risk but worthwhile activity and that this risk can be minimized by adequate planning, proper equipment, and appropriate staffing. Prehospital transport of the critically ill patient presents more problems because prior planning is more difficult.

Clinical data on transport of the critically ill patient are derived mainly from cohort trials (the area of prehospital fluid administration being the exception) and can provide guidelines in terms of personnel (physicians, nurses, and paramedics), mode of transport (air or road), and specific treatments (prehospital tracheal intubation and advanced lift support).

# INTRAHOSPITAL TRANSPORT OF THE CRITICALLY ILL

### **Adverse Effects**

Several observational studies suggest that significant physiologic disturbances (large variations in heart rate, blood pressure, or oxygen saturation) occur during 53% to 68% of intrahospital transports.<sup>4–6</sup> Physiologic variability is also common in stationary critically ill patients, occurring in 60% of such patients in a study by Hurst and colleagues, compared with 66% in transported patients.<sup>5</sup>

Many of these physiologic changes can be safely managed by an appropriately trained transport team, but serious adverse events do occur. Damm and colleagues<sup>7</sup> found a cardiac arrest rate of 1.6% in a prospective observational study of 123 intrahospital transports. Waydhas and associates<sup>8</sup> found that a reduction in the Pao<sub>2</sub>/Fio<sub>2</sub> ratio occurred in 83.7% of patients when transported using a transport ventilator and that this was severe (>20% reduction from baseline) in 42.8%. Furthermore, the changes persisted for more than 24 hours in 20.4% of transports. Two large cohort studies using logistic regression analysis<sup>9,10</sup> found out-of-unit transport to be an independent risk factor for ventilator-associated pneumonia (odds ratios,  $3.1^9$  and  $3.8^{10}$  in ICU patients. Intrahospital transport is also one of the factors associated with unplanned extubation.<sup>11</sup>

When compared with Acute Physiology and Chronic Health (APACHE) II and III matched controls, patients requiring intrahospital transport were found to have a higher mortality rate (28.6% versus 11.4%) and a longer ICU length of stay.<sup>12</sup> None of the excess mortality was directly attributable to complications of the transport, and the authors concluded that the findings reflected a higher severity of illness in patients who required transportation. Serious adverse events did, however, occur in 5.9% of transports.

### Predicting Adverse Events during Intrahospital Transport

Factors associated with an increased risk for adverse events during transport include pretransport secondary insults in head-injured patients, high injury severity score,<sup>13</sup> and high Therapeutic Interventions Severity Score (TISS) but not APACHE II score.<sup>14</sup> Age over 43 years and FIO<sub>2</sub> higher than 0.5 are predictive of respiratory deterioration on transport.<sup>15</sup>

The number of intravenous pumps and infusions, as well as the time spent outside the unit, has been shown to correlate with the number of technical mishaps.<sup>16</sup> The Australian ICU Incident Monitoring Study<sup>17</sup> found that 39% of transport problems were equipment related, with 61% relating to patient or staff management issues. Factors limiting harm were rechecking of the patient and equipment, skilled assistance, and prior experience.

Hemodynamic variability is more frequent in patients being transferred to the ICU from the operating room than those transported for diagnostic procedures outside the ICU. This is probably related to emergence from anaesthesia.<sup>18</sup>

### Risk-to-Benefit Ratio of Intrahospital Transport

Observational studies suggest that the therapeutic yield for intrahospital transport is high. Hurst and colleagues found that the results of diagnostic testing facilitated by the transport resulted in a change in treatment in 39% of patients.<sup>5</sup> Out-of-unit radiologic studies in ICU patients tend to be high yield. For instance, computed tomography scanning of the thorax has been shown in observational studies to change the clinical course in 26% to 57% of cases.<sup>19,20</sup>

### Management of Transport

Although a cohort study has found that transport ventilators reduce variability in blood gas parameters when compared with manual bagging,<sup>21</sup> Gervais and associates<sup>22</sup> found that manual bagging with a tidal volume monitor was in fact superior to mechanical ventilation in terms of blood gas variability. In addition, an observational study<sup>23</sup> found no significant variation in blood gas parameters in 20 patients transported using manual ventilation by a respiratory therapist. A similar pediatric study<sup>24</sup> came to the same conclusions. Changes in blood gas parameters have been shown to correlate with hemodynamic disturbances (arrhythmias, hypotension).<sup>21</sup>

Capnometry (Etco<sub>2</sub>) monitoring reduces Paco<sub>2</sub> variability in adults.<sup>25</sup> In children, manual ventilation without Etco<sub>2</sub> monitoring resulted in only 31% of readings falling within the intended range.<sup>26</sup>

A single randomized controlled trial (RCT) found that hypothermia was common in trauma patients undergoing intrahospital transport (average temperature on return to the unit was  $34.7^{\circ}$ C) and that this was prevented by active warming during transport.<sup>27</sup>

Who should accompany the critically ill patient during transport? Stearley and colleagues reported that transport of patients by a specially trained transport team was associated with a rate of complications (15.5%) that was much lower than historical controls.<sup>28</sup> Interestingly, physician attendance was not clearly correlated with a reduced risk for mishap in an observational study of 125 transports.<sup>14</sup>

### INTERHOSPITAL TRANSFER

The number of interhospital transfers of critically ill patients is increasing dramatically<sup>1</sup> due to a reduction in the numbers of hospitals, centralization of specialist services, and reconfiguration of health care services between acute and elective medicine.<sup>3</sup> The benefits of transport to the patient need to be weighed against the not inconsiderable risks of the transport process.<sup>2,15,29–32</sup> There are few RCTs on this subject and conclusions have to be drawn from nonrandomized, cohort, or uncontrolled studies.

### Adverse Effects

A variety of published audits and descriptive studies have shown that the interhospital transport of critically ill patients is associated with an increased morbidity and mortality during and after the journey.<sup>2,15,29–33</sup> Even with specialist mobile intensive care teams, mortality before and during transport is substantial (2.5%) despite a low incidence of preventable deaths during transport (0.02% to 0.04%).<sup>33</sup> Other authors have reported a higher intertransport mortality rate and have found that 24% to 70% of incidents are avoidable.<sup>29,32</sup> Physiologic derangements occur during 25% to 34% of adult<sup>15,32</sup> and 10% to 20% of neonatal and pediatric transports.<sup>30,31</sup> In adults, the nature of these disturbances is most often respiratory or cardiovascular, the most common being arterial desaturation and reduced Pao<sub>2</sub>/ FiO<sub>2</sub> ratio (hypoxemia),<sup>15</sup> arterial hypotension and tachy-cardia,<sup>32</sup> respectively. The most common complications observed during pediatric and neonatal transportation are hypothermia, respiratory complications, and loss of intravenous access.<sup>30,31</sup>

# Does Interhospital Transport Contribute to Mortality?

The long-term outlook for critically ill patients that require interhospital transport is worse than for those who do not require transport. Transported patients have higher ICU mortality and longer ICU stays than controls.<sup>34,35</sup> Durairaj and colleagues compared 3347 patients who required transfer with patients directly admitted to an ICU. They found a 4% increase in mortality in the transferred group despite adjustment for diagnosis.<sup>35</sup> It is unclear whether this resulted from loss of "the golden hour" or whether there was a series of confounders resulting in increased mortality as a result of increased severity of illness.

### **Prediction of Adverse Events**

Prediction of deterioration during interhospital transport has proved difficult. The APACHE II, TISS, and Rapid Acute Physiology Score (RAPS) scoring systems do not correlate with events in adults,<sup>14,15,36</sup> and the Pediatric Risk of Mortality Score (PRISM) score has proved similarly unreliable in children.<sup>37</sup> Variables predicting deterioration in adults include older age, high FIO<sub>2</sub>, multiple injury, and inadequate stabilization.<sup>15,38</sup>

### Planning of the Transport

The importance of planning and preparing for interhospital transport cannot be overstated because poor planning has been shown to lead to an increased incidence of adverse events and mortality.<sup>38,39</sup> In an audit of transfers to a neurosurgical center, 43% were found to have inadequate injury assessment, and 24% received inadequate resuscitation. Deficiencies in assessment and resuscitation before transfer were identified in all patients who died.<sup>38</sup> Guidelines have been developed to address this issue in many jurisdictions, but inadequate assessment and resuscitation remain a problem. Price and colleagues found that the development of national guidelines led to only modest improvements in patient care, with an incidence of hypoxia and hypotension that remains unacceptably high.<sup>40</sup>

### Selection of Personnel

It is recommended that a minimum of two people in addition to the vehicle operators accompany a critically ill patient during transport.<sup>39</sup> The team leader can be a nurse or physician depending on clinical and local circumstances. It is imperative that the team leader has adequate training in transport medicine and advanced life support. Adequately trained nurses have been shown to be as safe at transporting

critically ill children as doctors.<sup>41,42</sup> Appropriately staffed and equipped specialist retrieval teams have been shown to be superior to occasional teams at transferring critically ill adults<sup>43</sup> and children.<sup>44</sup> Vos and colleagues,<sup>44</sup> in an observational study, demonstrated an 80% reduction in critical incidents during pediatric interhospital transport undertaken by a specialist retrieval team.

### Mode of Transport

The choice between the three options of road, helicopter, and fixed wing transport are affected by three main factors: distance, patient status, and weather conditions. A retrospective review of 1234 adult transfers demonstrated no difference in mortality or morbidity between patients transferred by air versus road.<sup>45</sup> A prospective cohort study revealed that air transport is faster than ground transport, and for transfers of less than 225 km, helicopter transport is faster than fixed wing.<sup>46</sup> Moylan and colleagues found that severely injured patients undergoing interhospital transport had reduced mortality when carried by air compared with surface transport.<sup>47</sup>

### **Equipment and Monitoring**

Comprehensive lists of equipment and medications needed for transport of critically ill patients are available elsewhere and are beyond the scope of this chapter.<sup>39,48</sup> Transport ventilators have been shown in intrahospital transfers to provide less ventilatory fluctuations than hand ventilation.<sup>24</sup> A bench trial of transport ventilators, however, revealed that they were inferior in delivering set tidal volume, in triggering, and in the tendency to trap gas, compared with ICU ventilators.<sup>49</sup> This suggests that extra care in the monitoring of ventilation is warranted when changing from an ICU to a transport ventilator. Uncontrolled observational studies have shown that point-of-care blood gas analysis during interhospital

transfer allows early identification and treatment of changes in gas exchange and metabolic parameters.<sup>50,51</sup>

### PREHOSPITAL TRANSPORT

Most research in the area of prehospital transport has focused on trauma patients because of the potential for early appropriate intervention to improve outcome.

### **RETRIEVAL SYSTEMS**

There are four main infrastructural factors, which have been addressed in clinical studies:

- 1. Mode of transport
- 2. Prehospital personnel
- 3. Prehospital time
- 4. Receiving care facility

### Mode of Transport

The comparison between road and helicopter transport has been the focus of a great deal of research.<sup>52</sup> Three large retrospective analyses have looked at the effect of helicopter versus road transport on mortality in adult<sup>53,54</sup> and pediatric<sup>55</sup> trauma patients. Kerr<sup>54</sup> found that severely injured adults (ISS > 31) had a lower mortality when transported by air; a similar reduction in mortality was demonstrated in a pediatric population.<sup>55</sup> Brathwaite,<sup>53</sup> however, found no difference in mortality between modes.

### **Prehospital Personnel**

Five studies<sup>56–60</sup> have addressed the issue of physicianversus emergency medical technician (EMT)-delivered prehospital care for trauma patients. Of these, one RCT and three of four retrospective analyses found a reduction in mortality in the physician-delivered group (Table 89-1). The evidence also indicates that physicians tend to treat patients more aggressively than EMTs.

Study	No. of Subjects	Study Design	Outcome
Baxt & Moody, 1987 <sup>56</sup>	Blunt trauma EDC: 316, PDC: 258	Prospective randomized	Mortality reduced in PDC (35% less)
Garner et al, 1999 <sup>57</sup>	Blunt trauma EDC: 140, PDC: 140	Retrospective observational single-center	Lower mortality in the PDC group (13 fewer deaths per 100 patients) after adjustment for severity of injury More procedures performed in PDC group
Iirola et al, 2006 <sup>58</sup>	Blunt trauma EDC: 77, PDC: 81	Retrospective multicenter, historical controls	No mortality difference More procedures performed in PDC group
Osterwalder, 2003 <sup>59</sup>	Blunt trauma EDC: 71, PDC: 196	Prospective single center, observational cohort	OR of death using logistic regression analysis: 37 (CI, 2-749) in EDC group compared with PDC group
Roudsari et al, 2007 <sup>60</sup>	Trauma patients, EDC: about 5000, PDC: about 4000	Retrospective observational multicenter comparison	Reduced early mortality (OR, 0.70; 95% CI, 0.54-0.91)

### Table 89-1 Effect of Inclusion of a Physician on Outcomes from Prehospital Care

CI, confidence interval; OR, odds ratio; PDC, physician-delivered care, EDC, emergency medical technician-delivered care.

### **Prehospital Time**

Severely injured patients have been shown in cohort trials to suffer increased mortality,<sup>61</sup> length of stay, and complications,<sup>62</sup> with prehospital times of more than 60 minutes.

### **Receiving Care Facility**

Several large cohort studies have found a reduction in mortality for severely injured trauma patients when they are transferred directly to a level I trauma center.<sup>63–65</sup> The largest of these included more than 6000 patients from 15 regions in the United States. Patients treated primarily in level I trauma centers had lower in-hospital (odds ratio [OR], 0.8; 95% confidence interval [CI], 0.66 to 0.98), and 1-year mortality (OR, 0.75; 95% CI, 0.60 to 0.95) rates. Subgroup analysis suggested that the mortality benefit was primarily confined to more severely injured patients.<sup>66</sup>

### **AUTHORS' RECOMMENDATIONS**

- Transport of the critically ill patient has become a necessary and important part of clinical practice. It is often overlooked.
- Three types of critical care transport mechanisms exist: prehospital transport of injured patients, interhospital transport of patients requiring an escalating level of care, and intrahospital transport of patients requiring investigational or therapeutic procedures.
- Although physiologic derangements are common during transport, current data suggest that they are not more common than in the stationary ICU patient.
- The risk to the patient of the transport itself can be reduced by appropriate planning and training of personnel and attention to pretransport stabilization of the patient.
- Interhospital transport of critically ill patients is best undertaken by experienced specialist transport teams.
- The prehospital interventions that are associated with improved outcome in observational studies are as follows: (1) helicopter transport of severely injured patients; (2) presence of a physician on the prehospital transport team; (3) injury to hospital times of less than 60 minutes; and (4) transfer directly to a level I trauma center.

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# How Are Patients Who Are Admitted to the Intensive Care Unit after Common Poisonings Diagnosed and Managed?

Alan Weier, Kurt Kleinschmidt

The critically ill poisoned patient poses significant diagnostic and management challenges to an ICU staff. First, there are many harmful agents physicians must consider as potential causes of the patient's illness. Second, the patient's history is often unavailable, and providers must rely on physical examination, toxidromes, and laboratory data to guide diagnosis and management. Finally, management strategies are often controversial.

In this chapter, we review diagnostic strategies using toxidromes and the laboratory, discuss acetaminophen and salicylate toxicity in moderate detail, present the evidence regarding decontamination strategies, clarify the appropriate use of *N*-acetylcysteine (NAC) as an antidote for acetaminophen overdose, and provide national practice guidelines.

### DIAGNOSIS

### Toxidromes

Toxidromes are combinations of specific signs and symptoms that reflect drug class effects on particular neuroreceptors (Table 90-1). Management strategies are often determined by the toxidrome without concern for the specific agent that caused the signs and symptoms. The anticholinergic toxidrome is reflected by tachycardia, warm and dry skin, hypoactive bowel sounds, mydriasis, and urinary retention. A delirium occurs in more severe cases. This toxidrome is noted after overdosing on antihistamines, tricyclic antidepressants, and many antipsychotics. The sympathomimetic toxidrome also involves tachycardia and mydriasis and may include delirium, but the skin is diaphoretic. The cholinergic toxidrome includes diaphoresis, salivation, lacrimation, urination, defecation, miosis, and bradycardia. A severe exposure is lethal by bronchospasm and bronchorrhea. The opioid toxidrome consists of pinpoint pupils, respiratory depression, and unresponsiveness. Sedative-hypnotics are similar to opioids but without the pupillary changes. Unfortunately, toxidromes are imperfect because symptoms from multiple coingestants can overlap, clouding the clinical picture.

### Laboratory

Most laboratories provide urine screens for the most common drugs of abuse, but these have not been shown to alter patient management or outcomes.<sup>1</sup> Although interpretation of the results varies with the particular screen used by an institution, some general points can be made. A "positive" screen does not reflect current intoxication; clinical symptoms are generally gone long before the screen becomes "negative." Cannabinoids remain positive for weeks or months after exposure. Benzodiazepines yield false-negative results because of the complexity of their metabolism. Amphetamines are often associated with false-positive results because of their structural similarity to many legal medications.

Quantitative serum tests for some drugs are available, but the indications for testing are variable, and there are no consensus guidelines. Quantitative levels that most commonly affect patient care are for acetaminophen, salicylate, lithium, digoxin, methanol, and ethylene glycol. Although phenytoin, valproic acid, and carbamazepine levels are often available, elevated levels only confirm the drug's presence. Levels infrequently affect ongoing care because patients are observed anyway until they recover from these sedating or dizzying agents. Acetaminophen and salicylate levels are discussed later.

### DANGEROUS POISONINGS: TWO IMPORTANT AGENTS

### Salicylates

Salicylate poisoning is very common and sometimes fatal because these drugs are available as stand-alone and combination products for analgesia and fever and in liniments.<sup>2</sup> In 2006, analgesics were the drug class most frequently involved in adult exposures, and aspirin alone accounted for 61 deaths.<sup>3</sup> The salicylate toxidrome includes nausea, vomiting, dyspnea, diaphoresis, dizziness, and hearing changes. Poisoned patients typically suffer from mixed respiratory alkalosis and anion-gap metabolic acidosis.<sup>4,5</sup>

Toxidrome	Vital Signs	Signs
Anticholinergic	HR↑	Bowel sounds ↓ Delirium* Dry mouth Mydriasis or normal Skin dry
Sympathomimetic	$\begin{array}{l} HR\uparrow\\ BP\uparrow\end{array}$	Agitated Delirium* Mydriasis Skin diaphoretic
Opioid	RR↓ and/or shallow	Mental status ↓ Miosis
Sedative-hypnotic	RR↓ and/or shallow*	Mental status $\downarrow$
Cholinergic	HR↓	Bronchoconstriction Bronchorrhea Diaphoresis Lacrimation Miosis Salivation Urination

Table 90-1 Clinical Presentations of Toxidromes

\*If severe.

BP, blood pressure; HR, heart rate; RR, respiratory rate;  $\uparrow$ , increased;  $\downarrow$ , decreased.

Serum salicylate levels are most commonly reported in milligrams per deciliter (mg/dL), although they also are reported in mg/L. This may result in a misinterpretation of a level by a factor of 10. Therapeutic levels range from 15 to 30 mg/dL. Toxicity results from tissue distribution and not from the salicylate in the blood. Thus, serum levels and toxicity do not necessarily correlate. For example, a serum salicylate level could be decreasing because it is either being distributed into tissues (the patient will be sicker) or being eliminated by the kidney.

Management of salicylate toxicity is difficult. Toxicity is resolving if serial salicylate levels are decreasing *and* the patient's symptoms are resolving. If a salicylate-toxic patient is intubated, the patient must be hyperventilated to maintain a compensatory respiratory alkalosis. Intravenous sodium bicarbonate is indicated in patients with clinical symptoms. Urine alkalinization enhances salicylate elimination by "trapping" the salicylate ion in the renal tubules and enhancing it.<sup>6</sup> Hemodialysis is indicated when the salicylate level is 100 mg/dL or greater, the significant metabolic derangements do not rapidly clear with fluids, or there is renal insufficiency.<sup>7</sup>

### Acetaminophen

Acetaminophen (APAP) is a significant problem because it is widely available alone and in combination products. Because APAP toxicity has no early symptoms, a level is obtained in all cases of possible intentional overdoses.

Most APAP is metabolized to inactive, harmless metabolites, but 5% to 10% is oxidized by the P-450 system into the hepatotoxic *N*-acetyl-*p*-benzoquinoneimine (NAPQI).<sup>8</sup> NAPQI is detoxified through conjugation with glutathione. This results in nontoxic species that are eliminated in the urine.<sup>9</sup> After overdoses of APAP, the glutathione supply is rapidly used, resulting in free NAPQI and subsequent hepatotoxicity. Hepatitis occurs after an ingestion of 150 mg/kg.<sup>10</sup> After higher doses, acute liver failure (ALF) may occur within days if no treatment is provided.<sup>11</sup>

The Rumack-Mathew nomogram guides the use of NAC in acute (single exposure) overdoses when the time of ingestion is known.<sup>12</sup> The treatment line is based on a 4-hour half-life starting with a toxic 4-hour serum concentration of 150  $\mu$ g/mL. This screening tool has a sensitivity of almost 100% when strictly applied.<sup>13</sup> Levels before 4 hours after exposure generally do not guide therapy. Unlike salicylates, there is a limited role for repeat APAP levels.

Traditionally, a toxic level is treated with oral NAC for 72 hours.<sup>14</sup> At present, if aspartate aminotransferase (AST) remains normal after 20 to 48 hours from exposure, treatment is often stopped.<sup>14</sup> Acetadote is a pyrogen-free intravenous (IV) form of NAC. If a patient presents within 10 hours of an acute exposure, a bolus followed by a 20-hour IV infusion may be used. Acetadote may be used for patients who present beyond 10 hours after exposure, but the course of therapy will need to be longer than 20 hours—typically 36 to 72 hours. Therapy is extended beyond 72 hours if ALF elevations are present.

For patients with chronic (more than one) exposure, an APAP level is done to confirm the presence of acetaminophen, but the nomogram is not used. These patients are treated with NAC for 36 hours (72 hours if the AST is abnormal).

### MANAGEMENT PRINCIPLES

Basic management of poisoned patients includes airway and hemodynamic management. Comatose patients require assessment for hypoglycemia and treatment with oxygen, naloxone, and thiamine. The competitive benzodiazepine (BZ) antagonist flumazenil is not used in undifferentiated acute overdose patients because its use in BZdependent patients may result in intractable seizures.<sup>15</sup>

Gastrointestinal decontamination strategies used to decrease absorption include gastric emptying (GE) with ipecac or gastric lavage, single-dose activated charcoal (AC), or whole bowel irrigation (WBI). Their use is not supported by data. This merits discussion (see later).

An elimination strategy like multidose activated charcoal (MDAC) may be considered, although there are few data to support its widespread use.<sup>16</sup> Urine alkalinization (UA)<sup>17</sup> and hemodialysis (HD)<sup>18</sup> are also important elimination strategies for consideration for select poisons. However, it is important to note that neither of these strategies has been shown to change clinical outcomes.

Unfortunately, few true antidotes exist. However, the timely use of some is very important. NAC was noted previously. Digoxin-binding antibodies and hydroxocobalamin for cyanide are also very effective. Fomepizole is a competitive inhibitor of alcohol dehydrogenase used for methanol and ethylene glycol toxicity. It prevents the formation of toxic acid metabolites created by the metabolism of the alcohols. Although fomepizole does not help after a toxic alcohol is metabolized, it is still given in the setting of acidosis because more of the parent toxic alcohol may remain.

Sodium bicarbonate is used to treat several dangerous poisons. In addition to its role in correcting severe acidosis from toxic alcohols and cyanide, it is most commonly used to treat toxicity due to salicylates and sodium channel blocking agents such as tricyclic antidepressants. It enhances renal elimination of salicylates. Conversely, its primary purpose in sodium channel toxicity is to provide enough sodium to overcome the blockade; efficacy is reflected by narrowing of the QRS segment.

### THE EVIDENCE

### **Decontamination Strategies**

Many studies address the options for decontamination of poisoned patients but four in particular frame current thinking because they have the best methodology and largest patient numbers (Table 90-2). In 1985, Kulig compared management with GE versus without GE in a randomized, prospective study of 592 drug overdose patients.<sup>19</sup> Patients in the GE arm were treated with syrup of ipecac if they were alert or gastric lavage if they were obtunded. All received AC. Patients were classified as either mildly, moderately, or severely poisoned using predefined criteria and were followed to determine whether improvement or deterioration took place. Admission rates, severity scores, and clinical deterioration were equal between groups. Charcoal administration was delayed a mean of 2.2 hours in patients receiving ipecac. Obtunded patients who were lavaged within 1 hour of ingestion had a better clinical course than those who were not decontaminated. However, this group contained only 19 patients, and the benefit was not statistically significant. A larger study might have demonstrated significance. One lavage patient suffered esophageal perforation, and one ipecac patient developed an aspiration pneumonitis.

The authors concluded that satisfactory clinical outcomes could be achieved without routine GE with ipecac and that this intervention was of no benefit to patients presenting hours after ingestion. Gastric lavage was of questionable value if done more than 1 hour after ingestion, and GE was not required for all overdosed patients.

Albertson and others did a prospective, randomized comparison of AC, 1 g/kg alone, versus AC plus ipecac in 200 adult patients with mild to moderate overdoses.<sup>20</sup> Patients were awake and cooperative, had a stable level of consciousness, were not vomiting, did not receive ipecac before arrival, and did not ingest a substance that was a contraindication for ipecac treatment. There were no significant differences in the hospitalization rates and lengths of stay between groups. Among patients discharged from the emergency department (ED), the ipecac group spent significantly more time in the ED. Four patients in the ipecac group developed aspiration pneumonias, compared with none in the nonipecac group. The authors concluded that in awake, cooperative poisoned patients, AC is as effective as AC plus ipecac.

Merigian and others prospectively determined whether asymptomatic patients would clinically deteriorate if GE was withheld, if AC altered the clinical outcome of asymptomatic poisonings, and if the use of GE altered the clinical course of symptomatic patients.<sup>21</sup> Designation as asymptomatic or symptomatic was based on their mental status, Glasgow Coma Scale, and vital signs. Asymptomatic patients received AC on even days but not on odd days. All symptomatic patients received AC, whereas those on even days also received GE with ipecac or gastric lavage before AC. They were followed for predefined changes in clinical status. Among the 451 asymptomatic patients, the AC and no-AC groups had equal outcomes. Among the 357 symptomatic patients, the GE and no-GE groups had equal hospital admission rates. The GE patients were admitted to the ICU twice as often as the no-GE patients, but the lengths of stay were not different. The intubation rate was nearly 4 times greater in the GE arm. Aspiration pneumonia occurred significantly more often in the GE

Study	No. of Subjects	Study Design	Intervention	Control	Outcomes
Kulig et al, 1985 <sup>19</sup>	592	R, P	GE and AC	AC only	GE group with more complications Obtunded patients lavaged within 1 hr had a nonstatistically significant improved course
Albertson et al, 1989 <sup>20</sup>	200	R, P	Ipecac and AC	AC only	Ipecac group had longer ED stays and four aspirations; otherwise, groups were equal
Merigian et al, 1990 <sup>21</sup>	808: ASX ( <i>n</i> = 451), SX ( <i>n</i> = 357)	R, P	ASX: AC only, SX: GE and AC	ASX: observation, SX: AC only	ASX: ND SX: GE/AC group had more ICU admissions, intubations, and aspirations
Pond et al, 1995 <sup>22</sup>	876	R, P	GE and AC	AC only	ND in course, days hospitalized, or complications

Table 90-2 Summary of Randomized Controlled Trials Looking at Gastrointestinal Decontamination of Poisoned Patients

AC, activated charcoal; ASX, asymptomatic patients; ED, emergency department; GE, gastric emptying (lavage or ipecac); ICU, intensive care unit; ND, no difference; R, randomized; P, prospective; SX, symptomatic patients.

arm (n = 8) than in the no-GE arm (n = 0). The authors concluded that GE was unnecessary for selected asymptomatic patients and had limited benefit in the routine management of symptomatic patients and that the benefit of AC in asymptomatic patients was unproved.

Pond and others modeled the Kulig study, testing whether AC alone is as safe and effective as AC plus GE in acute adult poisonings.<sup>22</sup> This prospective controlled trial randomized 876 patients into GE and no-GE arms based on even or odd day of presentation. The GE patients received ipecac if alert or lavage if obtunded. All patients received AC. Patients were categorized as mildly, moderately, or severely toxic based on predefined criteria, and they were followed for category changes. The AC administration was delayed in the GE group. When adjusted for severity, there was no significant change in clinical course. There was no difference in complications or the number of days hospitalized. The authors concluded that GE can be omitted from the treatment regimen for adults after acute overdose.

WBI uses polyethylene glycol to mechanically flush bowel contents through the gastrointestinal tract. Some volunteer studies have shown that WBI decreases the bioavailability of ingested drugs, but no controlled clinical trials have been performed, and there is no evidence that clinical outcomes of poisoned patients are improved. WBI is contraindicated in patients with bowel obstruction, perforation, ileus, hemodynamic instability, or compromised airways. The simultaneous use of AC and WBI may decrease the effectiveness of the charcoal, but WBI should still be considered for potentially toxic ingestions of sustained-release or enteric-coated drugs, iron, or packets of illicit drugs.<sup>23</sup>

### **Elimination Strategies**

MDAC and urine alkalinization (UA) are commonly used to enhance poison elimination in overdosed patients. MDAC involves repeated oral dosing of AC to maintain a concentration gradient across the gut. It encourages poison migration from the blood into the intestinal lumen ("gut dialysis"). In addition, the persistent presence of AC also disrupts the enterohepatic circulation of agents that undergo biliary elimination. MDAC significantly increases drug elimination in animal and volunteer studies, and there is some evidence confirming enhanced elimination in patients poisoned with life-threatening amounts of certain drugs. However, MDAC has not been shown to affect clinical outcomes.<sup>16</sup> Although MDAC is primarily used to enhance elimination, in salicylate toxicity, it is used to decrease absorption of the erratically absorbed salicylates. However, the data are contradictory and MDAC use remains controversial.<sup>16</sup>

Because some toxins, particularly salicylates, are weak acids, urine alkalinization traps ions in the renal tubules in the presence of relatively alkaline urine. Alkalinization involves infusing NaHCO<sub>3</sub> IV to produce urine with a pH of greater than 7.5. Hypokalemia is the most common complication and may require correction.<sup>17</sup> The pharma-cokinetic benefits have been demonstrated in animal and human volunteer studies. However, there are no studies reflecting improved clinical outcomes.

### GUIDELINES

The American Academy of Clinical Toxicology and the European Association of Poisons Centres and Clinical Toxicologists (AACT/EAPCCT) have published "position papers" on the management of poisoned patients. These papers are based on the best available evidence and function as clinical practice guidelines. The position of these organizations on some decontamination strategies follows.

### Gastric Lavage

"Gastric lavage should not be employed routinely, if ever, in the management of poisoned patients." This stance stems in part from experimental studies showing variable ability to return study marker. Studies reflected complications, including hypoxia, dysrhythmias, laryngospasm, gastrointestinal perforation, and aspiration pneumonia, but no clear benefit to clinical outcomes.<sup>24</sup>

### Syrup of Ipecac

"Syrup of ipecac should not be administered routinely in the management of poisoned patients." There is no evidence from clinical trials that ipecac improves outcomes, and there are insufficient data to support its use soon after poison ingestion. Furthermore, ipecac may delay administration of or reduce the effectiveness of AC, antidotes, or WBI.<sup>25</sup>

### Single-Dose Activated Charcoal

Single-dose AC "should not be administered routinely in the management of poisoned patients." Its administration may be considered if a patient has ingested a potentially toxic amount of a poison that is known to be absorbed by charcoal and presents within 1 hour of ingestion. Volunteer studies reveal the effectiveness decreases with times greater than 1 hour, but the potential for benefit after the first hour cannot be excluded. There is no evidence that AC improves clinical outcome.<sup>26</sup>

### Whole Bowel Irrigation

"Whole bowel irrigation should not be used routinely in the management of the poisoned patient." WBI should be considered for potentially toxic ingestions of sustained-release or enteric-coated drugs, particularly for patients with delayed presentations. It should be considered for ingestions of substantial amounts of iron because the morbidity is high and AC is of no use. WBI for removal of packets of illicit drugs is also a potential indication.<sup>23</sup>

### **Multidose Activated Charcoal**

MDAC "should be considered only if a patient has ingested a life-threatening amount of carbamazepine, dapsone, phenobarbital, quinine or theophylline." Studies have shown enhanced elimination of these drugs, but none has demonstrated clinical benefit. The use of MDAC to decrease absorption in salicylate poisoning is controversial, and data are insufficient to recommend its use in this setting.<sup>16</sup>

### Urine Alkalinization

Volunteer and clinical studies indicate that "urine alkalinization should be considered as first line treatment for patients with moderately severe salicylate poisoning who do not meet the criteria for HD."<sup>17</sup>

### AUTHORS' RECOMMENDATIONS

- Toxicologists are available to assist when you call the national poison center number, 1-800-222-1222.
- The diagnosis of critically ill poisoned patients is facilitated by identification of toxidromes.
- Thoughtful use of urine screens and serum drug levels may be helpful.
- Management is founded on supportive care and timely use of antidotes when appropriate.
- GE with ipecac or gastric lavage has not been shown to benefit patients and may actually cause harm. Thus, it should not be used in the routine management of poisoned patients.
- AC may be considered if the patient presents within 1 hour of ingestion of a the toxin known to be adsorbed by charcoal and if the risks for the poisoning outweigh the risk for AC administration.
- WBI has limited but well-defined roles in specific poisonings, specifically in iron ingestions.
- MDAC should be considered for patients poisoned with lethal amounts of carbamazepine, dapsone, phenobarbital, quinine, or theophylline. The use of MDAC in salicylate poisoning is controversial, but we believe it should be considered in the patients with large salicylate ingestions.
- UA is recommended in salicylate-toxic patients with clinical symptoms.

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# 91 How Does One Care for the Heart-Beating, Brain Dead, Adult Organ Donor Patient?

David J. Powner

It seems intuitive that optimal donor care should yield the best organs and be associated with the best graft and recipient survival. However, this aspect of the transplantation process has not received the intense scientific investigation needed to define *optimal* or to generate an evidence-based foundation on which clinical practice can be based. Recommendations from authoritative groups are shown in Table 91-1,<sup>1–5</sup> but these are derived more from customary critical care, medical transplantation, and surgical practice than from interventional or prospective observational investigations of donor care. Therefore, such guidelines generally emphasize maintaining physiologic and laboratory variables "within normal limits."

Many extended (expanded) acceptance criteria for organs include donor variables beyond the normative ranges yet preserve acceptable results. These broader criteria, however, are often reported in small series of donors or within the experience of a single or a few combined centers. Larger prospective studies have not explored the limits of variability in most physiologic or laboratory parameters that still permit selection of acceptable organs.

The selection and allocation process of donor organs depends on many variables. Some are fixed (e.g., age, cause of brain death, sex, preexisting comorbid conditions, body mass index), whereas others may be amenable to interventions during donor care (e.g., cardiovascular and pulmonary function, fluid and electrolyte treatment, identification and treatment of infection, hormone administration). This discussion emphasizes the latter group of variables and data, if available, that might influence therapy. The Donor Risk Index<sup>6</sup> shows how "fixed" criteria may be inter-related. However, the relationship between fixed criteria and variables that can be manipulated and among variables that can be modified remains largely unknown and unexplored. For example, can a young male donor with traumatic brain injury tolerate more variation in his central venous pressure than an older female donor after subarachnoid hemorrhage, yet still yield good organs? The complex database needed to answer such inquiries remains a challenge for the future.

This chapter, therefore, highlights many issues for which controversy or the absence of evidence-based data fails to provide concrete guidance to the critical care practitioner responsible for these complex patients. Because all donor organs are influenced by the prevailing systemic physiology (e.g., oxygen delivery, blood electrolyte composition, regional and systemic cytokines), general parameters of optimal care are addressed as well as factors that may affect each transplantable organ. The limited evidence-based data are emphasized, but the reader should approach this chapter understanding that most recommendations follow general critical care guidelines.

### **GENERAL DONOR CARE**

No prospective data identify optimal or the lowest or highest "allowable" values for blood pressure, cardiac output or its determinants, serum glucose, electrolyte or hemoglobin concentrations, body temperature, or time taken for donor treatment.

### **Treatment Time**

The traditional practice of rapid organ assessment and allocation intended to minimize the time donor organs were exposed to a harmful hormonal and physiologic milieu after brain death. Assertive cardiovascular interventions,<sup>7</sup> however, have produced better overall organ perfusion, recovery, and even reclamation of organs previously declined. Therefore, many centers have extended treatment times to allow such therapy.

### **Glycemic Control**

The potential harmful effects of hyperglycemia in critically ill or injured patients are well documented.<sup>8</sup> However, limited data and preferences from transplantation centers encourage modestly elevated blood glucose so as to possibly increase glycogen deposition in the donor liver<sup>9,10</sup> and to stimulate pancreatic islet cells to produce insulin before explantation.<sup>11</sup> Therefore, recommendations from Table 91-1 may be slightly higher than glucose concentrations commonly sought through critical care guidelines. Neuroglycopenia produced by hypoglycemia during insulin therapy would not be a concern in the brain dead donor. Severe hypoglycemia and other indicators of severity of illness are associated with increased

Donor Care	
Authoritative Groups	Guideline Parameters
United Network for Organ Sharing Critical Pathway, 1999 <sup>1</sup> Crystal City Consensus Conference, 2002 <sup>2</sup> University of Wisconsin, 2004 <sup>3</sup> University of Texas/ New England Organ Bank, 2006 <sup>4</sup> Canadian Council for Donation and Transplantation, 2006 <sup>5</sup>	Central venous pressure, 4-12 mm Hg Pulmonary artery occluded pressure, 8-12 mm Hg Cardiac index $> 2.4 \text{ L/min/m}^2$ Cardiac output $> 3.8 \text{ L/min}$ Mean arterial pressure, 60 mm Hg Systolic blood pressure, $>90$ and $<120$ mm Hg Glucose, 70-150 mg/dL pH, 7.40-7.45 Paco <sub>2</sub> , 30-35 mm Hg Pao <sub>2</sub> $> 80-90$ mm Hg Hemoglobin, $>10$ g/dL Hematocrit, $>30\%$ Urine output, 1-3 mL/kg/hr

Table 91-1 Recent Recommendations for Donor Care

mortality after statistical analysis.<sup>12,13</sup> However, a mechanism, other than its effect on the brain, and a true causal relationship between hypoglycemia alone and death have not been defined.

The clinical importance of an immune-suppressive effect induced by hyperglycemia is unclear.<sup>14</sup> The beneficial responses to infection or inflammation may be adversely affected, but a degree of immunosuppression in transplanted organs might benefit the recipient.

### Transfusion Therapy and Coagulopathy

The optimal hemoglobin and hematocrit levels for donor patients have not been a topic of research and are unknown beyond the recommendations in Table 91-1. Although the requirement for oxygen carrying capacity might be less because the brain, a major oxygen-consuming organ, is dead, cardiac output often is compromised during donor care. The reduction in cardiac output places oxygen delivery to transplantable organs at risk. The same controversies about transfusion therapy that have been addressed<sup>15</sup> among other critical care patients apply to the donor, particularly as related to additional inflammatory mediator burden, acute lung injury, and possible transmission of viruses to the recipient.<sup>16</sup> The potential effect of a compromised immune status due to transfusion is unknown.

Similarly, an optimal coagulation profile is unknown and has received little attention. Ongoing hemorrhage either before or during organ removal is not desirable, but "intrinsic" anticoagulation may be beneficial for organ perfusion. Infusion of the coagulation factors contained in fresh-frozen plasma and platelet concentrates has been associated with acute lung injury in critically ill medical patients.<sup>17</sup> How these findings relate to donors is unclear, but further study is warranted to ensure that donor lungs are not harmed. Recombinant factor VIIa represents a special concern. Although often used for off-label indications during traumatic and neurosurgical bleeding, the value of this drug has not been evaluated among donors. Financial considerations and a measurable (1% to 10%)<sup>18,19</sup> incidence of rapidly evolving thromboembolic complications<sup>20</sup> that might affect immediate and subsequent organ function are concerning. Platelet transfusion likewise may precipitate lung injury and release proinflammatory substances.<sup>17</sup> The benefit or potential harm of supplemental platelet infusions when antiplatelet drugs have recently been used (e.g., cerebral thrombolysis) or to treat thrombocytopenia remains unknown.

### **Body Temperature**

After brain death, most donors are poikilothermic and develop mild to moderate hypothermia. The possible advantage of maintaining some level of hypothermia in reducing donor organ metabolism has not been evaluated. Hypothermia, however, may be harmful by worsening polyuria, coagulopathy, and dysrhythmias.<sup>21</sup>

### **Hormone Replacement**

It is often assumed that brain death causes loss of hypothalamic-pituitary axis integration and secondary loss of adrenal, thyroid, growth, and sex hormone secretion. Human data have documented preservation of both hypothalamic and pituitary hormones after brain death.<sup>22,23</sup> Data<sup>24</sup> have also shown that some donors do not respond to adrenocorticotropin hormone stimulation, indicating that primary hypoadrenalism may result from brain death or the donor's antecedent injuries or diseases. The use and interpretation of adrenocorticotropin stimulation tests during critical illness remain controversial<sup>25,26</sup> and have not been evaluated during donor care. It is common practice to administer corticosteroid in support of lung transplantation<sup>27</sup> with a dose above "stress" coverage that also would, of course, provide treatment of either primary or secondary adrenal insufficiency. Supplemental mineralocorticoid administration might be considered if the donor has hyponatremia, but this is unusual owing to the high frequency of diabetes insipidus. When corticosteroids are given, additional doses or an infusion may be needed if donor care extends beyond 8 to 12 hours.

The retrospective observational data from Rosendale and colleagues<sup>28</sup> indicate more organs were recovered when various combinations of hormones were given, although other aspects of the donors' status were not reported. Further, analysis indicated that not all hormones appeared to have a beneficial effect when separately administered. Corticosteroids appear to be the exception. Therefore, corticosteroid dosing, if not administered for lung support, should be considered at full stress coverage if hypotension persists despite adequate fluid and vasoactive drug administration.

Thyroid hormone has been widely accepted both for routine administration and as a "rescue" medication to treat hypotension refractory to other inotropic or vasopressor agents. Routine therapy is not recommended,<sup>5,29</sup> and other use remains controversial.<sup>29</sup> If administered, the recommended dose is 2 to 3 mg of intravenous triiodothyronine (T<sub>3</sub>) per hour titrated to a desired blood pressure.<sup>29</sup> Because  $T_3$  is rarely available as an intravenous preparation, tetraiodothyronine ( $T_4$ ), 100 µg intravenous bolus followed by 50 µg every 12 hours, is advocated, although the peripheral conversion of  $T_4$  to  $T_3$  is expected to be low.<sup>5</sup>

Polyuria is common after brain death. It places organs at risk from hypovolemia, hypotension, and hypoperfusion. Etiologies include physiologic diuresis, residual effects of diuretics given for treatment of intracranial hypertension, osmotic diuresis due to residual mannitol or hyperglycemia, or diabetes insipidus. Polyuria from causes other than DI usually does not produce significant hypernatremia. Hypernatremia in the donor has been associated with reduced liver function after transplantation, and serum concentrations above 155 mEq/L should be avoided or treated.<sup>30</sup> During treatment of diabetes insipidus, intravenous replacement when urine output is above 150 to 200 mL with balanced salt solutions or hypotonic saline is suggested. The large volumes often required may result in significant hyperglycemia if dextrose and water solutions are used. Aqueous vasopressin may be administered in repeated intravenous boluses (5 to 10 U) or titrated as an infusion to limit urine output to a desired amount. Desmopressin (DDAVP) is also effective as intravenous boluses (0.5 to  $2 \mu g$ ) repeated to achieve the desired urine output goal.<sup>31</sup>

### Nutrition

Limited attention has been given to the effects of nutrition on donor organ function. In many cases, the circumstances that caused brain death evolve rapidly, and providing nutrition would seem a secondary consideration.

Singer and associates,<sup>32,33</sup> however, advocate continuation of established nutritional supplementation in patients in whom brain death has evolved more slowly. They propose that ongoing nutrition favorably affects the hypercatabolic state induced by brain injury, brain death, and the release of numerous cytokines and hormones. The additional provision of nutrients may facilitate glycogen deposition in the liver, enhance the availability of fatty acids and glutamine useful to the heart, and provide omega-3 fatty acids or amino acids helpful for renal protection.<sup>33</sup> No investigational data in humans are available to provide direction.

### **Reperfusion and Preconditioning**

One proposed mechanism of injury to transplanted organs is the production and release of free radicals and other harmful substances at the time of organ implantation, rewarming, and reperfusion. A similar occurrence has been proposed during donor care when significant hypotension is followed by resuscitation and improved tissue perfusion.<sup>34</sup>

An episode of controlled hypotension, however, may precondition some organs (especially the liver) before explantation, perhaps increasing tolerance to possible reperfusion injury after implantation.<sup>35</sup> Deliberate induction of hypotension during donor care for this purpose is not commonly practiced but remains a topic for future investigation.<sup>36</sup>

### CARDIOVASCULAR SUPPORT

The evolution of brain death may produce severe cardiovascular injury and instability. This consequence is thought to be due to the production of cytokines from the brain and remote organs, release of large quantities of catecholamines and other vasoactive substances from ischemic brain, and pathologic discharge from sympathetic and parasympathetic neurons.<sup>37,38</sup> These sequelae have been demonstrated best in animal preparations wherein brain death is abruptly induced.<sup>39</sup> Tachydysrhythmia and bradydysrhythmia, as well as elevated systemic blood pressure, systemic vascular resistance, and cardiac output, are rapidly followed by loss of vascular tone, peripheral vasodilation, and severely reduced myocardial contractility. The cycle of transient but profound hypertension followed by hypotension is a familiar clinical sequence and appears more common when brain death evolves rapidly.

This complex cardiovascular response to brain death includes coronary artery constriction leading to myocardial "stunning" or ischemia followed by vasodilation that increases arterial and perhaps venous capacitance. Therefore, assessment and manipulation of preload, afterload, and contractility often are necessary. The accuracy and utility of central venous and pulmonary arterial pressure monitoring, although advocated by some, remains unclear.<sup>7</sup> Echocardiographic imaging helps evaluate intravascular volume and assess contractility and the presence of segmental or global ventricular dysfunction. Algorithms have recommended a sequential rapid administration of colloid or crystalloid fluids followed by either inotropic or vasopressor therapy to maintain a desired blood pressure.<sup>3,4</sup> No study has determined that any single or combination of vasoactive drugs is superior in maintaining the mean arterial pressure above the usually recommended 65 to 70 mm Hg. Despite close adherence to a standardized treatment protocol to maintain blood pressure, urine output, and normothermia, Dominguez-Roldan and associates found frequent episodes wherein a negative base excess and increased lactate production were documented.<sup>40</sup> These findings suggest that occult episodes of hypoperfusion occur during donor care.

Adjunctive vasopressin infusion is often used for blood pressure support even though its serum concentration among donors is not low.<sup>28,41,42</sup> Although vasopressin infusion in patients with sepsis may cause myocardial, bowel, and skin ischemia,<sup>43,44</sup> these complications have not been evaluated among donors. Similarly, as noted previously, intravenous boluses or infusion of thyroid hormone to augment cardiac contractility remain controversial.<sup>29</sup>

A cardiac arrest before or during donor care would seemingly eliminate the heart from consideration for transplantation. However, successful transplantation of such hearts has been reported.<sup>38</sup> Resuscitation methods should follow standard American Heart Association practice except that atropine is not effective after brain death so that an agent with a direct positive chronotropic effect in the myocardium should be substituted.

Data from Papworth Hospital<sup>7</sup> have shown that aggressive resuscitative treatment in the operating room of

hearts unacceptable for transplantation may improve oxygen delivery and perfusion of other organs. Such therapy may also permit sufficient recovery of cardiac function to allow the heart to be transplanted. These technologies presumably would be equally effective in the intensive care unit. Therefore, use of these aggressive techniques and prolonging resuscitative efforts to recover the maximal number of organs per donor may be indicated.

### PANCREATIC SUPPORT

Treatment during donor care that influences islet cell or either whole or partial pancreas transplantation is difficult to identify.<sup>11</sup> Donor hyperglycemia has been considered harmful, inconsequential, or beneficial to subsequent recipient graft or islet cell function. As reviewed,<sup>11</sup> serum glucose concentrations greater than 125 to 200 mg/dL (6.9 to 11.1 mmol/L) were found to be harmful in some investigations, whereas no adverse consequences of hyperglycemia to 300 mg/dL (16.7 mmol/L) were documented in others.<sup>11</sup> Therefore, no specific interventional recommendations can be made based on the limited data available.<sup>11</sup>

### LIVER SUPPORT

Multiple fixed variables have been evaluated and associated with the success or failure of liver transplantation. However, only a few variables that can be influenced during donor care have been studied. These include general organ perfusion, serum sodium, and liver glycogen loading.<sup>9</sup>

Hyperglycemia-related glycogen loading may improve the liver's tolerance to cold ischemia during transport and reduce reperfusion injury during rewarming.<sup>9,10</sup> Animal studies suggest such a benefit, but these have required nutritional manipulation over a longer time than generally is available for donor care. Intraoperative portal vein infusion of glucose and insulin in humans did improve some measures of liver graft function in the recipient,<sup>10</sup> but it is unclear whether such benefit can be expected from routine nutritional strategies.

Totsuka and associates, in a retrospective study in humans, indicated that hypernatremia (>155 mmol/L) reduced recipient graft function.<sup>30</sup> The graft dysfunction could be eliminated if donor treatment reduced serum sodium below that concentration. Other authors, however, have successfully implanted livers when the donor serum sodium was much higher.<sup>45</sup>

### LUNG SUPPORT

Variables important in lung acceptance that can be affected during donor care are those usually treated by critical care specialists. They include oxygenation and infection. Other variables, reviewed by Orens and associates,<sup>46</sup> from the Pulmonary Council of the International Society for Heart and Lung Transplantation, are not amenable to intervention.

The arterial partial pressure of oxygen (Pao<sub>2</sub>) as a function of the inspired oxygen (FIO<sub>2</sub>), that is, the PaO<sub>2</sub>/FIO<sub>2</sub> ratio, has been prominently used as a criterion for lung acceptance. Traditionally, a ratio of 300 or above obtained during ventilation with 100% oxygen and 5 cm H<sub>2</sub>O positive end-expiratory pressure was required. However, lungs demonstrating a lower ratio, at or below 250, now often are accepted.<sup>46</sup> Customary methods to improve or maintain ventilation-perfusion matching should be applied to improve the PaO<sub>2</sub> or lower FIO<sub>2</sub> requirements. Limited data<sup>47</sup> show that aggressive pulmonary and cardiovascular care do improve donor lung function and lead to successful transplantation.

Treatment of presumed bacterial lung infection should be initiated or continued. Sputum Gram stains alone, either negative or positive, do not predict recipient pneumonia,<sup>48</sup> but positive cultures from donor bronchoalveolar lavage specimens are associated with worse recipient outcomes.<sup>49</sup>

Administration of medroxyprednisolone has become routine and appears to be supported by the epidemiologic study of United Network for Organ Sharing (UNOS) data by Rosendale and colleagues.<sup>28</sup> In addition, Follette and coworkers found that a single dose of 15  $\mu$ m/kg was associated with an improved Pao<sub>2</sub>/Fio<sub>2</sub> ratio.<sup>27</sup> As previously noted, although additional corticosteroid dosing may be needed to support endocrine failure, it is not known whether it is needed to ensure best lung function.

The potential for increased interstitial lung water has been indirectly assessed largely through central venous or pulmonary artery pressures.<sup>46,50</sup> Recommendations are shown in Table 91-1. No study has compared these intravascular pressures to other measurements of lung water, however. Other factors that might influence tissue edema (such as oncotic pressure, osmolality, or serum albumin) have not been evaluated.

### **RENAL SUPPORT**

Maintaining urine output during donor care is supported by some evidence-based data.<sup>51</sup> Lucas and colleagues<sup>52</sup> reported that urine output great than 100 mL per hour during the final hour before explantation was associated with better recipient graft function than output below this level. Additional data from the Southeastern Organ Procurement Foundation, however, found no correlation between early graft performance and the donor's total output during the 24 hours before kidney removal. Urine output greater than 300 mL per hour was not beneficial.<sup>53</sup> Methods used to maintain or limit urine flow in these studies were not specified, but the authors emphasized standard critical care practices, including maintaining intravascular volume. Donor serum creatinine and creatinine clearance also influence later graft function and may be improved using customary methods to improve renal blood flow and urine output.<sup>51,52</sup>

Reports of decreased acute and chronic renal graft function make use of hetastarch for intravascular volume expansion controversial.<sup>51</sup> Conversely, the administration of dopamine and norepinephrine, but not epinephrine, has been suggested to be beneficial independent of their blood pressure effect, perhaps because of a suppressive effect on the production of proinflammatory mediators.<sup>54</sup>

### CONCLUSION

Donor care is often complex. Provision of the best possible organs to awaiting recipients demands careful attention to multiple variables. The paucity of evidence-based data that could be helpful in providing clinical guidance should challenge the critical care, organ procurement, and transplantation communities to develop and implement appropriately controlled investigations. These studies should examine the inter-relationships of "fixed" variables and those physiologic parameters that are amenable to change. Further exploration of the degrees of tolerable variability in each may maximize the recovery of suitable organs.

### AUTHOR'S RECOMMENDATIONS

- There are few evidence-based data to guide donor care. Expert opinion recommends maintenance or restoration of normal physiologic and laboratory parameters during treatment.
- Catecholamine surges, cytokine production, and neurovascular changes during the evolution of brain death may produce initial hypertension and increased systemic vascular resistance followed by vasodilation, organ dysfunction, hypotension, and reduced myocardial contractility.
- Aggressive critical care may reverse these harmful effects and return or preserve organ function to allow transplantation.
- Successful transplantation of organs from donors with abnormal parameters (extended or expanded criteria) suggests that research should define the acceptable variability in treatable physiologic and laboratory criteria and how such variables inter-relate with other "fixed" characteristics of donors.
- Such investigations may lead to new and more objective allocation criteria and an increased supply of organs that will provide acceptable function in the recipient.

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# 92 What Platelet Disorders Occur in the Intensive Care Unit and How Should They Be Treated?

Jill Cherry-Bukowiec, Lena Napolitano

Platelet disorders are common in the intensive care unit (ICU). Thrombocytopenia occurs often in critical illness, perhaps in up to 41% of patients.<sup>1</sup> Thrombocytosis and functional platelet disorders are less common and are found in up to 25% of ICU patients. Systematic evaluation of platelet disorders in critical care is essential to accurate identification and management of the cause. Importantly, thrombocytopenia has been associated with adverse outcomes. In contrast, thrombocytosis has been associated with improved outcomes in the ICU.

The reported incidence of thrombocytopenia in the critical care setting varies from 23% to 41% and is associated with mortality rates between 38% and 54% in retrospective studies<sup>2-9</sup> (Table 92-1). Although the incidence of severe thrombocytopenia (platelet counts  $< 50 \times 10^9/L$ ) is lower (10% to 17%), the association with adverse outcomes is even stronger. Sepsis and hemodilution are common etiologies of thrombocytopenia (HIT) is one potential etiology that warrants serious consideration in all patients. This chapter summarizes the pathogenesis and clinical consequences of platelet disorders in the ICU, describes the diagnostic process, and reviews currently available treatment options.

### PLATELET DERIVATION

Platelets are derived from bone marrow megakaryocytes. The process of platelet formation, or thrombopoiesis, occurs during terminal maturation. It is initiated by the development of the cytoplasmic demarcation membrane system, which delineates platelet fields. These fields are filled with granules and proteins that ultimately make up the contents of mature platelets. The latter are shed from pseudopods that mature megakaryocytes extend through endothelial cell junctions into the lumen of marrow capillaries. The pseudopods fracture and release shards of megakaryocytic cytoplasm, or proplatelets, that are the immediate antecedents of circulating platelets. A fully mature megakaryocyte is estimated to produce about 1 to  $1.5 \times 10^3$  platelets. Failure in the process of either megakaryocytopoiesis or thrombopoiesis will result in thrombocytopenia.

### THROMBOCYTOPENIA

### Definition of Thrombocytopenia

Thrombocytopenia is defined as a platelet count of less than 150,000/mm<sup>3</sup> or less than 150  $\times$  10<sup>9</sup>/L. The normal range for platelet count in adult humans is 150 to 450  $\times$  10<sup>9</sup>/L. Thrombocytopenia may result from decreased production or increased destruction of platelets. A patient is at risk for spontaneous bleeding when the platelet count falls below 20,000 and may warrant platelet transfusion.

### Epidemiology of Thrombocytopenia in the Intensive Care Unit

Data from a prospective observational cohort study of 329 adult surgical ICU patients documented that thrombocy-topenia (defined as a platelet count  $< 150 \times 10^9$ /L) was present in 41.3% (n = 136) of patients and independently predicted mortality. A drop in platelet count to 50% or less of levels at admission was associated with higher death rates (ICU mortality odds ratio [OR], 6.0; 95% confidence interval [CI], 3.0 to 12.0; P < .0001) than admission variables of severity of illness, including the Acute Physiology and Chronic Health Evaluation (APACHE) II score, the Simplified Acute Physiological Score (SAPS) II, and the Multiple-Organ Dysfunction Syndrome (MODS) score (adjusted OR, 4.2; 95% CI, 1.8 to 10.2).<sup>7</sup>

The relationship between the time course of platelet counts and mortality in critically ill patients (n = 1449) was examined in a prospective, multicenter, observational cohort analysis of patients in 40 ICUs from 16 countries in Europe, America, and Australia. Data on all ICU admissions in a 1-month period were collected. Patients younger than 12 years old and those with an ICU stay of less than 48 hours after uncomplicated surgery were excluded. Platelet counts were determined daily throughout the ICU stay, and thrombocytopenia was defined as a platelet count of less than  $150 \times 10^9$ /L. The platelet count decreased significantly after admission to reach a nadir on day 4 in all patients. Levels were lower in nonsurvivors (n = 313) than in survivors (n = 1131) throughout the ICU course. A total of 138 patients (54%) had thrombocytopenia on day 4. The mortality rate in these

Study	Design	No. of Subjects	Patient Type	Time Period	Definition Used	Incidence of Thrombocytopenia
Baughman	Retrospective	162	Medical ICU	1 yr	<100,000/mm <sup>3</sup>	$23\% < 100,000/\text{mm}^3$
et al, 1993 <sup>2</sup>	chart review					$10\% < 50,000/\text{mm}^3$
Bonfiglio et al, 1995 <sup>59</sup>	Retrospective chart review	314	Medical- surgical ICU	_	<200,000/mm <sup>3</sup>	_
Hanes et al, 1997 <sup>3</sup>	Prospective observational	63	Trauma ICU	_	<100,000/mm <sup>3</sup>	41%
Stéphan et al, 1999 <sup>4</sup>	Prospective cohort	147	Surgical ICU	6 mo, 1/1-6/30, 1996	<100,000/mm <sup>3</sup>	35%
Vanderschueren et al, 2000 <sup>9</sup>	Prospective cohort	329	Medical ICU	5 mo	<150,000/mm <sup>3</sup>	41.3%
Strauss et al, 2002 <sup>6</sup>	Prospective cohort	145	Medical ICU	13 mo	<150,000/mm <sup>3</sup>	44%
Crowther et al, 2005 <sup>60</sup>	Prospective cohort	261	Medical- surgical ICU	12 mo, 1/2001- 1/2002	<150,000/mm <sup>3</sup>	46%

Table 92-1 Incidence of Thrombocytopenia in the Intensive Care Unit

patients was increased twofold (33% versus 16%; P < .05). Thrombocytopenia was present by day 14 in 20% of the patients who stayed in the ICU for more than 2 weeks and was associated with a higher mortality rate (66% versus 16%; P < .05). This study documented that late thrombocytopenia is more predictive of death than early thrombocytopenia in critically ill patients. However, the specific etiology of thrombocytopenia was not addressed.<sup>8</sup>

A declining platelet count has also been identified as an early prognostic marker in critically ill patients with prolonged ICU stays.<sup>10</sup> In a study that included 1077 patients in the ICU for at least 5 days with no thrombocytopenia on admission, multivariable analysis indicated that a 30% decline in platelet count independently predicted hospital mortality (OR, 1.54; 95% CI, 1.12 to 2.14; P = .008).

### Diagnostic Evaluation of Thrombocytopenia in the Intensive Care Unit

Systematic evaluation of the numerous potential etiologies of thrombocytopenia in critical care is essential to accurate identification and management of the cause (Table 92-2). Sepsis is the most common etiology of thrombocytopenia in critical illness, accounting for 48% of cases of thrombocytopenia.<sup>11</sup> However, greater than 25% of ICU patients have more than one cause of thrombocytopenia.<sup>8</sup> Drug-induced thrombocytopenias present diagnostic challenges because many of the multiple medications administered to ICU patients may be the cause.<sup>12</sup> One such commonly administered drug is heparin, the most common cause of drug-induced thrombocytopenia due to immune mechanisms.

### Table 92-2 Potential Etiologies of Thrombocytopenia

### COMMON CAUSES

- Hemodilutional (postresuscitation, perioperative)
- Sepsis and health care-associated infections
- Drug-induced thrombocytopenias, including HIT
- Peripheral platelet consumption or destruction
- Disseminated intravascular coagulation
- Massive transfusion
- Laboratory error; clumping secondary to ethylenediamine tetraacetic acid (EDTA) in test tube, need smear to examine

### LESS COMMON CAUSES

- Liver disease
- Hypersplenism
- Primary marrow disorder, bone marrow failure
- Antiphospholipid antibody syndrome, lupus anticoagulant
- Immune thrombocytopenias (ITP, TTP, PTP)
- Intravascular devices (IABP, LVAD, ECMO, pulmonary artery catheter)

ECMO, extracorporeal membrane oxygenation; HIT, heparin-induced thrombocytopenia; IABP, intra-aortic balloon pump; ITP, idiopathic thrombocytopenic purpura; LVAD, left ventricular assist device; PTP, posttransfusion purpura; TTP, thrombotic thrombocytopenic purpura.

### Causes of Thrombocytopenia

The three most important causes of thrombocytopenia in the ICU are drug-induced thrombocytopenia, HIT, and disseminated intravascular coagulation (DIC). These will be examined in depth. A number of other etiologies of thrombocytopenia may occur in ICU patients. These include autoimmune or alloimmune thrombocytopenia, posttransfusion purpura, the thrombotic microangiopathies, and the HELLP syndrome. They will be covered briefly.

### Drug-Induced Thrombocytopenia

Drugs can induce thrombocytopenia by a number of mechanisms. In addition to those that are directly cytotoxic, thiazide diuretics, interferon, and alcohol can cause thrombocytopenia by inhibiting platelet production in the bone marrow. More commonly, drug-induced thrombocytopenia results from the immunologic destruction of platelets. Drugs can induce antibodies to platelets, either by acting as a hapten or functioning as an innocent bystander. Drugs such as gold salts and interferon can induce an ITP-like disorder. Some common ICU drugs that are associated with thrombocytopenia are detailed in Table 92-3.

The diagnosis of drug-induced thrombocytopenia most often is empirical. A temporal relationship between the administration of the drug and the development of thrombocytopenia, with no other explanations for the thrombocytopenia, must be present. Recurrent thrombocytopenia following re-exposure to the drug confirms the diagnosis. Identifying the drug that is causing severe thrombocytopenia in an acutely ill patient who is taking multiple drugs is often challenging. A complete list of all available reports of drug-induced thrombocytopenia is available at "Platelets on the Web."<sup>13</sup>

### Heparin-Induced Thrombocytopenia

HIT is unique among drug-induced thrombocytopenias because the offending antibodies also activate platelets and induce a hypercoagulable state. HIT is an anticoagulant-induced *prothrombotic* disorder caused by platelet-activating heparin-dependent antibodies of immunoglobulin G (IgG) class. The diagnosis of HIT should be considered when the platelet count falls to less than  $150 \times 10^9/L$  (or by >50% from baseline) between days 5 and 14 of exposure to any heparinoid product.<sup>14</sup> The presumptive diagnosis can be supported or refuted with a strong positive or negative laboratory test for HIT antibodies. The decrease in platelet count is usually moderate (mean platelet count,  $60 \times 10^9/L$ ) and recovers within few days

### Table 92-3 Common Drugs That Can Induce Thrombocytopenia

- Heparin
- Quinidine
- Amiodarone
- Captopril
- Thiazide Diuretics
- Ibuprofen
- Phenytoin
- Carbamazepine
- Glibenclamide
- Gold
- Tamoxifen
- Cimetidine
- Ranitidine
- Sulfonamides
- Vancomycin
- Piperacillin

of discontinuing heparin. Because heparin use is ubiquitous in hospitalized patients, a high index of suspicion on the clinician's part is necessary for proper recognition. It is essential to remember that heparin administration may have occurred recently in other hospitals or in areas outside the ICU. The reported mortality rate associated with HIT ranges between 10% and 20%.<sup>11–14</sup> The term *isolated HIT* refers to the development of HIT without any apparent HIT-associated thrombosis, whereas the *HIT thrombotic syndrome* (HITTS) denotes the clinical picture of acute thrombosis complicating HIT.

If HIT is strongly suspected in a critically ill patient, all heparin sources, including low-molecular-weight heparin (LMWH), should be discontinued promptly, and the indication for heparin use should be examined. If anticoagulation is essential an alternative anticoagulant such as a direct thrombin inhibitor should be substituted without awaiting laboratory confirmation of the presence of HIT antibodies. A clinicopathologic diagnostic approach that integrates clinical findings and the results of HIT antibody testing has been recommended.<sup>15,16</sup> The diagnosis is most accurate if platelet-activating antibodies are detected by anti-PF4-heparin enzyme immunoassay (EIA).<sup>17</sup> The 14Cserotonin-release assay (SRA) is a functional (platelet activation) assay that has high sensitivity and specificity for detecting the antibodies that cause HIT, and superior specificity compared with the anti-PF4-heparin EIA.

In the ICU, HIT is uncommon (<1%), even though 30% to 50% of patients develop thrombocytopenia.<sup>18</sup>

When considering the diagnosis of HIT, critical care professionals should monitor platelet counts in patients who are at risk for HIT and carefully evaluate for the "four Ts" detailed in Table 92-4A. The principles of treatment for suspected or confirmed HIT include the "six As" (see Table 92-4B). Due to its prothrombotic nature, early recognition of HIT and, if indicated, prompt substitution with a direct thrombin inhibitor such as argatroban or lepirudin or the heparinoid danaparoid (where available) reduces the risk for thromboembolic potentially life-threatening events. If HIT is confirmed, the diagnosis must be clearly recorded in the patient's medical record.<sup>19</sup> The American College of Chest Physicians, in their evidence-based clinical practice guidelines on treatment and prevention of HIT,<sup>20</sup> recommend the following:

- For patients receiving heparin in whom the clinician considers the risk for HIT to be more than 1.0%, we recommend platelet count monitoring over no platelet count monitoring.
- For patients who are receiving heparin or have received heparin within the previous 2 weeks, we recommend investigating for a diagnosis of HIT if the platelet count falls by more than 50% or a thrombotic event occurs, between days 5 and 14 (inclusive) after initiation of heparin, even if the patient is no longer receiving heparin therapy when thrombosis or thrombocytopenia has occurred.
- For patients with strongly suspected (or confirmed) HIT, whether complicated by thrombosis or not, we recommend use of an alternative, nonheparin anticoagulant (danaparoid, lepirudin, argatroban, fondaparinux, or bivalirudin) over the further use of unfractionated

	POINTS (0, 1, OR 2 FOR EACH OF 4 CATEGORIES: MAXIMUM SCORE $=$ 8)*			
	2	1	0	
Thrombocytopenia	>50% platelet fall to nadir $\geq$ 20	30%-50% platelet fall, or nadir 10-19, or >50% fall secondary to surgery	<30% platelet fall, or nadir <10	
Timing† of onset of platelet fall (or other sequelae of HIT)	Days 5-10 or ≤day 1 with recent heparin (past 30 days)	>Day 10 or timing unclear; or <day 1 with recent heparin (past 31-100 days)</day 	<day (no="" 4="" recent<br="">heparin)</day>	
Thrombosis or other sequelae	Proven new thrombosis; skin necrosis; or acute systemic reaction after intravenous unfractionated heparin bolus	Progressive or recurrent thrombosis; erythematous skin lesions; suspected thrombosis (not proved)	None	
Other cause(s) of platelet fall	None evident	Possible	Definite	

Table 92-4 A. Estimating the Pretest Probability of Heparin-Induced Thrombocytopenia: The "Four Ts"

\*Pretest probability score: 6-8 indicates high; 4-5, intermediate; and 0-3, low.

<sup>†</sup>First day of immunizing heparin exposure considered day 0.

From Warkentin TE. Heparin-induced thrombocytopenia: Diagnosis and management. Circulation. 2004;110:e454-e458.

### Table 92-4 B. Principles of Treatment for Suspected or Confirmed Heparin-Induced Thrombocytopenia: The "Six As"

- 1. Avoid and discontinue all heparin (including low-molecularweight heparin)
- 2. Administer nonheparin alternative anticoagulant
- 3. Anti-PF4/heparin antibody test for confirmation
- 4. Avoid platelet transfusion
- 5. Await platelet recovery before initiation of warfarin anticoagulation
- 6. Assess for lower extremity deep venous thrombosis

\*These recommendations are based on expert opinion.

Adapted from Napolitano LM, Warkentin TE, AlMahameed A, Nasraway SA. Heparin-induced thrombocytopenia in the critical care setting: Diagnosis and management. Crit Care Med. 2006;34:2898-2911, Table 8.

heparin (UFH) or LMWH therapy or initiation or continuation of vitamin K antagonists (VKAs).

- For patients with strongly suspected or confirmed HIT, we recommend against the use of VKA therapy (coumarin derivatives such as warfarin) until after the platelet count has substantially recovered (usually, to at least  $150 \times 10^9$ /L) over starting VKA therapy at a lower platelet count; that VKA therapy be started only with low maintenance doses (maximum, 5 mg of warfarin or 6 mg of phenprocoumon) over higher initial doses; and that the nonheparin anticoagulant (e.g., lepirudin, argatroban, danaparoid) be continued until the platelet count has reached a stable plateau and the international normalized ratio (INR) has reached the intended target range, and after a minimum overlap of at least 5 days between nonheparin anticoagulation and VKA therapy rather than a shorter overlap.
- For patients receiving VKAs at the time of diagnosis of HIT, we recommend use of vitamin K (10 mg orally or 5 to 10 mg intravenously).

Pathophysiology of Heparin-Induced Thrombocytopenia. HIT is an immune-mediated hypersensitivity reaction to the platelet factor 4 (PF4)-heparin complex. PF4 is a

heparin-binding tetrameric protein found naturally in platelet  $\alpha$ -granules and bound to heparan sulfate on endothelial surfaces. Binding of PF4 with heparin results in conformational changes in PF4 that produce an immune response (i.e., the production of IgG antibodies). Anti-PF4-heparin antibodies are produced by a relatively high percentage of heparin-treated patients, but only a minority of patients with antibodies will develop thrombocytopenia.<sup>21–23</sup> These antibody complexes also bind to heparin (or heparin-like molecules) on endothelial cells and monocytes, leading to tissue factor expression by these cells.<sup>24,</sup> Anti-PF4-heparin antibodies are transient and usually become undetectable a median of 50 to 85 days after the occurrence of HIT.<sup>26</sup> Antibodies may remain detectable at low levels for several months. If heparin is readministered to a patient who has high levels of HIT antibodies, abrupt onset of thrombocytopenia can occur. However, this event is unlikely to occur more than 100 days after any heparin exposure.

### Disseminated Intravascular Coagulation

DIC is a systemic disorder characterized by derangements of the coagulation and fibrinolytic systems that lead to widespread thrombosis and bleeding. It is commonly associated with trauma, sepsis, ischemia-reperfusion, malignancy, and other inflammatory conditions. Extensive intravascular fibrin deposition ensues. This results in microvascular thrombosis, impaired blood supply to organs, and ultimately multiple-organ failure. Consumption of platelets results in thrombocytopenia, whereas consumption of clotting factors results in coagulopathy. The combination may lead to diffuse hemorrhage.

The fundamental approach to treatment of DIC is prompt identification and aggressive management of the underlying disorder. Transfusion of blood products may be required, although there are no consensus guidelines regarding their appropriate use. Transfusion should not be performed purely in response to abnormal laboratory results. A combination of platelets, fresh-frozen plasma (FFP), and cryoprecipitate is indicated in the actively bleeding patient, the patient who requires an invasive procedure, and the patient at high risk for bleeding problems.<sup>27</sup>

### Autoimmune Thrombocytopenia

ITP is a common hematologic disorder manifested by immune-mediated thrombocytopenia.<sup>28</sup> ITP is an autoimmune disorder characterized by a low platelet count and mucocutaneous bleeding. The disorder is classified as primary or as secondary to an underlying disorder and as either acute ( $\leq 6$  months in duration) or chronic.<sup>29</sup> The diagnosis remains one of exclusion after the presence of other thrombocytopenic disorders has been eliminated. The goal of treatment is to raise the platelet count into a hemostatically safe range.<sup>30</sup> Corticosteroids and splenectomy are the mainstays of therapy. Other approaches include cyclophosphamide, intravenous immunoglobulin (IVIG), anti-Rh(D), anti-CD40L, anti-CD20, cyclosporine, and monoclonal Fc blockade and many others.<sup>31</sup>

### **Posttransfusion Purpura**

Posttransfusion purpura (PTP) is a rare bleeding disorder caused by alloantibodies specific to platelet antigens.<sup>32</sup> An antibody directed against the human platelet alloantigen (HAP-1a) is responsible for most of the cases. Platelet glycoprotein IIb/IIIa is a major antigen in platelets and is polymorphic. Most individuals have a leucine residue at position 33 (phospholipase A1 [PLA1]/PLA1 or human platelet alloantigen [HPA]-1a). About 1% to 3% of random populations, however, have a proline instead. Homozygotes with proline are termed phospholipase negative (PLA<sub>2</sub>/PLA<sub>2</sub> or HPA-1b), and when given blood products from HPA-1a-positive individuals, they produce an antibody reactive against HPA-1a. This alloantibody destroys both the transfused platelets and the patient's own platelets, leading to a severe form of thrombocytopenia that lasts for weeks or, in some cases, several months.

Most affected patients are multiparous women who presumably were previously sensitized during pregnancy. Alloimmunization by blood transfusions also have been implicated primarily. PTP typically occurs 10 days after a transfusion. This syndrome can be induced by a small amount of platelets contaminating a red blood cell transfusion or, occasionally, by FFP transfusion. Universal leukodepletion of the blood supply has reduced the number of reported cases of PTP significantly. The thrombocytopenia responds to IVIG.<sup>33</sup> On occasion, other platelet alloantigens have been implicated in PTP.

### **Thrombotic Microangiopathies**

Thrombotic microangiopathies are characterized by microvascular thrombosis associated with hemolytic anemia, thrombocytopenia, and red blood cell fragmentation. They represent a heterogeneous group of diseases of different etiologies. However, the entire group shares morphologic features. Hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) are classically associated with thrombotic microangiopathy. Differentiating these diseases from each other has been very difficult and often appears to be based on the convictions of various specialists as opposed to precisely defined criteria. Recent studies on von Willebrand factor and also on the alternative complement pathway have enhanced understanding of the pathogenesis of these diseases. It may be that they share a pathophysiologic mechanism (Fig. 92-1).<sup>34,35</sup> A recent Cochrane review documented that plasma exchange with FFP is the most effective treatment available for TTP. For patients with HUS, supportive therapy, including dialysis, is still the most effective treatment.<sup>36,37</sup>

### Thrombotic Thrombocytopenic Purpura

TTP is a rare but serious disorder that was initially described as a *pentad* of thrombocytopenia (with purpura), red blood cell fragmentation, renal failure, neurologic dysfunction, and fever. Recent evidence indicates that this disorder results from the presence of unusually large, abnormal multimers of the von Willebrand protein. These ultralarge precursors, normally synthesized in the endothelial cells, are processed by a plasma enzyme to normal-sized multimers. This enzyme is now identified as ADAMTS13, a metalloproteinase synthesized in the liver. The sporadic forms of TTP are caused by an antibody or toxin inhibiting the activity of ADAMTS13. The chronic, recurrent form of TTP may result from a congenital deficiency of the enzyme. The ultralarge multimers are thought to induce the aggregation of platelets that causes consumption. Occlusion of microvasculature by platelets in the brain, kidney, and other organs leads to the symptoms. A TTP-like syndrome has been associated with lupus, pregnancy, human immunodeficiency virus infection, and certain drugs (e.g., quinine, ticlopidine, clopidogrel, cyclosporine, chemotherapeutic agents).

TTP often is associated with a flu-like illness that occurs 2 to 3 weeks before presentation. Most patients with TTP do not have the classic pentad. The most common presentation is petechiae and neurologic symptoms. The neurologic symptoms can range from headache and confusion to seizures and coma. Fever is present in slightly more than half the patients.

### Hemolytic Uremic Syndrome

Patients with HUS have vascular lesions that are indistinguishable from those in patients with TTP. However, the renal vasculature is most affected, and there usually is minimal neurologic dysfunction. This is a catastrophic illness that predominantly affects children aged 4 to 12 months. It occasionally occurs in older children but is rare in adults. It follows an upper respiratory tract infection. In the tropics, epidemics of HUS are frequent and resemble an infectious disease. However, no causative organism has been identified. In North America, *Shigella*-like toxins (secreted by *Escherichia coli* serotype O157:H7 or *Shigella dysenteriae* serotype I) cause many cases of HUS. Diarrhea and abdominal cramps are prominent symptoms.

### **HELLP Syndrome**

The HELLP syndrome is a severe form of preeclampsia, consisting of hemolysis, elevated liver enzymes, and low platelets. It carries an unpredictable risk to mother and fetus. The syndrome of hemolysis, elevated liver enzymes, and low platelets is considered to be an atypical form of gestational hypertensive diseases.<sup>38</sup> There has been, to date, neither reliable early recognition nor effective



**Figure 92-1.** Hypothetical model for shared pathophysiology between hemolytic uremic syndrome (HUS) and TTP. In this proposed model, the inciting event for both HUS and thrombotic thrombocytopenic purpura (TTP) is a similar endothelial insult brought about by any of a variety of sources (or combination of sources) that results in widespread endothelial activation, inflammation, and damage, including the release of von Willebrand factor (vWF) and other contents of the Weibel-Palade bodies. The subsequent events may be determined in part by the level of systemic ADAMTS13 activity.

*Top:* In the case of systemic ADAMTS13 *deficiency*, ADAMTS13 is not available to process the newly released vWF, resulting in the wide-spread formation of vWF and platelet thrombi throughout the arteriolar circulation and the clinical picture of TTP.

Bottom: Conversely, in the case of systemic ADAMTS13 sufficiency, TTP is avoided by ADAMTS13-mediated release of platelet/vWF thrombi throughout the arteriolar circulation. For reasons that are not understood, circulating ADAMTS13 is not able to cleave efficiently the vWF that is released in the glomerular microcapillary circulation, resulting in thrombus formation, increased inflammation, glomerular damage, and the clinical picture of HUS. Potential reasons for the inability of ADAMTS13 to cleave vWF in the glomerular circulation may include unfavorable shear stress not permissive for the proper unfolding of vWF (decreasing access of ADAMTS13 to the sessile bond within the folded vWF A2 domain) and the local presence of molecules that may interfere with ADAMTS13 activity or with its interaction with vWF. (From Desch K, Motto D. Is there a shared pathophysiology for thrombotic thrombocytopenic purpura and hemolytic-uremic syndrome? J Am Soc Nephrol. 2007;18:2457–2460.)

prevention of HELLP syndrome. The early recognition of hemolysis (by determination of serum haptoglobin) and thrombocytopenia should alert to a possible diagnosis of HELLP. It is universally agreed that any fetus that has progressed beyond 32 weeks of gestation should be delivered immediately if HELLP is present.<sup>39</sup>

### THROMBOCYTOSIS

### **Definition of Thrombocytosis**

Thrombocytosis is defined as a platelet count above the normal value, in general more than 400,000 to 600,000/ mm<sup>3</sup> or more than 400 to  $600 \times 10^9$ /L (normal in adult humans, 150 to  $450 \times 10^9$ /L). Thrombocytosis is classified into primary and secondary forms. *Primary (clonal) thrombocytosis* is due to clonal thrombopoiesis and most often occurs in chronic myeloproliferative or in some myelodysplastic disorders. *Secondary (reactive) thrombocytosis* is due to a variety of underlying conditions involving an acute phase reaction. These include trauma, surgery, hemorrhage, malignancy, infection, and inflammatory diseases<sup>40–42</sup> (Table 92-5).

### Table 92-5 Major Causes of Thrombocytosis

- 1. Primary (clonal) thrombocytosis (chronic myeloproliferative diseases)
  - Essential (primary) thrombocythemia
  - Other myeloproliferative disorders (chronic myelogenous leukemia, polycythemia vera, myeloid metaplasia, myelofibrosis)
- 2. Familial thrombocytosis
- 3. Secondary (reactive) thrombocytosis
  - Acute hemorrhage
  - Trauma
  - Major surgery
  - Iron deficiency anemia, hemolytic anemia
  - Postsplenectomy
  - Recovery ("rebound") from thrombocytopenia
  - Malignancies
  - Chronic inflammatory and infectious diseases (inflammatory bowel disease, connective tissue disorders, temporal arteritis, tuberculosis, chronic pneumonitis)
  - · Acute inflammatory and infectious diseases
  - Response to intense exercise
  - Reaction to drugs (vincristine, epinephrine, all-*trans*-retinoic acid, cytokines, and growth factors)

# Epidemiology of Thrombocytosis in the Intensive Care Unit

The etiology and clinical significance of thrombocytosis has been retrospectively reviewed in a cohort of medical and surgical hospitalized patients (n = 732).<sup>43</sup> Primary thrombocytosis was present in 12.3% (n = 89) of patients with an elevated platelet count of  $500 \times 10^9/L$  or higher. Secondary thrombocytosis was observed in 87.7% (n = 643). The most frequent causes of the secondary disorder are tissue damage (42%), infection (24%), malig-(13%), and chronic inflammation (10%). nancv Importantly, primary thrombocytosis was associated with significantly higher platelet counts (mean, 872; standard deviation [SD], 274) compared with secondary causes (mean, 597; SD, 105; P < .001). Additionally, primary thrombocytosis was associated with a significantly increased incidence of thromboembolic complications (12.4% versus 1.6%; P < .001). Although complications of primary thrombocytosis were both arterial and venous, thromboemboli in secondary thrombocytosis were found only in the venous system.

Data from a retrospective review of 226 ICU adult patients found that thrombocytosis (defined as a platelet count >  $450 \times 10^{9}$ /L) was present in 21.7% (*n* = 47) of patients and was associated with a lower ICU (P = .003) and hospital mortality (P = .006) but a longer ICU stay (P < .0001).<sup>44</sup> Another study prospectively examined data from 176 trauma ICU patients with thrombocytosis (characterized as a platelet count >  $600 \times 10^9$ /L). Thirty-six patients (20.4%) developed thrombocytosis at a mean time of 14.0  $\pm$  4.0) days. Platelet counts normalized 35.0  $\pm$  13.0 days after ICU admission. Identifiable predisposing factors included infection in 30 patients (83%), acute lung injury in 17 (47%), hemorrhage in 27 (75%), and catecholamine administration in 24 (67%). Venous thromboembolic complications occurred in 3 patients while in the ICU (1.7%). The ICU mortality was comparable among patients with and without thrombocytosis (8% versus 14%; P = .34).<sup>45</sup>

# Diagnostic Evaluation of Thrombocytosis in the Intensive Care Unit

Evaluation of thrombocytosis in critically ill patients relies on the patient's past medical history and recent hospital course. Although there are many potential causes of thrombocytosis (see Table 92-5), secondary (reactive) causes are most common. In a 5.5-year review of 280 patients with extreme thrombocytosis, 82% had secondary reactive causes, and 14% had a myeloproliferative disorder (Table 92-6).<sup>46</sup> At present, there are no diagnostic criteria that definitively distinguish clonal from secondary thrombocytosis. However, some clinical and laboratory features can be helpful in determining the most likely cause of an elevated platelet count (Table 92-7). For example, measurements that change in association with acute phase responses, such as C-reactive protein, fibrinogen, erythrocyte sedimentation rate, and interleukin-6, may be useful in diagnosing secondary (reactive) thrombocytosis.

## Table 92-6 Incidence of "Extreme" Thrombocytosis\*

Etiology	Total (280 Cases)
REACTIVE THROMBOCYTOSIS	231 (82%)
Infection (%)	72 (31)
Postsplenectomy (or hyposplenism) (%)	43 (19)
Malignancy (%)	33 (14)
Trauma (%)	32 (14)
Inflammation (noninfectious) (%)	21 (9)
Blood loss (%)	13 (6)
Uncertain etiology (%)	9 (4)
Rebound (%)	8 (3)
MYELOPROLIFERATIVE DISORDERS	38 (14%)
CML (%)	16 (42)
ET (%)	11 (29)
PV (%)	5 (13)
IMF (%)	2 (5)
Unclassified (%)	4 (11)
UNCERTAIN ETIOLOGY	11

\*Platelet count >1000  $\times$  10<sup>9</sup>/L.

CML, chronic myeloid leukemia; ET, essential thrombocythemia; IMF, idiopathic myelofibrosis; PV, polycythemia, vera.

From Buss DH, Cashell AW, O'Conner ML, et al. Occurrence, etiology and clinical significance of extreme thrombocytosis: A study of 280 cases. *Am J Med.* 1994;96:247, with permission of Excerpta Medica, Inc.

### Table 92-7 Clinical and Laboratory Features Helpful in Distinguishing Essential Thrombocythemia from Reactive Thrombocytosis

Feature	ET	RT
Chronic platelet increase	+	_
Known causes of RT	_	+
Thrombosis or hemorrhage	+	_
Splenomegaly	+	_
BM reticulin fibrosis	+	_
BM megakaryocyte clusters	+	_
Abnormal cytogenetics	+	_
Increased acute phase reactants	-	+
Spontaneous colony formation <sup>†</sup>	+	-

\*Acute phase reactants include C-reactive protein and fibrinogen.

<sup>†</sup>Erythroid colonies.

BM, bone marrow; ET, essential thrombocythemia; RT, reactive thrombocytosis. From Tefferi A, Hoagland HC: Issues in the diagnosis and management of primary thrombocythemia. *Mayo Clin Proc.* 1994;69:651.

### Primary (Clonal) Thrombocytosis

Clonal thrombocythemias are myeloproliferative neoplasms in which platelet counts are elevated. Some of the more commonly encountered clonal thrombocythemias include essential (primary) thrombocythemias and other myeloproliferative disorders such as chronic myelogenous leukemia, polycythemia vera, myeloid metaplasia, and myelofibrosis. These etiologies are commonly diagnosed prior to ICU admission.

Diagnosis of essential thrombocytosis requires persistent thrombocytosis (> $450 \times 10^9$ /L) in the absence of other identifiable causes. In essential thrombocytosis, *megakaryocytes* are abnormal and are more sensitive to *growth factors*. Patients often manifest symptoms of hemorrhage, thrombosis of the microvasculature or large veins and arteries, and splenomegaly. Microvascular ischemia of the digits may be associated with erythromelalgia, a syndrome characterized by intense burning or throbbing pain on the plantar surfaces of the hands and feet. Neurologic complications occur in about 25% of patients with essential thrombocytosis. Eighty percent of adults with essential thrombocytosis survive more than 100 months, with 5 of 95 treated patients experiencing a leukemic

conversion. In 2008, the World Health Organization updated the diagnostic criteria for differentiating polycythemia vera, essential thrombocythemia, and primary myelofibrosis<sup>47</sup> (Table 92-8).

### **Familial Thrombocytosis**

Patients with familial thrombocytosis may exhibit thrombotic complications that may be difficult to distinguish from sporadic essential thrombocythemia. Familial forms of thrombocytosis are recognized as a group of genetically heterogeneous disorders that can be caused by an autosomal dominant defect or other multiple modes of inheritance. In the autosomal dominant disorder, mutations in the thrombopoietin gene cause thrombopoietin overproduction and markedly elevated platelet levels. Other genetically heterogeneous disorders in which thrombopoietin levels are normal have also been described.

### Secondary (Reactive) Thrombocytosis

Secondary (reactive) thrombocytosis is the most common form in the general population. Physiologic stressors such

	PV <sup>a</sup>	ET <sup>a</sup>	PMF <sup>a</sup>
Major criteria	(1) Hgb > 18.5 g/dL (men) > 16.5 g/dL (women) or Hgb > 17 g/dL (men), or > 15 g/dL (women) if associated with a sustained increase of $\geq 2$ g/dL from baseline that cannot be attributed to correction of iron deficiency or <sup>c</sup>	(1) Platelet count $\ge 450 \times 10^9/L$	(1) Megakaryocyte proliferation and atypia <sup>b</sup> accompanied by either reticulin and/or collagen fibrosis, or in the absence of reticulin fibrosis, the megakaryocyte changes must be accompanied by increased marrow cellularity, granulocytic proliferation and often decreased erythropoiesis (i.e., pre-fibrotic PMF)
	(2) Presence of JAK2V617F or similar mutation	(2) Megakaryocyte proliferation with large and mature morphology. No or little granulocyte or erythroid proliferation	(2) Not meeting WHO criteria for CML, PV, MDS, or other myeloid neoplasm
		<ul> <li>(3) Not meeting WHO criteria for CML, PV, PMF, MDS, or other myeloid neoplasm</li> <li>(4) Demonstration of JAK2V617F or other clonal marker or no evidence of reactive thrombocytosis</li> </ul>	(3) Demonstration of JAK2V617F or other clonal marker or no evidence of reactive marrow fibrosis
Minor criteria	<ol> <li>(1) BM trilineage myeloproliferation</li> <li>(2) Subnormal serum Epo level</li> <li>(3) EEC growth</li> </ol>		<ol> <li>(1) Leukoerythroblastosis</li> <li>(2) Increased serum LDH</li> <li>(3) Anemia</li> <li>(4) Palpable splenomegaly</li> </ol>

Table 92-8 2008 World Health Organization Diagnostic Criteria for Polycythemia Vera, Essential Thrombocythemia, and Primary Myelofibrosis

<sup>a</sup>Diagnosis of PV requires meeting either both major criteria and one minor criterion or the first major criterion and two minor criteria; diagnosis of ET requires meeting all four major criteria; diagnosis of PMF requires meeting all three major criteria and two minor criteria.

<sup>b</sup>Small to large megakaryocytes with aberrant nuclear/cytoplasmic ratio and hyperchromatic and irregularly folded nuclei and dense clustering. <sup>c</sup>or Hgb or Hct > 99th percentile of reference range for age, sex, or altitude of residence or red cell mass >25% above mean normal predicted.

Hgb, hemoglobin, Hct, hematocrit; Epo, erythropoietin; EEC, endogenous erythroid colony; WHO, World Health Organization; CML, chronic myelogenous leukemia; MDS, myelodysplastic syndrome; LDH, lactate dehydrogenase.

From Tefferi A. Essential thrombocytopenia, polycythemia vera, and myelofibrosis: Current management and the prospect of targeted therapy. Am J Hematol. 2008;83:491–497. Copyright 2008, John Wiley & Sons. Reprinted with permission of John Wiley & Sons, Inc.

as infections, inflammation, trauma, asplenia, anemia, drug reactions, and malignancies increase endogenous levels of the thrombopoietin, interleukin-1, interleukin-6, interleukin-11, other cytokines, and catecholamines that appear to be involved with increasing platelet production.

### **Thrombocytosis Treatment**

The greatest challenge in formulating a treatment plan for ICU patients is to correctly diagnose the cause of thrombocytosis. Treatment for patients with reactive thrombocytosis should be directed at the underlying disease. The abnormal platelet count itself does not increase the risk for thrombotic complications. Therefore, antiplatelet or platelet-lowering therapy is not indicated. In contrast, clonal thrombocytosis often requires treatment to reduce platelet counts, especially for high-risk patients.<sup>48</sup> This group includes those with a history of bleeding or thrombotic complications, age greater than 60 years, other cardiovascular risk factors, or extremely high platelet counts (>1500 × 10<sup>9</sup>/L) (Table 92-9).<sup>49</sup>

Some of the agents employed to decrease platelet counts include hydroxyurea, interferon- $\alpha$ , and anagrelide. Low-dose aspirin (40 to 325 mg) has been used to reduce the risk for thrombosis in patients with thrombocytosis with platelet counts less than  $1500 \times 10^9/L$ .<sup>50</sup> A multicenter, open-label, randomized trial in 815 patients with

essential thrombocythemia at high risk for vascular events concluded that hydroxyurea plus low-dose aspirin was superior to anagrelide plus low-dose aspirin. Anagrelide plus aspirin was associated with increased rates of arterial thrombosis (P = .004), serious hemorrhage (P = .008), and myelofibrotic transformation (P = .01) but a decreased rate of venous thromboembolism (P = .006).<sup>51</sup> Platelet apheresis and phlebotomy have been used to rapidly decrease platelet counts in patients with life-threatening complications from thrombocytosis. An algorithmic approach to the management of thrombocytosis is depicted in Figure 92-2.

### FUNCTIONAL PLATELET DISORDERS

Platelets play a key role in both hemostasis and thrombosis. Therefore, platelet function is important in the ICU patient, particularly those with bleeding risk. A number of platelet function tests are available for clinical diagnostic testing (Table 92-10).

### **Normal Platelet Function**

Under normal conditions, platelets circulate as inactive discoid anuclear cell fragments. These must be "activated" by molecules, such as collagen, thromboxane A2, adenosine diphosphate, and thrombin exposed by damage to

### Table 92-9 Risk Stratification for Treatment of Patients with Essential Thrombocythemia

MRC PT1 criteria	Italian Society of Haematology practice guidelines (Barbui et al, 2004)	Elliott and Tefferi (2005)
Low risk		
Patients aged < 40 years with all of the following: NO prior thrombosis NO hypertension or diabetes Platelet count < 1000-1500 × 10 <sup>9</sup> /L	Patients <40 years AND platelet count < $1500 \times 10^9$ /L AND no prothrombotic comorbidity or 40-60 years AND platelet count 1000-1500 × $10^9$ /L NO vascular risk factors/familial thrombophilia or 40-60 years AND platelet count < $1000 \times 10^9$ /L NO vascular risk factors/familial thrombophilia	None of factors below
Recommentation. uspirin atone		Recommentation. nu
Intermediate risk Patients aged 40-60 years with all of the following: NO prior thrombosis NO hypertension or diabetes Platelet count < 1000-1500 × 10 <sup>9</sup> /L	40-60 years AND platelet count < 1000 × 10 <sup>9</sup> /L AND vascular risk factors/familial thrombophilia	or <60 years, NO thrombosis + either platelet count >1500 $\times$ 10 <sup>9</sup> /L or cardiovascular risk factor (e.g., smoking, diabetes)
Recommendation: randomize aspirin versus HU + aspirin	Recommendation: no consensus on treatment	Recommendation aspirin + no consensus
High risk		
Patients either age >60 years or with one of the following: Prior thrombosis or hemorrhage Hypertension or diabetes Platelet count > 1000 × 10 <sup>9</sup> /L (1500 <60 years)	ANY of age > 60 years, prior thrombosis/ hemorrhage, platelet count > $1500 \times 10^9$ /L OR <40 years AND prothrombotic comorbidity AND platelet count < $1500 \times 10^9$ /L OR 40-60 years, platelet count 1000-1500 × $10^9$ /L AND vascular risk factor/familial thrombophilia	Age >60 years OR thrombosis
Recommendation: HU + aspirin for most patients	Recommendation HU (if >60 years OR 40-60 years AND major thrombosis with aspirin) Anagrelide/ Interferon (if age <40 years OR 40-60 years NO major thrombosis)	Recommendation >40 years HU, <40 years HU or interferon

From Harrison CN. Essential thrombocythaemia: Challenges and evidence-based management. Br J Haematol. 2005;130:153–165.



Figure 92-2. Approach to the management of thrombocytosis. (From Schafer AI. Thrombocytosis: Current concepts [review article]. N Engl J Med. 2004;350:1211–1219, Fig. 3.)

Table 92-10 Established Platelet Function Tests				
Platelet Function Test	Aspects of Platelet Function Measured	Advantages	Disadvantages	
Bleeding time	In vivo screening test	Physiological	Insensitive, invasive, and high inter-operator CV	
Aggregometry – turbidometric methods	Responsiveness to panel of agonists	Diagnostic	Labor intensive, non- physiological	
Aggregometry – impedance methods	Responsiveness to panel of agonists	Whole blood test	Insensitive	
Aggregometry & luminescence	Combined aggregation and ADP release	More information	Semi-quantitative	
Adenine nucleotides	Stored and released ADP	Sensitive	Specialized equipment	
Thromboelastography (TEG)	Global hemostasis	Predicts bleeding	Measures clot properties only, insensitive to aspirin	
Glass filterometer	High shear platelet function	Simple	Requires blood counter	
Platelet release markers—e.g., βTG PF4	<i>In vivo</i> platelet activation markers	Simple, systemic measure of platelet activation	Prone to artifact	

From Harrison P. Progress in the assessment of platelet function. Br J Haematol. 2000;111:733-744.

vascular endothelium.<sup>52</sup> Normal platelet activation involves four stages: adhesion, aggregation, secretion, and procoagulant activity.<sup>53</sup> For proper platelet function, many intracellular molecules and structures must be both present and working within the platelet. These structures include receptors (glycoprotein Ib/IX/V and glycoprotein IIB/IIIa), granules ( $\alpha$ -granules and dense granules), and membranes.<sup>54–57</sup> The function of each of these structures is detailed in Table 92-11.

### **Definition of Functional Platelet Disorders**

Any abnormality involving the structure of the platelet or its contents or interference with the process of platelet adhesion, aggregation, or secretion may result in a functional platelet disorder. Functional platelet disorders can be classified as either inherited or acquired. An algorithm for evaluating patients suspected of having a platelet disorder is depicted in Figure 92-3.<sup>54</sup>

Table 92-11 Platelet Struc	ctures and Their Associated Functions
Structure	Function
RECEPTORS	
Glycoprotein Ib/IX/V	Receptor for insoluble von Willebrand factor (vWF)
Glycoprotein IIb/IIIa	Receptor for fibrinogen, vWF, fibronectin, vitronectin, and thrombospondin
Glycoprotein VI	Collagen receptor
Glycoprotein Ia-IIa	Collagen receptor
GRANULES	
α-Granules	Contain adhesive proteins (vWF and thrombospondin, plasma proteins (immunoglobulin G and albumin), cellular mitogens (platelet-derived growth factor and transforming growth factor- $\beta$ ), coagulation factor V, and protease inhibitors ( $\alpha_2$ -macroglobulin and $\alpha_2$ -antiplasmin), which play an important role in hemostasis, inflammation, and wound repair
Dense granules (dense bodies or δ-granules)	Contain adenine nucleotides (adenosine diphosphate and adenosine triphosphate), ionized calcium, histamine, serotonin, and epinephrine, pyrophosphate, and polyphosphate
Lysosomes	Secrete acid hydrolazes, cathepsins D and E, elastase, and other degradative enzymes
PLASMA MEMBRANES	
Plasma membrane	Mucopolysaccharides for absorption of procoagulant plasma proteins
Submembrane	Receptor glycoproteins



**Abbreviations:** BT: bleeding time; PFA: Platelet function abnormalities; N: Normal; TTP: Thrombotic thrombocytopenia purpura; HUS: Hemolytic uremic syndrome; DIC: Disseminated intravascular coagulation; WBCs: White blood cell count; MYH9: Myosine heavy chain gene disorders; ITP: Immune thrombocytopenic purpura; vWD: von Willebrand's disease; TAR: Thrombocytopenia and absent radi; AD: Autosomal dominant; AR: Autosomal recessive; ADP: Adenosine diphosphate.

Figure 92-3. Algorithm for evaluation of a patient with suspected platelet disorders. (From Sharathkumar AA, Shapiro A. Platelet Function Disorders, 2nd ed. Treatment of Hemophilia Monograph. World Federation of Hemophilia; April 2008, No. 19.)

### **Acquired Platelet Disorders**

Functional platelet disorders are among the most common acquired hematologic abnormalities encountered in the ICU. They often are discovered incidentally on routine laboratory tests. Importantly, the degree of laboratory value derangement does not correlate with bleeding risk. The decision to treat an acquired functional platelet disorder is determined by clinical examination and risk to the patient. Acquired platelet disorders can be classified as intrinsic or extrinsic. Treatment of patients with acquired disorders of platelet dysfunction presenting with bleeding symptoms is quite complex and challenging. Recommendations for treatment are included in Table 92-12.

### **Inherited Platelet Disorders**

A number of patients may present with a prior diagnosis of an inherited platelet disorder. However, because a significant portion of inherited platelet disorders exhibit variable patterns of penetrance, a disorder may first be identified incidentally on routine laboratory tests. Operative procedures can uncover abnormalities in clot formation. Sepsis, organ failure, metabolic derangements, and drugs may exacerbate bleeding tendencies. A list of well-recognized inherited platelet disorders is listed in Table 92-13.<sup>58</sup>

### AUTHORS' RECOMMENDATIONS

- Platelet disorders are common in the ICU.
- Thrombocytopenia (defined as a platelet count of  $<150,000/mm^3$  or  $<150 \times 10^9/L$ ) is the most common platelet disorder (up to 50% of ICU patients) and is associated with adverse outcome.
- HIT is caused by an antibody that binds to the heparin-platelet factor IV complex on the platelet surface.
- The diagnosis of HIT should be considered when the platelet count falls to less than 150 × 10<sup>9</sup>/L (or >50% from baseline) between days 5 and 14 of exposure to any heparinoid product.
- Once HIT is suspected in a critically ill patient, prompt discontinuation of all heparin sources, including LMWH, is appropriate. In cases in which thrombosis places the patient at significant risk, substitution of an alternative anticoagulant (direct thrombin inhibitor) should be accomplished without waiting for laboratory confirmation of the presence of HIT antibodies.
- TTP most commonly presents with a *pentad* of thrombocytopenia (with purpura), red blood cell fragmentation, renal failure, neurologic dysfunction, and fever. Plasma exchange with FFP is the most effective treatment for this disorder.
- HUS is best treated with supportive therapy, including dialysis.
- Thrombocytosis (defined as a platelet count of >400,000/mm<sup>3</sup> or >400  $\times$  10<sup>9</sup>/L) is common (up to 25% of ICU patients) in critically ill patients and is associated with improved outcome. Secondary (reactive) thrombocytosis is the most common form of this disorder. It may occur in response to trauma, infection, and inflammation and usually does not require therapy.
- Functional platelet disorder in the ICU are common and may be acquired or hereditary.

Site of Platelet Dysfunction	Systemic Illness	Bleeding Severity	Potential Mechanism	Platelet Aggregation Abnormalities	Treatment
Intrinsic disorders of platelet function	Chronic myeloproliferative disorders	Mild to moderate	<ul> <li>Defect at the level of committed megakaryocyte:</li> <li>1) Abnormal lipid peroxidation and responses to thromboxane A2</li> <li>2) Subnormal serotonin uptake and storage</li> <li>3) Abnormal expression of Fc receptors</li> <li>4) Combined defect in membrane expression and activation of GPIIb/IIIa complexes</li> <li>5) Acquired storage pool disorder</li> <li>6) ↓ HMWM of plasma and platelet vWF</li> </ul>	Inconsistent or defective aggregation	• Treatment of underlying disorder
	Myelodysplastic syndrome/ leukemias	Mild to moderate	<ol> <li>Defective megakaryopoiesis:</li> <li>Dilated canalicular system and abnormal microtubular formation</li> <li>Reduced or giant granules may form by the fusion of several single granules</li> <li>Acquired membrane defect with abnormal glycoprotein expression</li> </ol>	Inconsistent or multiple aggregation defects	<ul> <li>Treatment of underlying disorder</li> <li>Amicar<sup>®</sup></li> </ul>
Extrinsic disorders of platelet function	Uremia	Mild	<ol> <li>Platelet GPIb/IX receptor number and function normal or ↓</li> <li>↓ shear-induced platelet aggregation with high shear rates, possibly due to ↑ proteolysis by</li> </ol>	↓ aggregation with collagen, ADP, and epinephrine	<ul> <li>Dialysis</li> <li>Correction of anemia</li> <li>DDAVP</li> <li>Conjugated estrogens</li> </ul>

### Table 92-12 Acquired Disorders of Platelet Dysfunction Presenting with Bleeding Symptoms

Site of Platelet Dysfunction	Systemic Illness	Bleeding Severity	Potential Mechanism	Platelet Aggregation Abnormalities	Treatment
			<ul> <li>ADAMTS13 vWF metalloprotease</li> <li>3) Defective activation-dependent receptor function GPIIb/IIIa for binding fibrinogen and vWF</li> <li>4) Defective platelet secretion of ADP</li> </ul>		<ul> <li>Platelet transfusion</li> <li>rFVIIa</li> <li>Cryoprecipitate</li> <li>Humate-P<sup>®</sup></li> </ul>
	Liver dysfunction	Mild to severe	Altered platelet membrane palmate and stearate metabolism	↓ aggregation to collagen, thrombin, ristocetin; absent secondary aggregation waves after aggregation with ADP and epinephrine	<ul> <li>Correction of underlying disorder</li> <li>Platelet transfusion</li> <li>DDAVP</li> </ul>
	Paraproteinemia	Mild to severe	Nonspecific binding of immunoglobulins to platelet surface +/- specific antigen/ antibody interactions	Defective aggregation	<ul> <li>Plasmapheresis</li> <li>Treatment of underlying disorder</li> <li>Platelet transfusions only during life-threatening bleeding</li> </ul>
	Disseminated intravascular coagulation		Platelet activation by thrombin acquired storage pool defect	↓ aggregation	<ul> <li>Treatment of underlying disorder</li> <li>Platelet transfusion</li> </ul>
	Cardiopulmonary bypass		<ol> <li>Platelet activation and fragmentation due to hypothemia, contact with fibrinogen-coated synthetic surfaces, contact with blood/ air interface, damage caused by blood suctioning, and exposure to traces of thrombin, plasmin, ADP, or complement</li> <li>Drugs (e.g., heparin, protamine, and aspirin<sup>®</sup>) and production of fibrin degradation products expected to impair platelet function</li> </ol>	Abnormal <i>ex vivo</i> platelet aggregation in response to several agonists, ↓ platelet agglutination in response to ristocetin, and poor release reaction due to deficiency of alpha and dense granules	<ul> <li>Platelet transfusion</li> <li>DDAVP</li> <li>Aprotinin</li> <li>Antifibrinolytics</li> <li>rFVIIa</li> </ul>
	Hypothermia		<ol> <li>↓ plasma soluble P-selection expression</li> <li>↓ levels of thromboxane B2</li> </ol>	$\downarrow$ platelet activation	Correction of hypothermia

### Table 92-12 Acquired Disorders of Platelet Dysfunction Presenting with Bleeding Symptoms-Cont'd

GP, glycoprotein; HMWM, high-molecular-weight multimers; vWF, von Willebrand factor; ADP, adenosine diphosphate; DDAVP, desmopressin (1-deamino-8-D-argine vasopressin); rFVIIa, recombinant factor VIIa. From Sharathkumar AA, Shapiro A. *Platelet Function Disorders*, 2nd ed. Treatment of Hemophilia Monograph. World Federation of Hemophilia; April 2008, No. 19.

Disorder	Defect	Diagnosis	Treatment
Bernard-Soulier syndrome	Glycoprotein Ib/IX deficiency	<ul> <li>Prolonged bleeding time</li> <li>Thrombocytopenia</li> <li>Giant platelets on peripheral blood smear</li> <li>Flow cytometry can demonstrate abnormalities of platelet membrane glycoprotein</li> <li>Do not aggregate in response to ristocetin</li> <li>Normal aggregation in response to adenosine diphosphate (ADP), epinephrine, and collagen.</li> </ul>	<ul> <li>Epsilon aminocaproic acid</li> <li>Desmopressin acetate (DDAVP)</li> <li>Platelet transfusions</li> <li>Recombinant activated factor VII</li> </ul>
von Willebrand disease	<ul> <li>Type I Partial deficiency of vWF</li> <li>Type II Qualitative deficiency of vWF</li> <li>Type IIA Selective absence of high- molecular-weight vWF multimers</li> <li>Type IIB Multimers with increased affinity for platelet GP Ib</li> <li>Type IIM Decreased platelet binding with normal high-molecular-weight vWF multimers</li> <li>Type IIN Decreased multimer affinity for FVIII</li> <li>Type III Complete vWF deficiency</li> <li>Mixed phenotype caused by compound heterozygosity</li> </ul>	<ul> <li>Normal platelet count and morphology</li> <li>Prolonged bleeding time</li> <li>Normal prothrombin time (PT)</li> <li>Variably decreased activated partial thromboplastin time (aPTT)</li> <li>Variably decreased FVIII activity (ristocetin cofactor)</li> <li>Variably decreased vWF antigen</li> <li>Abnormal platelet function test</li> <li>von Willebrand factor multimers test (classify type of vWD)</li> </ul>	<ul> <li>Desmopressin acetate (DDAVP)</li> <li>Factor VIII concentrate rich in von Willebrand factor infusions (Humate-P<sup>®</sup>, Alphanate<sup>®</sup> or Koate DVI<sup>®</sup>)</li> </ul>
Glanzmann's thrombasthenia	Glycoprotein IIb/IIIa deficiency (no <i>fibrinogen</i> bridging can occur)	<ul> <li>Prolonged bleeding time</li> <li>Failure of plugging on the Platelet Function Analyzer 100 (PFA-100)</li> <li>Flow cytometry and monoclonal antibodies confirm the diagnosis of Glanzmann thrombasthenia</li> <li>Aggregate in response to ristocetin</li> <li>Decreased aggregation in response to adenosine diphosphate (ADP), epinephrine, and collagen</li> </ul>	<ul> <li>Platelet transfusions</li> <li>Recombinant activated factor VII</li> </ul>
Gray platelet syndrome	Alpha-granules (Alpha Body) Deficiency	<ul> <li>Prolonged bleeding time</li> <li>Macrothrombocytopenia</li> <li>Gray platelets have large but few granules, giving them a gray appearance on Wright-Giemsa stained blood smear.</li> </ul>	<ul><li>Desmopressin acetate (DDAVP)</li><li>Platelet transfusions</li></ul>
Quebec platelet syndrome	increased storage of urokinase-type plasminogen activator (u-PA) causing degradation of platelet alpha-granule prote deficiency of α-decrease in alpha-granule multimerin	- Prolonged bleeding time	- abnormal aggregation with epinephrine
Chediak-Higashi syndrome	-Dense-granules (Dense Body) Deficiency	<ul> <li>Normal platelet count and morphology</li> <li>Prolonged bleeding time</li> <li>abnormal platelet aggregation</li> </ul>	- bone marrow transplant
Wiskott-Aldrich syndrome	- Thrombocytopenia - small platelets	- absent isohemagglutinins	<ul><li>platelet transfusions</li><li>Bone marrow transplantation</li></ul>

### Table 92-13 Hereditary Platelet Disorders

From Salles II, Feys HB, Iserbyt BF, et al. Inherited traits affecting platelet function. Blood Rev. 2008;22:155-172.

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# 93

# When Is Transfusion Therapy Indicated in Critical Illness and When Is It Not?

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Transfusion of blood products is one of the most common therapies ordered in the intensive care unit (ICU). It is estimated that 4 million patients are transfused a total of 8 to 12 million units of packed red blood cells (PRBCs) annually in the United States alone and that most transfusions occur either in surgical or critically ill patients. Several studies in various countries have documented that the incidence of PRBC transfusion in the ICU varies between 20% and 50% (Table 93-1).<sup>1–5</sup> In addition to anemia, about 40% of critically ill patients have a low platelet count or elevation in their coagulation parameters at some point during their ICU stay. Most of these hematologic derangements, however, are asymptomatic, and numerous studies in the past decade have shown that outcome is either not changed or worsened following transfusion to normalize these values. Although there are some well-designed trials that can be used to formulate guidelines regarding transfusion of PRBC in critically ill patients, there are no good studies that can be used to determine which patients benefit and which do not from platelet or plasma transfusion in the ICU. This chapter reviews the available evidence on best transfusion practices in the ICU, including a review of the use of recombinant factor VIIa.

### BASIS FOR TRANSFUSION OF BLOOD PRODUCTS: BENEFITS AND RISKS

Outcomes related to transfusion practices are only now being studied in well-designed prospective trials. Although there are many trials related to transfusion of PRBC, there is a dearth of information related to practice patterns and outcomes from use of non-red blood cell products. The few data that do exist appear to suggest the same riskbenefit effects as have been found for PRBC transfusion. However, these findings need to be validated using welldesigned multicenter studies.

### Packed Red Blood Cell Transfusion

The normal blood volume is 7% to 8% of ideal body weight. This corresponds to a hemoglobin level of 14 to 16 g/dL and a hematocrit of 40% to 45%. Transfusion of

red blood cells can help restore both circulating blood volume and oxygen carrying capacity, as described by the following formula:

$$Vo_2 = CO \times Cao_2$$

where Cao<sub>2</sub> is arterial oxygen content (mg%/L) and equals  $[1.39*(Sao_2)*(Hb) + 0.003 \times Pao_2]$  and Vo<sub>2</sub> is oxygen delivery (g%/min), Hb is hemoglobin level (g/dL), CO is cardiac output (L/min), Sao<sub>2</sub> is arterial oxygen saturation (%), and Pao<sub>2</sub> is arterial oxygen tension (mm Hg). Most often, attempts are made to increase O<sub>2</sub> delivery by increasing the oxygen saturation or hemoglobin concentration because increasing cardiac output significantly will result in increased myocardial oxygen consumption. This will increase demand and may precipitate ischemia in patients with coronary artery disease.<sup>6</sup>

Anecdote and historical practice dictated that the ideal hemoglobin/hematocrit value in hospitalized patients is 10 g/dL or 30%. The basis for this claim lies in part on rheologic calculations suggesting that this was the level at which there was an optimal balance between oxygen carrying capacity (where high is better) and viscosity (where low is better). Such a balance would minimize cardiac work and maintain peripheral oxygen delivery. As recently as the 1990s, this recommendation was supported, in part, by two large retrospective studies in Jehovah's Witness populations that showed a significant increase in perioperative mortality if the preoperative hemoglobin was 6 g/dL as opposed to 12 g/dL (odds ratio of 2.5 for each gram that the postoperative hemoglobin was less than 8 g/dL).<sup>7,8</sup> The risk for death was highest in patients with known cardiovascular disease. Unfortunately, these findings have not been validated prospectively.

In a single prospective randomized blinded study, blood transfusion, used as part of a "sepsis bundle," was found to improve survival in patients with septic shock whose hemodynamic parameters did not correct with intravenous fluids.<sup>9</sup> However, because the interventions in this study were delivered as a bundle, it is not possible to determine the relative effect of transfusion alone on outcome. Three smaller randomized studies have found that PRBC transfusion does not improve oxygen delivery
Table 93-1 Prevalence of Transfusion in Critical Care Units							
Study	No. of Subjects	Percentage Transfused	Study Design				
Vincent et al, 2002 <sup>5</sup>	1307	53	Multinational, prospective, observational				
French et al, 2001 <sup>1</sup>	1808	20	Multinational, prospective, observational				
Walsh et al, 2004 <sup>2</sup>	1023	40	Multicenter, prospective, observational				
Corwin et al, 2004 <sup>3</sup>	4892	44	Multicenter, prospective, observational				
Rao, 1999 <sup>54</sup>	1247	53	Retrospective, subgroup analysis				
Hebert et al, 1999 <sup>4</sup>	5298	25	Prospective, randomized, blinded trial				

or uptake in septic patients in the ICU, but these studies were not powered adequately to detect how transfusion may alter overall outcome.<sup>10-12</sup> A large retrospective study in trauma patients found that patients who manifest metabolic acidosis as measured by base deficit on arrival to the hospital require blood transfusion to maintain adequate hemodynamic parameters and oxygen delivery.<sup>13</sup> However, although many practitioners would advocate transfusing hemodynamically unstable or acidemic patients to a hemoglobin value of 10 mg/dL, the appropriate hemoglobin level for this patient population has not been evaluated prospectively at this time.

Many recent studies have addressed the role of PRBC transfusion in asymptomatic, hemodynamically stable, nonbleeding, anemic critically ill patients. A single randomized blinded prospective study in 1999 and several subsequent observational studies found that patients who are transfused above a hemoglobin value of 7 g/dLhave either the same or better outcomes than those who are transfused to a hemoglobin value of 10 g/dL.<sup>3–5</sup> These findings are consistent with many other studies and one meta-analysis that also document an increased risk for infection after PRBC transfusion (Table 93-2).<sup>3,5,14-21</sup> Other studies have documented an increased risk for death after RBC transfusion.<sup>3,5</sup> Based on these studies, current guidelines regarding PRBC transfusion in critically ill but asymptomatic and resuscitated (i.e., hemodynamically normal) patients call for a hemoglobin transfusion trigger of 7 g/dL (Table 93-3). Patients with evidence of ongoing bleeding or end-organ dysfunction, specifically unstable angina or acute coronary syndrome, were excluded from all clinical trials.

Transfusion of blood products carries many risks. These include transmission of blood-borne pathogens, transfusionassociated circulatory overload (TACO), transfusion-related acute lung injury (TRALI), and transfusion-related immunomodulation (TRIM). Clinically significant transfusion reaction is rare under current guidelines and is most commonly due to clerical error. Interestingly, this adverse event is rarely seen in exsanguinating patients. Although the reason for this is uncertain, it is likely due to alterations in the immune system resulting from severe injury and massive transfusion.<sup>22</sup> TRALI and TRIM most likely are variants of the same disorder— an exaggerated inflammatory response and altered or deranged immune system due to transfusion of foreign protein.<sup>23</sup> Both entities are likely under-reported owing to lack of

#### Table 93-2 Incidence of Postoperative Infection in Transfused Patients<sup>16</sup>

Study*	No. of Subjects Transfused (Percentage Infected)	No. of Subjects Not Transfused (Percentage Infected)
Chang, 2000	282 (26)	1067 (14)
Tartter, 1998	59 (44)	162 (11)
Houbiers, 1999	446 (39)	251 (23)
Koual, 1997	395 (27)	292 (16)
Vignali, 1995	48 (33)	75 (9)
Heiss, 1993	58 (27)	62 (12)
Agarwal, 1993	1355 (34)	4011 (9)
Ford, 1993	778 (9)	345 (2)
Edna, 1992	125 (22)	359 (5)
Jensen, 1992	104 (13)	93 (2)
Doersten, 1992	51 (47)	53 (27)
Johnson, 1992	138 (16)	79 (9)
Fernandez, 1992	254 (7)	122 (5)
Trivlzi, 1992	24 (21)	85 (4)
Murphy, 1991	50 (32)	34 (3)
Wobbes, 1990	260 (40)	288 (29)

\*Data from Hill GE, Frawley WH, Griffith KE, et al. Allogeneic blood transfusion increases the risk of postoperative bacterial infection: A metaanalysis. *J Trauma*. 2003;54:908–914. Refer to this source for complete references on these studies.

unique diagnostic criteria and adequately designed studies aimed to address their incidence. TRALI is defined as noncardiogenic pulmonary edema that occurs within 4 hours of transfusion. TRALI has a reported incidence of 1 in 5000 to 10,000 transfusions<sup>24</sup> and is most common following transfusion of plasma. TRIM is best exemplified by reports showing the association between PRBC transfusion and infection<sup>15,16,18,19,25,26</sup> and reports documenting a chimeric state in which donor leukocytes can be found in the peripheral blood of transfused trauma patients

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Component	Recommendations	Comment
Packed red blood cells	Transfusion trigger: Hemoglobin of 7 Hemoglobin of 10	Resuscitated, nonbleeding, well-perfused patients Unstable angina, end-organ hypoperfusion Appropriate transfusion trigger remains undetermined in pregnancy and liver disease.
Fresh-frozen plasma	Transfuse 10-15 mL/kg	Indicated for coagulopathy (e.g., warfarin reversal), active hemorrhage, planned procedure with high risk for bleeding in coagulopathic patients, and known factor deficiency
Cryoprecipitate	10-pack transfusion	Indicated coagulopathy due to hypofibrinogenemia, reversal of thrombolytic therapy, von Willebrand deficiency with severe bleeding, disseminated intravascular coagulation
Platelets	Transfusion trigger Platelet count of 12,000 Platelet count of 50,000 Platelet count of 100,000	Risk for spontaneous bleeding Risk for bleeding (i.e., trauma, postoperative status) Patient with a risk for ongoing bleeding or intracranial hemorrhage

Table 93-3 Suggested Guidelines for Blood Component Therapy

years after the transfusion.<sup>27–29</sup> Mechanisms underlying TRIM are only now being elucidated.<sup>23</sup>

#### **Plasma Transfusion**

The plasma portion of donated whole blood contains most of the necessary clotting factors of the coagulation cascade. However, there are decreased concentrations of factors V, VII, and VIII due to degradation and of fibrinogen (factor I) due to dilution. It is dosed as 15 mL/kg (ideal body weight), and generally 4 U results in 40% factor recovery.<sup>30</sup> It is vital to know this dosing regimen because plasma is frequently underdosed; most patients require at least 4 U (1 L) of plasma to reverse coagulopathy effectively, assuming that acidosis and hypothermia are also addressed. Plasma is commonly used in the ICU to rapidly treat coagulopathy with concomitant hemorrhage or in anticipation of an invasive procedure in a coagulopathic patient. Coagulopathy may result from treatment with warfarin or other exogenous anticoagulants. A retrospective study found that each 30-minute delay in administration of the first unit of plasma decreases the odds of correction of warfarin-induced coagulopathy by 20% in patients with intracerebral bleeding, underscoring the need for rapid and accurate reversal of the drug.<sup>31</sup>

There is wide variability in the manner in which physicians use fresh-frozen plasma (FFP) in nonbleeding coagulopathic patients.<sup>32</sup> Many physicians use FFP prophylactically to reverse coagulopathy in nonbleeding patients despite published guidelines recommending against this and an unknown risk-to-benefit ratio.<sup>33,34</sup> Others cite mild coagulopathy as a reason to use FFP as a volume expander in nonbleeding volume-depleted patients.<sup>35</sup> To date, there are no universally agreed on guidelines for use of FFP in nonbleeding patients. Suggested indications and dosing are shown in Table 93-3.

Transfusion of plasma has the same risks as transfusion of red blood cells, but the incidence of adverse events is higher for all possible complications. The most frequent adverse event associated with plasma transfusion is TRALI. Recent theory postulates that this reflects variability in plasma protein (and presumably antibody) content in the fluid being transfused.<sup>24</sup> This proposed mechanism is supported by a randomized blinded crossover study that found that this risk is higher following transfusion of plasma obtained from multiparous women.<sup>36</sup> A recent retrospective study found a relative risk for infection of 3 in critically ill surgical patients who received FFP, a finding that is consistent with the risk for infection after PRBC transfusion.<sup>37</sup> Hemolytic transfusion reactions also are possible after transfusion of plasma because plasma contains variable titers of anti-A and anti-B antibody.

#### Cryoprecipitate Transfusion

Cryoprecipitate is the precipitated fraction obtained from thawing FFP at 4°C. This method of isolation means that cryoprecipitate is pooled from the FFP obtained from multiple donors. Cryoprecipitate is rich is factor VIII, von Willebrand factor, factor XIII, and fibronectin. Most importantly, it is the only blood component that contains concentrated fibrinogen and thus the main indication for use is in treatment of coagulopathy due to hypofibrinogenemia.<sup>34</sup> Therefore, it may be useful in the management of disseminated intravascular coagulation with hemorrhage and in reversal of thrombolytic agents. Dosed adequately, plasma can also be used to replete fibrinogen, but hypofibrinogenemia can be reversed more quickly using cryoprecipitate. Cryoprecipitate is dosed as a 10-pack transfusion; each 10-pack raises the fibrinogen level 75%.30 Bleeding patients with known von Willebrand factor deficiency also should received cryoprecipitate to optimize platelet function, whereas nonbleeding patients with this disorder can be treated with desmopressin (DDAVP; see Table 93-3).

Risks associated with transfusion of cryoprecipitate are the same as those reported for the other blood components. However, the incidence of TRALI and TRIM is probably lower than that associated with transfusion of plasma because the total volume of cryoprecipitate transfused is much less than plasma, minimizing the recipient's exposure to foreign protein antigen. The risk for transmission of blood-borne pathogens, however, may be higher because of the pooled nature of this product. There are no well-designed studies assessing outcomes or adverse events related to transfusion of cryoprecipitate.

#### Platelet Transfusion

Platelet transfusion is less common than red blood cell or plasma transfusion. Despite the fact that the platelet count can be determined easily and quickly, there is no reliable method to test platelet function. The sole possible exception is thrombelastography. Although the absolute platelet count may be falsely reassuring because it may not correlate with function, it is generally agreed that spontaneous bleeding can occur with platelet counts less than 12,000 cells/µL. Although not validated in studies, many clinicians recommend that a minimal platelet count of 50,000 cells/ $\mu$ L should be maintained, if possible, for patients at significant risk for bleeding (e.g., trauma or postoperative patients), and a target of 80,000 to 100,000 cells/ $\mu$ L is recommended for patients who are bleeding or at risk for intracranial hemorrhage. These are also the levels that most surgeons agree are needed to allow for general surgical and neurosurgical intervention, respectively.

There are no studies that can be used to recommend timing and volume of platelet transfusion in nonbleeding critically ill patients. Further, although there are no good studies to determine the impact that use of aspirin or nonsteroidal anti-inflammatory drugs have on hemorrhage after injury, a review of the literature suggests that use of aspirin may worsen intracranial hemorrhage after traumatic brain injury.<sup>38</sup> An open-label, ex vivo study in volunteers showed that platelet transfusion can reverse the platelet dysfunction caused by clopidogrel,<sup>39</sup> and platelet transfusion may be prudent in patients with traumatic brain injury who were prescribed antiplatelet medications, including nonsteroidal anti-inflammatory drugs. The efficacy of platelet transfusion to reverse the effects of antiplatelet medications for other causes of hemorrhage remains speculative. Suggested guidelines regarding platelet transfusion are noted in Table 93-3.

#### MASSIVE EXSANGUINATION AND TRANSFUSION

Patients requiring massive transfusion are a unique cohort in whom aggressive transfusion is needed for hemodynamic support and reversal of coagulopathy. The most commonly used definition of massive transfusion is transfusion of 10 U of PRBC within 24 hours. This definition, however, does not direct attention to the coagulopathy that also exists in these patients and fuels the process underlying the hemorrhage.<sup>40</sup> Most recently, noncontrolled and retrospective studies from the military suggest that aggressive transfusion using PRBC-to-plasma ratios that approach 1:1 may result in earlier arrest of hemorrhage and mortality benefit.<sup>41</sup> Although these findings need to be substantiated in larger, prospective studies, it is prudent to treat exsanguinating patients with aggressive transfusion of PRBC, plasma, and platelets, while also preventing hypothermia, acidosis, and other causes of ongoing coagulopathy.

#### **RECOMBINANT FACTOR VIIA**

#### Mechanism of Action and Clinical Use

Recombinant factor VIIa is approved for use in hemophiliacs with antibody to factor VIII or IX. However, many case reports and small series found that it also may have a role in arresting hemorrhage from other causes. Recombinant factor VIIa works by binding to exposed tissue factor in an area of endothelial injury, thereby activating platelets and forming a platelet plug. It then stimulates the coagulation cascade by activating thrombin on the platelet plug. Fibrinolysis is inhibited through factor VIIa-mediated activation of thrombin-activatable fibrinolysis inhibitor.

Factor VIIa has been shown to decrease or arrest hemorrhage after injury. Two parallel randomized blinded placebo-controlled studies found that the drug was associated with a 50% relative reduction in severity of hemorrhage in bluntly injured patients but was not found to have a transfusion-sparing effect in victims of penetrating trauma.<sup>42</sup> However, the doses used in these studies were much higher than the commonly accepted dose of 90  $\mu$ g/kg, a difference that has substantial cost implications in this expensive drug. Nonrandomized case series and anecdotal reports suggest that a dose of 90  $\mu$ g/kg also has a transfusion sparing effect, but this has not been systemically studied in humans. Further, no study has shown mortality benefit associated with use of factor VIIa.

Off-label use of factor VIIa has also been studied in other conditions.<sup>43</sup> Despite initial reports that factor VIIa may decrease the severity of spontaneous intracranial hemorrhage,<sup>44</sup> a large randomized controlled trial did not find any difference in mortality or neurologic outcome with administration of this drug.<sup>45</sup> In a randomized study, recombinant factor VIIa was shown to decrease the incidence of rebleeding in patients with esophageal varices, but patients required a total dose of  $800 \,\mu\text{g/kg}$  over 30 hours.<sup>46</sup> This again calls the cost-efficacy of this agent into question. Many case reports and small series suggest that factor VIIa also may be effective in arresting postpartum hemorrhage, but prospective studies are needed to validate these findings.<sup>47-50</sup> Lastly, a series of case reports and retrospective reviews suggest that factor VIIa can be used to rapidly reverse the anticoagulant effects of warfarin. However, once again, prospective studies have not been performed to validate these findings or to determine how the reversal affects ultimate clinical outcome.

Uncontrolled case series and retrospective reports suggest that factor VIIa is most effective when administered early in exsanguinating patients (before 8 U of PRBC have been transfused).<sup>51</sup> Further the efficacy of this agent is markedly diminished if the pH is less than 7.1, the platelet count is less than 50,000 cells/mL, the prothrombin time is greater than 17.6 seconds, or the lactate is greater than 13 mg/dL.<sup>52</sup>

#### Adverse Events Associated with Recombinant Factor VIIa

Factor VIIa has been associated with thromboembolic complications, particularly when used in an off-label fashion. This is especially true in patients older than 55 years because this cohort is likely to have ulcerated plaque (with exposed tissue factor) due to atherosclerosis. Reports from the U.S. Food and Drug Administration suggest that the incidence of thromboembolic disease is 0.02% when the drug is used in hemophiliac patients, but the incidence of myocardial infarction, stroke, or pulmonary embolism may be as high as 8% when the agent is used in other populations.<sup>53</sup> Moreover, there is an almost equal incidence of arterial and venous thrombi after administration of the drug.

#### CONCLUSION

There remains a paucity of high-level evidence to guide transfusion practice in the ICU. The robust studies performed to date argue for a restrictive policy of PRBC transfusion in critically ill patients who are not hemorrhaging and are not manifesting signs of end-organ ischemia. Similarly, patients who have other asymptomatic derangements in coagulation should not be transfused unless an invasive procedure with propensity for hemorrhage is planned. Patients who require ongoing transfusion support should be treated aggressively with transfusion of PRBC, plasma, and platelets based on low-level studies from the military. Future studies specifically evaluating the latter recommendation are needed.

#### **AUTHORS' RECOMMENDATIONS**

- PRBC transfusion is used to augment the oxygen carrying capacity of blood.
- The PRBC evidence-based transfusion trigger in critically ill, resuscitated patients is a hemoglobin level of 7 g/dL.
- The PRBC transfusion trigger in patients with end-organ dysfunction or shock remains uncertain. Common practice uses a hemoglobin level of 10 g/dL as a trigger for transfusion if the patient fails crystalloid resuscitation.
- Complications of PRBC transfusion can be grouped into transfusion reaction (clerical), volume overload (TACO), and immune dysfunction (TRALI and TRIM).
- FFP transfusion is used to reverse diffuse coagulopathy and is dosed as 15 mL/kg.
- · FFP transfusion is the highest association with TRALI.
- Cryoprecipitate contains factor VIII, von Willebrand factor, factor XIII, and fibronectin.
- Cryoprecipitate transfusion is used to treat disseminated intravascular coagulation or to reverse thrombolytic-induced hemorrhage (i.e., hypofibrinogenemia).
- Platelet transfusion can be used to reverse clopidogrel-induced (and possibly aspirin-induced) thrombocytopathy.
- A platelet count of 50,000 to 100,000 cells/dL is needed for operation, depending on the nature of the procedure planned.
- Other than thromboelastography, there is no readily available test to evaluate platelet function clinically.
- Retrospective studies suggest that a PRBC/FFP/platelet ratio approaching 1:1:1 may decrease net transfusion needs.
- Recombinant factor VIIa may decrease net transfusion needs but has not been shown to affect survival.
- Use of Factor VIIa is associated with a high rate of thromboembolic arterial and venous complications in patients older than 55 years.

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## 94 Is There a Better Way to Deliver Optimal Critical Care Services?

#### Jeremy M. Kahn

Critical illness is defined by a high risk for morbidity and mortality. The mortality rate is about 5% among all hospitalized patients but approaches 15% among patients admitted to an intensive care unit (ICU).<sup>1</sup> In fact, in some critical illness syndromes, such as sepsis and acute lung injury, the death rate can approach 50%.<sup>2,3</sup> Critical care also is extremely costly. ICU costs represent about 15% of all hospital costs, and, in the United States, the total cost of critical care services is estimated at 1% of the gross product.<sup>4</sup>

Given the social and financial investment we have in critical care, it is remarkable how little attention has been paid to the organization of critical care services. For most of their history, ICUs were physically separate from other areas of the hospital but were managed in a manner that was similar to other wards. No special attention was paid to physician staffing patterns or team-based approaches to care. Only recently have industrialized countries set out to standardize the way ICUs are organized. Several factors have contributed to this newfound interest. These include the development of intensive care medicine as a separate physician specialty, the rise of the patient safety and quality movements, and spiraling health costs for the sickest hospitalized patients. Payers, government agencies, and regulators are now extremely interested in how to optimally organize critical care to maximize patient-centered outcomes and minimize costs.<sup>5</sup> Additionally, for the first time, there is a significant evidence base regarding how ICUs should be structured and managed. We can now use the tools of evidence-based medicine to inform our decisions about how to best organize critical care resources and delivery.

#### INTENSIVIST-LED, MULTIDISCIPLINARY CARE

The current gold standard for the organization of critical care services is the intensivist-led, multidisciplinary care team. This care model is usually led by a board-certified intensivist who provides direct care to all critically ill patients in the ICU. The intensivist also is responsible for overseeing a multidisciplinary, collaborative team of nurses, clinical pharmacists, respiratory therapists, and nutritionists. Under this care model, the primary physician either cedes responsibility for care to the ICU team or maintains some decision-making capacity, with the intensivist functioning as a consultant. Intensivist-led multidisciplinary care is endorsed by clinician specialty organizations and business groups as a key evidence-based practice in the management of critically ill patients.<sup>6–8</sup>

To date, two systematic reviews have examined the effect of intensivist physician staffing on patient outcomes.9,10 The first review identified nine studies that examined the relationship between increasing the intensity of physician ICU coverage and in-hospital mortality.<sup>9</sup> The unadjusted relative-risk reduction under a higher intensity model ranged from 15% to 60%. Under a range of conservative assumptions, the authors estimated that about 50,000 lives per year could be saved in the United States were full-time intensivist staffing to be fully adopted in urban areas. The second systematic review examined the effect of high-intensity physician staffing on multiple different outcomes, including mortality and length of stay.<sup>10</sup> These authors identified 16 studies that reported hospital mortality and 18 studies that reported hospital length of stay. In the unadjusted meta-analysis, high-intensity staffing was associated with a significant reduction in hospital mortality (risk ratio, 0.71; 95% confidence interval, 0.62 to 0.82) and hospital length of stay.

A major limitation of the studies in these systematic reviews is that most were single-center, before-after studies, frequently performed in academic hospitals. This design carries several potential biases. These include confounding due to time trends, coincident interventions, and variation in case-mix as well as problems of external validity. Additionally, the studies examined widely varying organizational changes. These ranged from daily rounds by an intensivist to completely closing the ICU. Without a standard definition of what constitutes highintensity staffing, we can only conclude that more intensivist involvement is probably better. It is not clear which specific care model is ideal. Since the publication of these reviews, the evidence base has been broadened somewhat. Several multicenter, cross-sectional studies that better adjust for differences in severity of illness and case-mix between care models are now available (Table 94-1).<sup>11-16</sup> With one exception, these studies provide consistent evidence in support of the intensivist physician staffing model. Although these observational studies do not provide definitive evidence that higher-intensity staffing is causally

Table 94-1 Summary of Multicenter Cohort Studies on Intensivist Physician Staffing for Critically III Adults

Study	Population	No. of Centers	No. of Patients	Outcome Measure	Risk Estimate*
Pronovost et al, 1999 <sup>11</sup>	Abdominal aortic surgery	46	2987	In-hospital mortality	0.33 (0.20-0.52)
Diringer & Edwards, 2001 <sup>12</sup>	Intracerebral hemorrhage	42	1038	In-hospital mortality	0.39 (0.22–0.67)
Dimick et al, 2001 <sup>13</sup>	Esophageal resection	35	366	In-hospital mortality	0.66 (0.16–2.5)
Nathens et al, 2006 <sup>14</sup>	Trauma	68	2599	In-hospital mortality	0.78 (0.58-1.04)
Treggiari et al, 2007 <sup>15</sup>	Acute lung injury	23	1075	In-hospital mortality	0.68 (0.53–0.89)
Levy et al, 2008 <sup>16</sup>	All ICU patients	100	101,832	In-hospital mortality	1.40 (NP)

\*Adjusted odds ratio or risk ratio comparing patients managed under a high-intensity staffing model with patients managed under a low-intensity staffing model. Definitions of high- and low-intensity staffing models differed among studies; high-intensity typically refers to complete transfer of care to an intensivist or a mandatory consult model.

NP = not provided.

related to improved outcomes in the ICU, they add to the wealth of supporting evidence in favor of intensivist physician staffing.

Care delivery that includes the active participation of pharmacists, nutritionists, and respiratory therapists is the second component of the intensivist-led, multidisciplinary care model. Multidisciplinary care makes intuitive sense but lacks the same evidence base as intensivist physician staffing. Lower nurse-to-patient ratios, pharmacist participation on rounds, and a team approach may result in lower mortality, reduced errors, and shortened length of stay.<sup>17–21</sup> One large, state-wide study showed that daily interdisciplinary rounding is associated with lower mortality, an effect seen even in ICUs without intensivist physician staffing.<sup>22</sup> Two studies have examined interdisciplinary communication and collaboration using validated instruments to measure the relationship between ICU climate and outcome.<sup>23,24</sup> Neither study was able to show a significant relationship between climate and mortality, although one found lower resource use in ICUs with improved workplace climate.<sup>23</sup>

Taken together, the above evidence suggests that the intensivist-led, multidisciplinary care model results in improved outcomes in the ICU. This care model may not, however, be viable in all ICUs. There is a significant lack of trained intensivists to provide care that precludes their involvement in the care of every critically ill patient. Current evidence suggests that only a small fraction of ICUs are staffed with intensivists.<sup>25</sup> This problem is expected to worsen as the population ages and demand for critical care services rises.<sup>26</sup> The intensivist physician workforce shortage is echoed in other fields-critical care nurses, pharmacists, and respiratory therapists are all in short supply.<sup>7</sup> Even if we wanted to adopt the intensivist-led multidisciplinary care model in every ICU, it would be impossible given the current state of the critical care workforce. Many other barriers to universal adoption of intensivist staffing exist. These include nonintensivist concerns about losing autonomy and income as well as hospital concerns about the costs of implementation of full-time intensivist staffing.<sup>27</sup> Further, intensivists by themselves clearly are not a cure for poor quality. Several studies documenting deficiencies in the use of lungprotective ventilation for acute lung injury were performed in ICUs with full-time intensivist staffing,<sup>28,29</sup> and not all studies of intensivist staffing have shown a mortality benefit.<sup>16</sup>

#### **ALTERNATIVE CARE MODELS**

Given the limitations of universal intensivist staffing, it is important to think about the mechanism by which intensivists improve outcomes and whether these improvements can be achieved in other ways. Intensivists may directly increase use of evidence-based care practices or may simply be a marker for other organizational factors associated with improved quality of care.<sup>30</sup> If the latter is true, it may be possible to expand access to high-quality critical care in ways other than universal intensivist staffing.

#### **Protocol-Based Care**

Protocols are decision-making tools in which differential interventions are applied based on explicit directions and regular patient assessments. Whether implemented by physicians, nonphysician providers, or technologic adaptations, protocols serve to standardize care practices, reduce unnecessary variation in care, and aid in the implementation of evidence-based therapies.<sup>31</sup> Multiple different protocols have been associated with improvements in the quality of critical care. These include protocols for sedation, weaning, lung-protective ventilation in acute lung injury, early adequate resuscitation in severe sepsis, and intensive insulin therapy in post–cardiac surgery patients.<sup>32–37</sup>

Protocol-based care offers a unique opportunity to improve care for patients who do not have access to a dedicated intensivist. Many protocols can be implemented by nurses, pharmacists, and respiratory therapists. Hospitalists specializing in acute care might be able to provide necessary physician services in the ICU with minute-to-minute care decisions governed by protocols.<sup>38</sup> This is not to say that protocols are superior to major decisions made by a qualified intensivist. In settings with optimal physician staffing, protocols have not consistently resulted in improved outcomes.<sup>39</sup> However, few ICUs are staffed with the trained intensivists and multidisciplinary clinicians necessary to provide such optimal care. Overall, the evidence suggests that global outcomes are improved when routine care decisions are both standardized and taken out of the hands of individuals.

#### **Physician-Extenders**

Nurse practitioners (NPs) and physician assistants (PAs) provide effective health care in both the outpatient and acute care setting.<sup>40</sup> In conjunction with a trained intensivist, it is likely that these individuals can provide quality care in the ICU. Theoretically, physician-extenders like NPs and PAs could improve the efficiency of critical care—a single intensivist might only care for 10 to 12 patients per day, whereas an intensivist aided by a physician-extender might be able to provide care for twice that number at a lower cost per patient. Thus, the physician-extender model might be an innovative way to expand access to the intensivist-led model of critical care. NPs and PAs can perform some invasive procedures such as central venous and arterial line placement. Physicianextenders also may offer the benefit of increased patient, family, and nurse satisfaction through improved communication.41,42

The current literature relating physician-extenders to outcomes in the ICU is limited. What studies do exist support the notion that care models including NPs and PAs result in outcomes at least equivalent to other care models. Time-series studies in which care teams involving NPs are compared with those without NPs in medical, trauma, and pediatric ICUs have indicated no worsening in mortality, lengths of stay, or complication rates.<sup>43–47</sup> A study of critical care outreach appeared to show that NPs could reduce ICU readmissions among patients discharged from the ICU.<sup>48</sup> In a specialized weaning unit for patients receiving prolonged mechanical ventilation, an intensivist-NP team resulted in similar outcomes to an intensivist-fellow team.<sup>49</sup>

A recent survey of surgery residency programs found that physician-extenders were frequently employed to overcome the staffing challenges faced by mandated limitations in trainee work hours.<sup>50</sup> Many countries in North America and Europe are taking steps to standardize the role of NPs and PAs in the acute care setting and to codify the training requirements necessary to work in critical care.<sup>51</sup> It is likely that the role of physician-extenders in the ICU will continue to expand and to improve both the efficiency of intensivists are not available.

#### Telemedicine

ICU telemedicine uses an electronic medical record and video-conferencing technology to provide critical care from remote locations. Telemedicine is a relatively old concept, having been applied with varying success in a countless number of diverse care settings.<sup>52</sup> Under an ICU telemedicine model, patients can have their vital signs, respiratory patterns, laboratory studies, and some aspects of the physical examination remotely monitored by a single intensivist. Multiple different telemedicine

applications and care models exist. These range from continuous multibed monitoring to selective monitoring through robotic telepresence.<sup>53–55</sup> It is unlikely that ICU telemedicine offers advantage over a trained intensivist at the bedside. The power of telemedicine is that one intensivist can monitor multiple patients in multiple hospitals simultaneously or provide consultation in rural areas where an intensivist is not available. Additionally, some telemedicine applications use software that can quickly identif physiologic deterioration, potentially allowing for earlier interventions. ICU telemedicine may also be viewed as a communication tool, facilitating nurse-physician collaboration during off hours.

Many barriers exist to the wide adoption of ICU telemedicine, either as an alternative or as a complement to full-time intensivist staffing. To date, there are few wellconducted studies examining the effect of ICU telemedicine on patient-centered outcomes (Table 94-2). All six published studies used a before-after approach that may not adequately account for temporal trends or variation in case mix.<sup>56-61</sup> While earlier studies suggested an improvement in outcomes, later studies have not confirmed this finding, and there is significant potential for bias. More data are needed to determine whether remote ICU monitoring can positively affect the outcomes of critical care. Additionally, the costs of telemedicine are substantial. In the absence of robust data on cost-effectiveness, it is impossible to conclude whether ICU telemedicine represents an efficient use of health care resources.

Like any tool, the potential benefits of telemedicine lie not in *if* we use it but in *how* we use it. The history of the pulmonary artery catheter teaches us that more information and fancier equipment do not necessarily translate into better outcomes.<sup>62</sup> ICU telemedicine may be a powerful tool to export intensivist-level expertise to rural areas but may be redundant in large hospitals with highly skilled nurses and in-house physicians. As we await further evidence, it is important to weigh the potential benefits of adopting an ICU telemedicine program against the use of those resources, such as critical care nurses or onsite physicians, that develop human capital more clearly associated with outcomes.

#### Regionalization

It may be possible to expand access to intensivist-led multidisciplinary care by routinely transferring critically ill patients to large referral centers. This approach is referred to as regionalization of care.<sup>63</sup> Regionalization would capitalize on the observation that high-volume providers demonstrate better outcomes in the care of critically ill patients.<sup>64,65</sup> By concentrating the care of critically ill patients in a few large volume centers, we may be able to improve overall survival for critically ill patients. Regionalization also might lower costs by creating economies of scale-hospitals, like other service industries, are typically more efficient when they provide a greater amount of service.<sup>66</sup> Successful regionalization efforts in trauma care and neonatal care support the value of regionalization of care.<sup>67,68</sup> A multidisciplinary conference endorsed by the major critical societies recently called for

Table 94-2 Summary of Studies Examining the Effect of Intensive Care Unit Telemedicine on Adult Patient Outcomes

Study	Design	Time Period	ICU Types	No. of Patients	Major Findings
Rosenfeld et al, 2000 <sup>56</sup>	Single-center, before-after	11 mo	SICU	628	↓ Unadjusted in-hospital mortality ↓ Total complications
Breslow et al, 2004 <sup>57</sup>	Single-center, before-after	18 mo	MICU, SICU	2140	↓ Unadjusted in-hospital mortality ↓ Unadjusted ICU and hospital LOS
Vespa et al, 2007 <sup>58</sup>	Single-center, before-after	24 mo	NICU	1218	Trend toward $\downarrow$ ICU LOS
Zawada, 2009 <sup>59</sup>	Multi-center, before-after	3.5 years	Multiple	5,426	↓ or no change in unadjusted in-hospital mortality ↓ ICU LOS
Thomas, 2009 <sup>60</sup>	Multi-center, before after	3.75 years	Multiple	4,142	No change in adjusted mortality No change in ICU complication rate No change in ICU LOS
Morrison, 2010 <sup>61</sup>	Multi-center, before after	12 months	Multiple	4,088	No change in adjusted in-hospital mortality No change in ICU LOS

ICU, intensive care unit; LOS, length of stay; MICU, medical intensive care unit; NICU, neurologic intensive care unit; SICU, surgical intensive care unit.

investigations into creating a formal, tiered system of regionalized critical care in the United States.<sup>5</sup>

Currently, there is no direct evidence that regionalization will result in improved survival in critically ill patients. An analysis of administrative data in the United States found that a large number of patients receive critical care in low-volume hospitals and that a significant number of lives might be saved by routinely transferring these patients to high-volume institutions.<sup>69</sup> However, this analysis only demonstrates the potential survival benefit under regionalization. There are many reasons why regionalization may not actually improve survival. Regionalization may overwhelm the capacity of large hospitals or decrease the ability of small hospitals to care for acutely ill patients. This has the potential to harm some patients and decrease survival benefits. Routine interhospital transfer of critically ill patients also carries inherent risks, although recent evidence suggests that interhospital transfer is safe even for extremely sick patients.<sup>70,71</sup> Regionalization also would have complex effects on hospital economics at both high- and low-volume hospitals, making the overall financial implications of implementing the system difficult to predict.

Empirical demonstration projects are required before a regionalized system should be widely adopted. Nonetheless, wide variation in the quality of care among hospitals, the relative safety of interhospital transport of critically ill patients, and the demonstrated volume-outcome effect in critical care make investigations into the feasibility of adopting regional care systems worthwhile.<sup>72</sup>

#### FUTURE DIRECTIONS

The organization of critical care services is in a state of near-constant evolution. We have come from an ad hoc system that merely centralized critically ill patients within the hospital to a system that emphasizes the benefits of multidisciplinary care led by trained intensivists. Nonetheless, continued calls for the expansion of an intensivist-led model of care may be unrealistic in the face of the limited supply of appropriate critical care providers. It is essential that we consider alternative care models for providing high-quality critical care to a broad range of patients. Protocol-based care, hospitalist care models, physician-extenders, ICU telemedicine, and regionalization all offer the potential for improved outcomes for critically ill patients. These care models are complementary to expanding intensivist staffing where feasible. In addition, efforts to disseminate best practices through education, benchmarking, and value-based purchasing initiatives are essential. All these alternative models require further research before they should be adopted widely. Attention should be focused on patient-centered outcomes and comparative cost-effectiveness. In the interim, we should maintain flexibility about the absolute need for universal intensivist staffing and be open to new and innovative ideas about how to optimally organize critical care services.

#### AUTHOR'S RECOMMENDATIONS

- Intensivist-led, multidisciplinary care is associated with improved patient outcomes in the ICU.
- Barriers to wide adoption of the intensivist care model include lack of trained intensivists, concerns about physician autonomy, and financial issues.
- Alternative care models may offer a way to obtain the benefits of intensivist staffing without adopting a full-time intensivist model.
- The strongest evidence supports integrating protocol-based care into daily practice.

- Physician-extenders may improve the efficiency of care without adversely affecting outcomes and may improve family satisfaction, but more experience is needed.
- ICU telemedicine and regionalization are innovative care models with great potential to improve care for critically ill patients, but are not yet supported by the available evidence.

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## 95

## What Is the Role of the Intensivist and of the Intensive Care Unit Medical Director?

Daniel Holena, Vicente Gracias, C. William Hanson III

Although the first intensive care unit (ICU) in the United States was created in the 1923, ICUs as they are recognized today did not come into common use until the 1950s as mechanical ventilation became more common. With the ever-increasing depth and breadth of medical knowledge, ICU care became more complex and refined. Even so, it was not until 1986 that the American Board of Medical Specialties approved specialty certification in critical care.

The critical care physician has been described as "the primary care physician of the ICU."<sup>1</sup> According to the 1992 Society of Critical Care Medicine guidelines, an intensivist is a physician who "[d]iagnoses, manages, and delivers the care of critically ill patients."<sup>2</sup> In addition, the intensivist possesses a broad set of medical skills and training that encompass all body systems as well as the ability to perform ICU-specific procedures (e.g., endotracheal intubation, placement of vascular catheters). In contrast to other specialties in medicine, critical care is defined not by the particular pathology being treated (e.g., cardiology, gastroenterology) or nature of interventions offered (e.g., surgery, interventional radiology) but rather by the patient population; intensivists treat critically ill patients with a both acute and chronic pathology in a wide variety of organ systems.

The degree of participation by intensivists in the care of ICU patients varies considerably from hospital to hospital in the United States. In the year 1997, intensivists provided care to only 37% of ICU patients.<sup>3</sup> The degree to which an intensivist participates in the care of the ICU patient may depend on the staffing infrastructure of the ICU. The three most common models employed are the open model, the closed model, and the semiclosed model.

In the open ICU, any physician involved in the care of the patient may write orders or call in a consultation. This may be problematic in that it is not always clear who is ultimately responsible for various aspects of patient care. Intensivist participation is not mandatory but may be available on request. A closed ICU implies that the intensivist assumes all responsibility for care, including writing orders and calling consultations for the duration of the ICU stay. Although this model ensures less ambiguity regarding who is responsible for the patient, primary physicians may feel excluded, and continuity of care may be compromised. In the semiclosed model, patient care plans are decided on jointly by the primary physician and intensivist; orders are typically placed through the ICU team. This model allows the primary physician to remain closely involved while at the same time maintaining a clear chain of command. A survey by Angus and colleagues in 2000 found that only about 23% of ICUs employ full-time intensivists, with nearly half of all ICUs conforming to the open model, in which multiple physicians comanage the patient without one clear coordinator.<sup>3</sup>

The involvement of the intensivist in the care of ICU patients should be held to the same evidence-based standard as any intervention in the ICU. To this end, we hope to provide the reader with a summary of the results of the available literature on the topic.

#### **EVIDENCE**

The idea that intensivist involvement in the care of ICU patients translates into improved outcomes is not new, having first been posited in the literature in 1977.<sup>4</sup> Since that time, many studies have examined whether the influence of the intensivist may confer better outcomes in ICU patients. The preponderance of published studies consist of retrospective analyses examining outcomes after increased intensivist presence compared with a historical control. Randomized prospective trials on this topic have not been performed to date and are unlikely to be performed in the future, primarily because of ethical and logistical concerns.<sup>5</sup>

In the earliest of these, Li and colleagues demonstrated that, after controlling for patient characteristics that predict mortality, the presence of intensivists in the ICU was associated with decreased mortality when compared with a historical control group in which ICU patients were cared for by their primary physicians.<sup>6</sup> A number of similar studies followed suit, with most demonstrating that the presence of an intensivist improves ICU mortality, hospital mortality, ICU length of stay, and hospital length of stay (Table 95-1).<sup>7–31</sup>

Table 95-1 Eff	ect of Intensi	ivists on	Intensive (	Care Unit Patient Outc	ome					
Authors	Evidence Level	Year	Study Design	Variable Studied	Pts. (#)	Population	ICU Mortality	Hospital Mortality	ICU LOS	Hospital LOS
Li et al	2b	1984	R, HC	Closed vs. open ICU	954	Mixed ICU	*	$\downarrow$	$\downarrow$	*
Pollack et al	2b	1988	R, HC	Closed vs. open ICU	262	PICU	$\downarrow$	*	$\leftrightarrow$	*
Reynolds et al*	2b	1988	R, HC	Closed vs. open ICU	212	MICU, septic shock	*	$\downarrow$	$\leftrightarrow$	$\leftrightarrow$
Brown et al	2b	1989	R, CS	Closed vs. open ICU	439	Mixed ICU	$\downarrow$	$\downarrow$	*	*
Pollack et al	2b	1994	R, CS	Presence of intensivist	5415	PICU	*	$\downarrow$	*	*
Carson et al	2b	1996	R, HC	Closed vs. open ICU	245	MICU	*	$\leftrightarrow$	$\leftrightarrow$	*
Manthous et al	2b	1997	R, HC	Closed vs. open ICU	930	MICU	$\downarrow$	$\downarrow$	$\downarrow$	$\downarrow$
Multz et al	2b	1998	R, HC	Closed vs. open ICU	306	MICU	*	$\leftrightarrow$	$\downarrow$	$\downarrow$
Tai et al	2b	1998	R, HC	Closed vs. open ICU	239	MICU	$\leftrightarrow$	*	$\downarrow$	$\leftrightarrow$
Ghorra et al	2b	1999	R, HC	Closed vs. open ICU	274	SICU	$\downarrow$	*	$\leftrightarrow$	*
Hanson et al	2b	1999	R, CC	Semi-closed vs. open ICU	200	SICU	*	$\leftrightarrow$	$\downarrow$	$\downarrow$
Pronovost et al	2b	1999	R, CS	Daily intensivist rounds	2987	Mixed ICU, post AAA repair	*	↓	$\downarrow$	$\downarrow$
Blunt et al	2b	2000	R, HC	24-hour intensivist coverage	824	Mixed ICU	*	↓	$\leftrightarrow$	$\leftrightarrow$
Kuo et al	2b	2000	R, HC	Closed vs. open ICU	667	SICU	$\downarrow$	*	$\downarrow$	*
Rosenfeld et al	2b	2000	R, HC	Tele-intensivist vs. open ICU	628	SICU	$\downarrow$	$\downarrow$	$\downarrow$	*
Baldock et al	2b	2001	R, HC	Closed vs. open ICU	962	Mixed ICU	*	$\downarrow$	*	*

Dimick et al	2b	2001	R, CS	Daily intensivist rounds	351	SICU, post- esophagectomy	*	$\downarrow$	*	↓
Diringer et al	2b	2001	R, CS	Neuro vs. general ICU	1038	ICH	*	$\downarrow$	$\downarrow$	$\downarrow$
Goh et al	2b	2001	R, HC	24-hour intensivist coverage	619	PICU	Ļ	*	$\downarrow$	*
Mirski et al	2b	2001	R, HC	Pre- and post- neurointensivist	128	ICH admitted to ICU	Ļ	*	$\leftrightarrow$	Ļ
Pronovost et al	2a	2002	SR	High vs. low intensivist presence	*	Mixed ICU	Ļ	Ļ	$\downarrow$	Ļ
Breslow et al	2b	2004	R, HC	Tele-intensivist presence	2140	MICU and SICU	$\leftrightarrow$	$\downarrow$	$\downarrow$	$\leftrightarrow$
Suarez et al	2b	2004	R, HC	Pre- and post- neurointensivist	2381	NICU	*	Ļ	Ļ	↓
Varelas et al	2b	2004	R, HC	Pre- and post- neurointensivist	2366	NICU	↓	*	↓	↓
Nathans et al	2b	2006	R, CS	Closed vs. open ICU	2599	Mixed ICU, trauma patients	*	$\leftrightarrow$	*	*
Treggiari et al	2b	2007	R, CS	Closed vs. open ICU	1075	Mixed ICU, ALI patients	*	Ļ	*	*
Levy et al	2b	2008	R, CS	Intensivist involvement	101,832	MICU, SICU, Mixed ICUs	*	$\downarrow$	*	*

 $R = retrospective, HC = historical control, CS = cross-sectional, CC = concurrent control, SR = systematic review, PICU = pediatric ICU, MICU = medical ICU, SICU = surgical ICU, AAA = abdominal aortic aneurysm, ICH = intracranial hemorrhage, ALI = acute lung injury, * = not measured, <math>\downarrow$  = decreased,  $\leftrightarrow$  = no change.

In 1999, this concept was reinforced by a cohort study from Hanson and colleagues that compared to two concurrent groups of patients admitted to a surgical ICU.<sup>16</sup> The control group was managed by the admitting surgeon in the open ICU model, whereas the study group was managed by a dedicated intensivist-led team in the semiclosed model. Patients cared for by the critical care team had a shorter ICU length of stay, shorter hospital length of stay, fewer complications, and decreased costs despite having higher admission APACHE II scores. Daily rounds by an intensivist have been shown to be associated with improved patient outcomes in specific disease states. A multi-institutional retrospective cohort analysis by Pronovost and associates demonstrated that, in patients undergoing abdominal aortic surgery, daily rounds by an intensivist were associated with decreased mortality as well as decreased risk for cardiac arrest, acute renal failure, and sepsis.<sup>17</sup> Similar studies showed that the lack of daily rounds by an intensivist was associated with increased ICU length of stay, complications, and costs in patients undergoing esophagectomy.<sup>22</sup> A more recent multi-institutional retrospective cohort study showed that having a closed model ICU is associated with decreased mortality in patients with acute lung injury.<sup>31</sup>

Although the preponderance of the literature suggests intensivists improve outcomes in ICU patients, significant heterogeneity exists in the role intensivists played in these studies. In some studies, the intensivist controlled all aspects of patient care, whereas in others, intensivists merely served as consultants. In a systematic review, Pronovost and associates parsed the available literature according to the degree of intensivist involvement.<sup>5</sup> They found that high-intensity ICU staffing (as defined by mandatory intensivist consultation, or a closed ICU) was associated with decreased mortality in most published studies. The benefits of decreased ICU mortality, decreased hospital mortality, decreased cost, and decreased ICU length are robust, being demonstrable in medical, surgical, and pediatric ICUs in both the academic and community settings.

In stark contrast to the previously discussed studies, in 2008, Levy and coworkers published a thought-provoking retrospective database analysis examining the effect of intensivist involvement on hospital mortality in 100,000 patients in 123 ICUs.<sup>32</sup> Even after controlling for patient severity of illness and other confounding variables, the authors found that hospital mortality rates were significantly higher when intensivists were involved, both in units where intensivist consultation was elective and in units where patients were managed exclusively by intensivists. Although contradictory to previous work in this area, the possibility exists that these findings are real, and further study is warranted. However, at this time, the vast preponderance of evidence still supports the idea that intensivists have a beneficial effect on patient outcomes.

The notion that admission to a subspecialty ICU is associated with better outcomes is implicit in the practice of Western medicine. For example, it is assumed that infants receive better care in neonatal ICUs, whereas burn patients receive better care in burn ICUs. Trends toward

increasing specialization within critical care have prompted studies suggesting that subspecialty ICU care may be associated with improved outcomes in particular groups of patients. It has been postulated that the involvement of an intensivist with advanced knowledge of specific physiology and pathophysiology may lead to beneficial effects on patient outcome.<sup>25</sup> In addition, the significant organizational changes that accompany the development of a specialized ICU likely contribute to any benefit incurred.<sup>29</sup> These efforts at validating subspecialty ICUs have best been supported by studies investigating outcomes in neurology and neurosurgery ICUs. In a 2001 study, Diringer and Edwards found that, in patients with intracranial hemorrhage, admission to a specialized neurologic or neurosurgical ICU was associated with decreased hospital mortality.23 Similarly, Suarez found in a 2004 study that the introduction of a specialized neurointensivist team led to decreased ICU but not long-term mortality as well as decreased ICU length of stay.<sup>28</sup>

Precisely how the intensivist involvement leads to improvements in patient outcomes is unknown, but it is likely to be multifactorial. Much in the same way that rapid intervention in specific disease states, such as trauma,<sup>33</sup> sepsis,<sup>34</sup> and myocardial infarction,<sup>35</sup> has been linked to better patient outcomes, it may be that the presence and availability of an intensivist benefits patients by more timely interventions in response to changes in patient physiology.<sup>17</sup> In an open ICU model, Engoren found that prompt patient evaluation (<6 hours) on ICU admission by an intensivist was associated with decreased mortality and hospital length of stay; for each hour in delay in physician evaluation after a patient's admission to the ICU, hospital mortality was increased by 1.6%.<sup>36</sup>

If patient outcomes are improved by the presence of an intensivist, one might expect these outcomes to vary temporally with intensivist availability. Research efforts along this line of inquiry consist only of retrospective analysis and have yielded inconsistent results. Some authors have found that patients admitted to the ICU on nights and weekends had higher mortality rates than those admitted during weekdays,<sup>37–39</sup> whereas other have demonstrated equivalent<sup>40-45</sup> or even improved<sup>46,47</sup> outcomes during "off" hours. Intensivist staffing in these studies was variable, with some having 24-hour in-house coverage and others off-site backup available by phone. Even if a difference in severity of illness-adjusted mortality does exist between weekday and weekend-weeknight admissions, it is difficult to ascribe this specifically to variations in intensivist staffing. Many other factors, including ancillary staffing, availability of radiographic imaging, and presence of other specialists, also may vary temporally.

It also may be possible that the physical presence of a critical care physician is not necessary to realize improved outcomes. In an alternative paradigm of ICU staffing, attention has recently been turned to telemedicine, in which patients are remotely monitored by intensivists in an "electronic ICU" (eICU). One theoretical benefit of this approach is that it provides intensivist input into ICU care where and when it might otherwise be unfeasible or impossible. As an example, many rural hospitals that do

not have dedicated critical care physicians on staff might benefit from telemedicine. The obvious drawback of this model is that physical examination and intervention are limited to whatever personnel are available by proxy. Theoretical concerns notwithstanding, in an observational cohort study comparing a 16-week intervention period to two baseline periods, Rosenfeld and associates found that remote monitoring and intervention by intensivists was associated with reduced ICU and hospital mortality, length of stay, complications, and costs.<sup>20</sup> A later retrospective analysis comparing an eICU intensivistmonitored period to a historical control had similar results.<sup>23</sup> The role of telemedicine in the care of the ICU patient is the subject of ongoing study. Currently, there are no studies that directly compare eICU care to more traditional models of intensivist-led care; the role the teleintensivist will play in the future of critical care remains unclear.

#### CONTROVERSIES

Despite the number of studies showing improved results with increased intensivist involvement, several caveats must be made clear. There currently is no level I evidence available; the best available evidence consists of a single level IIA study and a plethora of level IIB studies.<sup>48</sup> Even if these studies are taken at face value, it may be that the presence of an intensivist is merely a surrogate for other factors that mediate improved patient outcome. These include institution of standardized protocols or the availability of dedicated hospital staff. Because randomized controlled trials are unlikely to be performed, these factors will be difficult to remove as confounding variables. In addition, because nearly all of the studies regarding the benefits of intensivist presence have been performed by intensivists, the possibility of observer bias must be considered.4

Critical care is extremely resource intensive; it has been estimated that in 1994, about 1% of the gross domestic product was spent on intensive care.<sup>50</sup> In addition, because of the high acuity of ICU patients, medical errors are common in this population.<sup>51</sup> Interest in improving patient safety and controlling cost has led to the publication of guidelines by both government and commercial groups calling for increased intensivist involvement in the care of ICU patients. In perhaps the most widely hailed of these, in 2000 the Leapfrog group (a consortium of business leaders from more than 130 privately and publicly held companies) published health insurance purchasing guidelines designed to improve patient care and limit cost. One of three primary "leaps" based on the evidence from the available literature called for ICUs to be staffed by intensivists.<sup>52</sup> It has been estimated that greater than 54,000 deaths could be avoided annually by the implementation of this recommendation alone.<sup>53</sup> Currently, in the United States, only about one third of ICU care is provided by intensivists. As the U.S. population ages, the demand for ICU care has been predicted to increase at a rate that outstrips the training of critical care physicians. This will lead to a net decrease in the amount of ICU care provided by trained

intensivists.<sup>5</sup> Pressure from government and health care consumer organizations such as the Leapfrog group may serve to further increase demand for intensivists. It is unclear how this dearth of available manpower will be resolved.<sup>54,55</sup> Although initial studies appear promising, it remains to be seen whether telemedicine will emerge as a solution to this shortage.

## ROLE OF THE INTENSIVE CARE UNIT MEDICAL DIRECTOR

The role of the ICU medical director has not been rigorously studied in the medical literature. Nevertheless, the director of critical care plays a crucial role in the overall functioning of the ICU and thus may have a tremendous impact on overall patient outcomes. In 2003, the American College of Critical Care Medicine put forth a series of guidelines stating that the ICU medical director should be board certified in critical care medicine,<sup>56</sup> although this recommendation is not evidence based. A 1993 survey conducted by the Society of Critical Care Medicine reported that only 56% of ICU medical directors were board certified in critical care medicine and that this percentage varied widely with size and academic status of the hospital.<sup>57</sup> Other than being a skilled critical care physician, the ICU medical director must be able to provide leadership across a wide spectrum of areas, including but not limited to interdepartmental relations, financial planning, and disaster management planning (Table 95-2).

Role of the ICU Medical Director	Example
ICU administration	Co-management of the ICU with leaders from nursing, pharmacy, and respiratory therapy Development and implementation of evidence-based "best practice" guidelines Performance review and quality benchmarking Disaster management planning
Educational leadership	Instruction of all levels of participants in ICU care Education of external departments regarding the role of the ICU Policy creation and revison with local and national health care organization
Financial leadership	Management of scarce resources Bed allocation/patient triage Decision making on purchase and implementation of new drugs and techonology Delivery of cost-effective ICU care

### Table 95-2 Role of the Intensive Care UnitMedical Director

Hospitals rely on the leadership of the ICU medical director to ensure the smooth day-to-day function of the ICU. The astute medical director realizes that best outcomes are achieved when a collaborative approach to patient care in the ICU is used. It has been demonstrated that improved outcomes are achieved when care from ICU nurses,<sup>58-60</sup> respiratory therapists,<sup>61,62</sup> and pharmacists<sup>63–65</sup> is integrated into the ICU care plan. Just as the intensivist at the bedside must synthesize a plan from the input of the collaborative ICU team, so too must the ICU medical director ensure that the various departments involved in critical care are harmoniously integrated into the overall fabric of the ICU. In this endeavor, excellent interpersonal and mediation skills are a prerequisite; only when the ICU medical director is an effective leader can the highest quality of care be delivered. There is good evidence that implementation of "best practice" guidelines reduces complications and improves outcomes in the ICU.66-70 To develop and implement best practice guidelines, it is imperative that the ICU medical director diligently keep abreast of the latest literature and review new developments in the field. When evidence accrues that a practice is beneficial, the medical director is charged not only with implementing evidence-based best practice guidelines but also with tracking the outcomes of these interventions through time. As scrutiny from insurers and patient safety groups increases through time, it will become increasingly important to demonstrate that quality and safety standards are being met.

In addition to managing the day-to-day affairs, the ICU medical director must be prepared to provide leadership in the ICU in times of crisis. Throughout the world, mass casualty situations due to both natural and human causes occur frequently.<sup>71</sup> Severely injured patients during such events tend to self-select for survival in such a way that overwhelming surges in the requirement for intensive care have been the exception rather than the rule.<sup>72</sup> Nevertheless, the potential for a dramatic increase in demand for ICU beds certainly exists. If such a scenario arises, the ICU medical director must stand at the ready.<sup>73</sup> Of paramount importance to successful crisis management in the ICU is the development of a well-conceived disaster management plan. This plan should be coordinated with other key departments (e.g., emergency department, operating room) and integrated into a larger hospital-wide blueprint. Simulated implementation followed by appropriate revision ensures maximal preparedness.

Teaching is also a critical role of the ICU medical director. From medical students to intensivist attendings to nurse practitioners, the director must strive to teach evidence-based critical care to all care providers in the ICU. At least one study showed that resident physicians demonstrate increased scores on standardized critical care examinations after the institution of an intensivist as ICU medical director.<sup>12</sup> In addition to teaching other members of the hospital staff, ICU medical directors have a duty to educate the public at large. This duty to teach extends to both the general public, who may someday have direct experience with ICU care, and lawmakers and politicians, who are directly involved in the formulation of health care policy that may affect the ICU.

ICU directors often play a key role in the financial management of the ICU. As previously discussed, critical care is extremely expensive and consumes a large proportion of the gross national product annually.<sup>5</sup> It is the responsibility of intensivists and critical care directors to attempt to contain these costs while at the same time maintaining the highest quality of care. In addition to the already substantial baseline costs of ICU care, new devices, technologies, and medications are continuously being developed. Part of the role of the ICU medical director is to evaluate the costs and benefits of these new interventions and to make rational and responsible recommendations for use of resources. In many hospitals, an ICU bed is at times a scarce resource; with the aging of the population, this problem can only be expected to increase in prevalence. The critical care director is often called on to triage the critically ill when supply exceeds demand. Decisions regarding bed management and resource use can be fraught with logistical, ethical, and political conundrums. These issues often call for excellent arbitration skills in addition to strong leadership. Besides playing an important role in the triage of scarce resources, the critical care director must at times be a proponent of increases in staffing or infrastructure. If limited resources lead to unacceptable compromises in patient care, it is the responsibility of the medical director to vociferously advocate on behalf of those critically ill patients served by the ICU. As a leader, the director is the nexus of the various departments involved in providing ICU care. By listening to their concerns, not only can serious patient care issues be identified and addressed, but so too can the workplace be made into a healthier and happier environment for employees.

#### GUIDELINES

In 2000, the Leapfrog group issued the following recommendations regarding critical care<sup>52</sup>:

- 1. ICUs should be staffed by board-certified intensivists, who coordinate and manage care of patients.
- 2. Intensivists should staff ICUs during daytime hours, a minimum of 8 hours per day, 7 days per week.
- 3. Intensivists should respond to more than 95% of calls for assistance within 5 minutes.
- 4. The intensivist, a "fundamentals of critical care"– certified physician, or "physician-extender" (also described in some Leapfrog documents as "effectors"), should arrive at the bedside within 5 minutes in 95% of cases.

The first of these recommendations is clearly supported by a large body of evidence. Although the remainder of these guidelines appears reasonable, they are not in fact evidence based. Neither the optimal amount of time the intensivist should spend in the ICU nor the optimal response time has been well delineated by the current literature, and further study is required before these standards are given the same weight as the first recommendation.

#### **AUTHORS' RECOMMENDATIONS**

- Based on the available evidence consisting primarily of retrospective analyses, a grade B recommendation can be made that involvement of an intensivist in the care of ICU patients improves ICU mortality, hospital mortality, ICU length of stay, and hospital length of stay.
- No firm evidence-based recommendations can be made on the role of the ICU medical director; further scientific study is necessary.
- Although no level I data exist, most published investigations support the association between intensivist involvement in the care of ICU patients and improved outcomes. Observed benefits include decreased ICU mortality, hospital mortality, ICU length of stay, hospital length of stay, and cost.
- A growing body of literature demonstrates that neurocritical care patients may have better outcomes when managed in dedicated ICUs staffed by neurointensivists.
- The demand for ICU physicians is expected to exceed the supply in the coming decades; if these projections hold true, it is unclear how this need will be met. Telemedicine holds promise as a means to ameliorate this shortage.
- The role of the ICU medical director is critical to the efficient management of the ICU but has not been consistently defined in the literature. Roles of the ICU medical director include administration, quality control, financial management, and educational leadership.

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# 96 What Is the Role of Teamwork in the Intensive Care Unit?

#### Charles G. Durbin, Jr.

Almost 1% of the U.S. gross domestic product is expended in the care of patients admitted to an intensive care unit (ICU), and this percentage will continue to grow as the population ages.<sup>1</sup> Despite this huge investment of societal resources, mortality from critical illness and injury remains high in the United States compared with other nations that spend less. These discrepancies occur despite notable advancements in diagnosis and life support treatments available only in the United States. Medical errors and preventable complications are believed to contribute to the high mortality in hospitalized patients, especially in those who are critically ill. The complexity of the U.S. health system overall and hospitals in particular is an important factor contributing to the risk-filled environment in which patients receive care.

Individual clinician behaviors are probably minor issues in patient safety. However, the assignment of blame and delivery of punishment have been the traditional mechanisms to improve patient care in the United States. Fear of the medical-legal consequences of poor patient outcome as well as patient and family demands have contributed to the practice of ordering all possible tests, delivering unnecessary and harmful treatments (e.g., radiologic studies and antibiotics), obtaining multiple consultations, and emotional separation of the physician from the patient and family. This practice pattern leads to diffuse and inadequate decision making, poor coordination of care, delivery of inappropriate and unnecessary treatments, failure to provide needed treatment, the appearance of patient abandonment, family dissatisfaction with care, and increased health care costs. The problems of fractured care are especially troubling and potentially lethal to the critically ill patient. The solution to this situation requires a completely overhauled care delivery system.

There are many different models of ICU care delivery, and studies have suggested that differences in ICU organization may affect patient outcome and costs. For example, staffing ICUs with critical care-trained physicians (intensivists) improves clinical outcomes compared with having no dedicated specialist in the ICU. Possible reasons for this include that intensivists who are immediately available can detect and treat emerging problems, which may decrease patient morbidity and prevent mortality. ICU staffing with intensivists may also decrease costs because they can standardize care using best practices; reduce unnecessary ICU admissions, lessening the need for additional ICU beds; and prevent complications in critically ill patients that prolong length of stay (LOS).<sup>2</sup> Unit-based intensivists also change ICU culture and initiate and support the development of an ICU team. This last may be the most important contribution to improved care.

#### WHAT IS THE EVIDENCE SUPPORTING THE EFFECTIVENESS OF INTENSIVISTS IN INCREASING INTENSIVE CARE UNIT SURVIVAL?

The evolution of ICUs from postoperative recovery areas and the development of physicians who have decided to practice in these units has paralleled advances in life support technology and continuous physiologic monitoring. Critical care as a separate medical subspecialty in the United States has only been in existence for about 40 years. The Society of Critical Care Medicine was founded in 1970, and subspecialty certification has only been available since the mid-1980s. During the past 25 years, as the pool of certified intensivists has grown, research has described the impact of having an intensivist involved in the ICU. Most reports have analyzed changes in mortality, morbidity, LOS, and costs before and after the arrival of an intensivist in an existing, single open ICU. These studies usually demonstrated improvement when an intensivist was added, but study methodology has been weak and subject to many confounding influences.

In an attempt to reduce bias and improve understanding of influential organizational characteristics, Pollack and colleagues randomly selected 16 pediatric intensive care units (PICUs) from a national database of 235 participating PICUs representing unique combinations of four dichotomous attributes thought to be important quality indicators.<sup>3</sup> The characteristics selected were unit size, presence of an intensivist, medical school affiliation of the hospital, and whether there was coordination of care. Small size was defined as six or fewer beds and represented 42% of the 235 surveyed PICUs. To qualify as an intensivist, the physician had to meet the 1989 criteria of the American Board of Pediatrics, Anesthesiology, or Surgery for added qualifications eligibility or certification in critical care medicine. Primary teaching hospitals had to have a medical school affiliation and provide pediatrics clerkships to a majority of third-year medical students.

A unit was considered "coordinated" if the medical director was involved in the care of more than 90% of the patients or there was a 24-hour, 7-day-a-week physician staff dedicated solely to the PICU.<sup>4</sup>

The pediatric patient sample included 5415 consecutive admissions to the selected units during an average of 14 months between 1989 and 1992. The Pediatric Risk of Mortality (PRISM) score during the first 24 hours was used to express differences in observed mortally (actual to predicted deaths). The ICUs differed significantly with respect to descriptive variables, including mortality (range, 2.2% to 16.4%). Analysis of risk-adjusted mortality indicated that only the hospital teaching status and the presence of a pediatric intensivist were significantly associated with a patient's chance of survival. Paradoxically, the probability of patient survival after hospitalization in an ICU located in a teaching hospital was decreased (relative odds of dying, 1.79; 95% confidence interval [CI], 1.23 to 2.61; P = .002). In contrast, the probability of patient survival after hospitalization in an ICU with a pediatric intensivist was improved (relative odds of dying, 0.65; 95% CI, 0.44 to 0.95; P = .027). Significant, patient-related predictors of ICU LOS included PRISM, several diagnostic groups, three preadmission factors (operative status, inpatient/outpatient, previous PICU admission), and first-day use of mechanical ventilation.<sup>5</sup> The ratio of observed to predicted LOS varied among PICUs from 0.83 to 1.25, with three PICUs displaying significantly (P < .05) shorter and three PICUs longer LOS. The PICU factors associated (P < .05) with shorter (5% to 11%) LOS were presence of an intensivist, presence of residents, and coordination of care, whereas an increased ratio of PICU to hospital beds was associated with longer (P < .05) LOS. Medical school affiliation, admission volume, number of pediatric hospital beds, and PICU mortality rates did not have statistically significant effects on LOS after adjusting for patient factors. From this well-designed multi-institutional study, the presence of a pediatric intensivist was associated with improved patient survival and shorter than predicted LOS. Having an intensivist actively involved in more than 90% of patients' care (coordinated care, or closed unit) also independently predicted shorter PICU LOS.

In adult ICUs, there are several retrospective studies showing a similar benefit of intensivist staffing on patient outcomes. Specifically, the addition of board-certified critical care specialists is usually found to be temporally associated with improvements in both ICU and in-hospital mortality. Other prospective studies in various ICU settings have corroborated these retrospective findings. Given the limitations in conducting prospective randomized trials assessing intensivist impact on patient outcomes, there are now a multitude of nonrandomized studies that support the understanding that physicians trained in critical care not only can improve patient outcomes but also can improve the use of medical resources.

Pronovost and colleagues evaluated the effect of having an intensivist involved in care on patient outcome by combining reported comparative studies using meta-analysis (Table 96-1).<sup>6</sup> These authors selected all published, randomized, and observational controlled trials of critically ill adults or children between 1965 and 2001. Studies were considered if they included ICU attending physician staffing strategies and the outcomes of hospital and ICU mortality and LOS. Studies were selected and critiqued by two reviewers from the 2590 abstracts identified, and 26 relevant observational studies were selected (one of which included two comparisons). This resulted in 27 comparisons of alternative staffing strategies. Twenty of these focused on a single ICU.

To compare the physician staffing models, a unit was classified as "high intensity" when mandatory consultation by an intensivist was required or if the ICU was a closed unit directed by an intensivist, or as "low intensity" if no intensivist was present or only elective consultation with an intensivist was available to the unit patients. High-intensity intensivist staffing resulted in patient benefits, including improved hospital mortality (relative risk ratio of death, 0.71 (95% CI, 0.62 to 0.82) and shorter hospital and ICU LOS. Further, high-intensity staffing was associated with a lower ICU mortality in 14 of 15 studies (93%) with a pooled estimate of the relative risk for ICU mortality of 0.61 (95% CI, 0.50 to 0.75). High-intensity staffing reduced hospital LOS in 10 of 13 studies and reduced ICU LOS in 14 of 18 studies without case-mix adjustment. High-intensity staffing was associated with reduced hospital LOS in 2 of 4 studies and reduced ICU LOS in both studies that adjusted for case mix. Most importantly, no study found an increased LOS with high-intensity staffing after case-mix adjustment. This is the only meta-analysis available on ICU staffing models.

Employing a different experimental approach, several other multi-institutional prospective studies have confirmed improved mortality and shorter LOS with critical care physician staffing in patients with specific disorders (Table 96-2). Using data collected prospectively from a 68-center cohort group, Nathens and colleagues evaluated the relationship between an open unit and an intensivist

Table 96-1 Summary of Meta-Analyses on Impact of Intensivists on Intensive Care Unit Patient Outcomes

Study	No. of Trials	No. of Subjects (Intervention/No Intervention)	Intervention	Control	Outcomes
Pronovost et al, 2002 <sup>6</sup>	27	14,356/13,117	High intensity; intensivist staffing models	Low intensity; intensivist staffing models	Lower hospital mortality (relative risk [RR], 0.71; 95% confidence interval, 0.62-0.82); lower intensive care unit (ICU) mortality (RR, 0.61; 95% CI, 0.50-0.75); trend toward shorter ICU and hospital length of stay

## Table 96-2 Summary of Recent Prospective Studies on Impact of Intensivists on Intensive Care Unit Patient Outcomes in Specific Diseases and Conditions

Study	Disease Studied	No. of Subjects (Intervention/No Intervention)	Intervention	Control	Outcomes
Nathens et al, 2006 <sup>7</sup>	Trauma	5228/1561	Closed; intensivist model or intensivist as comanager	Open intensive care unit (ICU)	Hospital relative risk of death in the intensivist model ICUs was 0.78 (95% confidence interval [CI], 0.58-1.04) compared with an open ICU model. The beneficial effect was greatest in elderly patients, in whom the hospital relative risk of death was 0.55 (95% CI, 0.39-0.77).
Treggiari et al, 2007 <sup>8</sup>	Acute lung injury/ acute respiratory distress syndrome	684/391	Closed unit or high intensity; intensivist model	Open or intensivist by consultation only	Acute lung injury patients cared for in closed ICUs experienced reduced hospital mortality (adjusted odds ratio, 0.68; 95% CI, $0.53-0.89$ ; P = .004). Consultation by a pulmonologist in open ICUs was not associated with improved mortality (adjusted odds ratio, 0.94; 95% CI, $0.74-1.20$ ; P = .62).

model on patient mortality after severe injury.<sup>7</sup> In this study of 6789 patients, two thirds of whom where treated in an ICU staffed with an intensivist model (defined as an ICU where critically ill trauma patients were either on a distinct ICU service led by an intensivist or were comanaged with an intensivist) showed improvements in outcome compared with contemporaneous patients cared for in the open ICUs. After adjusting for differences in baseline patient characteristics, the hospital relative risk for death in the intensivist-model ICUs was 0.78 (95% CI, 0.58 to 1.04) compared with an open ICU model. The beneficial effect was greatest in elderly patients, in whom the hospital relative risk for death was 0.55 (95% CI, 0.39 to 0.77) in the intensivist-model group.

Treggiari and associates found that patients with acute lung injury (ALI) fare better when treated in closed units.<sup>8</sup> The participant ICUs from the King County Lung Injury Project, a population-based cohort of patients with ALI, were surveyed as to ICU structure, organization, and patient care practices using a self-administered questionnaire completed by the medical director and nurse manager. Closed ICUs were defined as units that required patient transfer to or mandatory patient comanagement by an intensivist, and open ICUs were defined as those relying on other organizational models. The main end point in this study was hospital mortality. Of 24 eligible ICUs, 13 ICUs were designated as closed and 11 as open. Complete survey data were available for 23 of the 24 ICUs (96%). Higher physician and nurse availability was reported in closed than in open ICUs. A total of 684 (63%) of 1075 patients with ALI were cared for in closed ICUs. After adjusting for potential confounders, patients with ALI cared for in closed ICUs experienced reduced hospital mortality (adjusted odds ratio, 0.68; 95% CI, 0.53 to 0.89; P = .004). Consultation by a pulmonologist in open ICUs was not associated with improved mortality (adjusted odds ratio, 0.94; 95% CI, 0.74 to 1.20; P = .62).

Although only a minority of ICUs in the United States are managed by an intensivist-directed team (estimated at 25%), I believe that this staffing model should be the standard because it is an effective method to improve safety, reduce mortality, and improve efficiency. Personnel shortages in key team member categories will inhibit attaining this ideal in the near future.

#### IS IT THE MULTIPROFESSIONAL TEAM OR THE INTENSIVIST (OR BOTH) THAT LEADS TO THE DIFFERENCE IN QUALITY?

Although the presence of intensivists has been the focus of most investigations, many believe that care in the ICU is best provided by a team of medical professionals who integrate their individual skills and knowledge at the patient's bedside and merge these various views with the patient's beliefs to develop and deliver a unique but evidenced-based, patient-centered care plan. The care team model has been proposed for many complex clinical environments. These include specialty clinics, ICUs, and emergency departments as well as primary care offices. The members of the team will change according to the environment and clinical issues but generally will include at least a lead physician, a nurse, appropriate allied health care practitioners, and the patient and family. This model of care is quite different from the traditional one in which a physician, often at a distance from the unit, independently determines the care plan, and the other health providers deliver what is ordered to a patient who has not been actively involved in medical decision making. The ICU team model requires face-to-face discussion and active participation of multiple specialties to develop the unified care plan that then is executed by the bedside caregivers and team members.

The potential benefits of the team model for the critically ill were emphasized by the founders of the Society of Critical Care Medicine more than 40 years ago. In the first issue of the journal Critical Care Medicine, the Society's President, Max Harry Weil, stated, "It is the purpose of our Society to improve the care of patients with acute life-threatening illnesses and injuries and to provide optimum facilities for this purpose. We commit ourselves to these ends by creating a good hospital environment with qualified teams of physicians, nurses, technicians and medically oriented engineers" (italics added for emphasis).<sup>9</sup> As mentioned, although most of the papers discussed previously support the presence of an intensivist model in improving ICU care, the team and team process have received little or no scientific study. Although it can be argued reasonably that the intensivist model implies that a critical care team is used to deliver care, without explicit investigation of individual ICU practices, strong conclusions about the impact of the team model independently of the intensivist cannot be made.

In further evaluating the studies selected by Pronovost and colleagues in the aforementioned meta-analysis,<sup>o</sup> there were 10 studies reporting change to daily multidisciplinary management rounds in closed units with a high-intensity intensivist model from an open model without these team rounds. All demonstrated improved survival when the team rounding model (with an intensivist) was introduced. The effect on LOS was less apparent, but no report favored a nonteam, nonrounding model. Multidisciplinary rounds can lead to improved collaboration and communication among caregivers that can result in increased safety and overall better performance, especially during crisis situations.<sup>10</sup> In a study of 147 ICUs with 107,324 patients throughout Pennsylvania it was found that the presence of multidisciplinary rounds even without a dedicated intensivist was associated with improved ICU mortality.<sup>11</sup> After adjusting for patient and hospital characteristics, multidisciplinary care was associated with significant reductions in the odds of death (odds ratio [OR], 0.84; 95% confidence interval [CI], 0.76-0.93 [P = .001]). When stratifying by intensivist physician staffing, the lowest odds of death were in intensive care units (ICUs) with high-intensity physician staffing and multidisciplinary care teams (OR, 0.78; 95% CI, 0.68-0.89 [P < .001]), followed by ICUs with low-intensity physician

staffing and multidisciplinary care teams (OR, 0.88; 95% CI, 0.79-0.97 [P = .01]), compared with hospitals with lowintensity physician staffing but without multidisciplinary care teams. The effects of multidisciplinary care were consistent across key subgroups including patients with sepsis, patients requiring invasive mechanical ventilation, and patients in the highest quartile of severity of illness.

Even without rigorous scientific study, some experts suggest that working teams of medical professionals are the future of health care delivery and can have a significant impact on hospital safety.<sup>12</sup> According to a report from the Institute of Medicine, Crossing the Quality Chasm, the team approach to health care delivery is part of the solution to the identified lack of safety, efficacy, and efficiency of the medical system in the United States and throughout the world.<sup>13</sup> In this report, it is suggested that health care teams become the standard for the future, replacing individual, autonomous practitioners. Further, to bring about this vision of health care, there is need "to invest in enhancing organizational capacity, building an information infrastructure, and in training multidisciplinary care teams."<sup>14</sup> There are no high-quality scientific data to support the contention that a team is the best delivery system for medical care, but there are suggestions from other highly complex, risky endeavors that this is true.

#### WHAT CAREGIVERS SHOULD BE MEMBERS OF THE MULTIDISCIPLINARY TEAM AND MAKE DAILY ROUNDS?

Besides intensivists and nurses (including nurse practitioners and clinical specialists), ICU multidisciplinary rounding teams usually include clinical pharmacists and respiratory therapists whose unique skills and knowledge have been shown to improve patient outcomes and LOS.15-21 Other members of the ICU rounding team may include dietitians, ethicists, occupational therapists, physical therapists, chaplains, speech and language pathologists, patient, families, and others. Team processes improve coordination of care. Better coordination results in improved survival with less expense. In Pollack's study discussed previously,<sup>4</sup> coordination was best achieved by managing a unit with an intensivist model whereby the team was responsible for developing and implementing most of the care plans. Communication failure is less likely when all participate during the discussion and decision process.

It has been recognized that not all teams behave the same. When asked about the quality of the professional interaction of the team, physician and nurse members often have dramatically differing opinions.<sup>22,23</sup> Physicians usually rate team collaboration higher than nursing (and other caregiving) colleagues. Clinical stress and administrative overhead can adversely affect team function by distracting members from the planning and evaluation process. Different patient concerns can benefit from different makeup and function of teams. The ICU and the operating room are similar: highly technical, emotionally charged environments with identifiable care teams. Poor communication has been identified as the primary source leading to medical errors and injuries in both environments. Improving communication by reducing the usual hierarchical

behaviors has improved safety in other risky industries, such as aviation. Applying lessons learned in the air to medical teams often is advocated. Team skills and communication methods can be taught, practiced, and acquired.<sup>24,25</sup> Crew resource management and training<sup>26</sup> may improve team function and safety in the operating room and ICU.<sup>27,28</sup> The impact of this approach to team function improvement remains to be studied.

#### WHAT MIGHT A DISTANT INTENSIVE CARE UNIT TEAM WITH COMPLETE, REAL-TIME ELECTRONIC ACCESS TO PATIENTS CONTRIBUTE TO IMPROVED OUTCOMES?

Advancements in electronic data management and communication have led to remarkably capable systems of remote patient monitoring and the development of telemedicine. The potential for improving ICU care by 24-hour remote monitoring (and interaction with the bedside team) was demonstrated almost 10 years ago and has been suggested as a way to deal with the shortage of ICU physicians.<sup>29</sup> Systems are commercially available and are being installed in a wide variety of ICUs. Anecdotal and systematic information on their impact is emerging. Although not the main thrust of this review, it seems appropriate to mention this emerging technology and the potential impact it might have on ICU structure and team function. As a technologyenabled care model, the electronic ICU, or eICU, represents a new paradigm for delivery of critical care services.<sup>30</sup> A major component of the model is the use of telemedicine to leverage clinical expertise and facilitate around-the-clock proactive care by intensivist-led teams of ICU caregivers. In addition, functional data presentation formats, computerized decision support, and smart alarms are used to enhance efficiency, increase effectiveness, and standardize clinical and operating processes. Further, the technology infrastructure facilitates performance improvement by providing an automated means to enhance application of best practices, measure outcomes, track performance, and monitor resource use. The eICU system is designed to support the multidisciplinary intensivist-led team model and incorporates comprehensive ICU re-engineering efforts to change practice behavior at the bedside.

Installation of an eICU system staffed remotely for 19 hours a day from noon until 7:00 AM in two ICUs in a community teaching hospital system resulted in improved acuity-adjusted mortality and reduced LOS.<sup>31</sup> The ICUs studied were open models, and this did not change during the study period. The magnitude of these improvements (mortality odds ratio, 0.73; 95% CI, 0.55 to 0.95) was similar to those reported in studies examining the impact of implementing on-site dedicated intensivist staffing models. However, factors other than the introduction of off-site intensivist staffing may have contributed to the observed results. These include the introduction of computer-based tools and the increased focus on ICU performance.

As eICU systems have expanded, the paradigm of ICU care delivery has evolved. This new care model provides an operational and technology platform that allows a multiskilled team to help ensure the consistent and timely achievement of the therapeutic goals established by the bedside team. With no other clinical responsibilities, the remote team is reliable and efficient. The responsibilities of the remote team may include frequent monitoring of the progress of each patient, titration of therapies to achieve care plan objectives, identification and initiation of treatment of emerging problems, enhancing communication among members of the care team, and monitoring of best practices use in care. The actual division of responsibilities between the on-site and remote teams varies depending on the particular ICU structure (e.g., on-site intensivists, hospital staff), culture, and time of day. One goal is to provide seamless 24-hour, 7-days-a-week oversight of all ICU patients and ensure the highest level of care possible.<sup>32</sup>

Because ICU staffing with an intensivist present during daylight hours is associated with improved patient outcomes, increasing this coverage to full time (24 hours, 7 days a week) should further improve care. Several ICU systems are based on this assumption, and, in pediatrics, this staffing pattern has become routine. Although no systematic data are available to support this contention, both logic and anecdote indicate that it is correct. Achievement of full-time coverage by an intensivist-based ICU team should be a quality goal. Shortages of all categories of ICU caregivers, including intensivists make this goal elusive.

#### AUTHOR'S RECOMMENDATIONS

- Critically ill adults and children cared for in ICUs managed by a board-certified (or eligible) intensivist experience lower riskadjusted mortality.
- ICUs managed by a board-certified intensivist are more efficient in that the ICU and total hospital LOS are shorter.
- There is a correlation with the "intensity" of the intensivist model in that the more involved the intensivist is in patient management (i.e., closed unit), the greater is the improvement in mortality and LOS.
- There are emerging but convincing data that 24-hour oversight by an intensivist (on-site or distant) offers even better outcomes and may be the optimal model for ICU care.
- An essential component of intensivist staffing is the presence of an ICU team-based model for patient management. This is the ideal care model for critically ill patients.
- Individual team members have been shown to improve specific components of patient care (e.g., daily rounding with clinical pharmacists reduce medication errors), and their involvement enhances measurable intermediate outcomes.
- The impact of a care team is greater than the sum of its parts; reinforcement and integration of clinical goals, reduced communication failures, and enhanced collaboration and safety are important benefits of well-functioning teams.

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## Is a Closed Intensive Care Unit Better Than an Open Intensive Care Unit?

Ho-Geol Ryu, Todd Dorman

Intensive care units (ICUs) started as intensive nursing care locations. In 1958 at Baltimore City Hospital, now known as Johns Hopkins Bayview Medical Center, full-time physician staffing was added. Thus began intensive multiprofessional team units. This historical perspective is important because it demonstrates that the first ICUs started as open care units. As direct physician involvement became a more integral part of ICU culture, interest in closing these ICUs also grew. Whether closing an open ICU improves clinical or financial outcomes is an extremely important question in today's health care environment. Health care costs continue to increase, placing pressure on the health care system to establish and support cost-effective care models. Given there are few apparent upfront costs of running an open ICU, and given the politics involved in many ICUs, migration to a closed unit has rightfully been questioned. Fortunately, there is sufficient evidence to inform all health care providers, health systems, and policy makers about the benefits associated with closing an open ICU.

#### DEFINITIONS

Before reviewing the evidence for closing ICUs, it is important to establish key terminology. Four models of care have been described in ICUs. These models range from open to closed and progress from less intensive physician coverage to more intensive physician coverage.<sup>1,2</sup> An *open* unit is one in which all staff physicians can admit, discharge, and manage their own patients in the ICU. The next level of intensity is known as the *elective consultation model*. This is an open unit in which an intensivist is available but will only see patients when directly and electively consulted. The next level of intensity is known as the *mandatory consult model*. This is found in units staffed with full-time intensivists who consult on all patients in the ICU. Last is a *closed* model of care in which the intensivist becomes the patients' attending physician of record during the stay in the ICU.

In 1997, the American Thoracic Society, the American College of Chest Physicians, and the Society of Critical Care Medicine organized the Committee on Manpower for Pulmonary and Critical Care Societies (COMPACCS). The charge to this committee was to document current and future needs for critical care and pulmonary specialists.

According to the COMPACCS survey, most ICUs in the United States cannot be classified as either open or closed. Of nearly 6000 noncoronary ICUs in the United States, 23.1% represented adaptations of the full-time intensivist model (closed). In these units, all or most of a patient's care is provided or directed by a dedicated physician trained in critical care. Open units were used in 14.2% of all units studied. The remaining 63% used either the consultant intensivist model, in which an intensivist consults for another physician but does not have primary responsibility for care (13.7%), or a multiple consultant model, in which a number of specialist consultants are involved in patient care without a designated consultant intensivist (45.6%).<sup>1</sup>

In their landmark article on the impact of organizational structure and outcomes during critical illness, Pronovost and associates regrouped these care paradigms into two distinct models.<sup>2</sup> The low-intensity physician staffing model combined the open and elective consult models, whereas the high-intensity physician staffing model combined the mandatory consult and closed models of care. This classification has the advantage of including most present ICUs and thus making models of care comparable for study. Consequently, we use this classification as a surrogate for the questions at hand, effectively converting the question, Is a closed ICU better than an open ICU? into, Is a high-intensity physician-staffed ICU better than a low-intensity physician-staffed ICU?

#### **OUTCOME MEASURES**

The performance measures of interest include clinical and financial outcomes. Clinical outcomes include morbidity and mortality and ICU and hospital length of stay (LOS). The financial outcomes of interest include ICU and hospital cost of care. Additional outcomes that are of interest and for which evidence exists include educational performance and impact on consultation numbers.

#### Intensive Care Unit and Hospital Mortality

ICU mortality has been shown to be lower in highintensity staffed ICUs in most (14 of the 15 studies, 93%) of the studies reviewed in the systematic review with an overall unadjusted risk ratio (95% confidence interval [CI]) of 0.61 (0.50 to 0.75).<sup>2</sup> Of the 12 studies that reported ICU mortality after adjusting for severity of illness, 9 studies (75%) found a decrease in mortality.

Hospital mortality also was lower in high-intensity staffed ICUs. In 16 of the 17 studies (94%) in the systematic review, the unadjusted risk ratio (95% CI) was 0.71 (0.62 to 0.82).<sup>2</sup> The one discrepant study did not show a statistically significant difference. Of the 14 studies that reported mortality after adjusting for severity of illness, 9 (64%) showed a decrease in mortality, while the remaining 5 studies did not show a statistically significant difference.

Data for these studies were collected in adult and pediatric ICUs, university and community hospital ICUs, American and international ICUs, full ICU populations, and subsets of ICU populations. Approaches include state-level analysis using multifactorial design and systematic review. The homogeneity of the data is quite striking. There is no randomized control trial because one would be impossible to design and conduct. In addition, given the homogeneity of the evidence, many would argue that randomization of patients to a low-intensity staffing model of care is unethical.

The exact mechanisms by which an intensivist improves mortality remain unknown. However, it has been hypothesized that being more familiar with the evidence regarding critical care and being able to rapidly detect and treat problems contribute to better outcomes. In addition, in the higher intensity model of care, the intensivist serves as an integrator of information and recommendations from a broad array of consultants. This individual then orchestrates the care episode by balancing decisions across a range of pathophysiologic states. Supporting this proposal is the trial done by Varelas and associates.<sup>3</sup> In this observational cohort study evaluating the impact of a neurointensivist-led ICU team on the mortality in a neurosciences ICU, there was a 21% relative reduction in mortality. The characteristics attributed to the documented improvement in outcome were introducing new and more intensive monitors, development of standard protocols, weekly meetings with nurse supervisors, and educational efforts directed at house staff and nursing. In addition, a similar study that evaluated the impact of a specialized neurocritical care team also found similar reductions in mortality (odds ratio, 0.7 [0.5 to 1.0]).<sup>4</sup>

Further evidence supporting the benefits of a highintensity physician-staffed model can be found in work of Nathens and colleagues.<sup>3</sup> This study analyzed data from designated and nondesignated trauma centers. Hospital mortality in this large multicenter (68 contributors) prospective cohort study was lower in high-intensity staffed ICUs.<sup>5</sup> After adjusting for severity of illness, the relative risk ratio (95% CI) was 0.78 (0.58 to 1.04). Subgroup analysis demonstrated a 45% reduction in hospital mortality in elderly patients (age > 55 years). Interestingly, these authors observed a 36% reduction in mortality associated with high-intensity staffed trauma ICUs in trauma centers and a 33% reduction in ICU mortality when the ICU director was board certified in critical care. This adds credence to the proposal that an intensivist improves outcome by being a dedicated expert. The concept that intensivists serve as content experts in the science of the care of the critically ill and injured is further supported by a recent retrospective cohort study. This investigation compared patients on mechanical ventilation for more than 4 days in high-intensity staffed ICUs with similar patients in low-intensity staffed ICUs. Data were obtained from 29 academic centers across the United States, and assessment included select quality indicators as primary outcome measures.<sup>6</sup> The study showed that patients in high-intensity staffed ICUs were more likely to receive deep venous thrombosis prophylaxis, stress ulcer prophylaxis, spontaneous breathing trials, interruption of sedation, and intensive insulin treatment. Another recent study addressed the effect of ICU staffing on hospital mortality in patients with acute lung injury.<sup>7</sup> This investigation compared 24 ICUs (13 closed and 11 open) and, after adjusting for confounders, found that patients in the closed ICUs were more likely to receive lung protective ventilation and had lower mortality with an odds ratio (95% CI) of 0.68 (0.52 to 0.89). Taken together, these studies all support the hypothesis that intensivists orchestrate care and are more consistent at applying up-to-date and relevant evidence resulting in higher quality of care (better clinical outcomes).

### Intensive Care Unit and Hospital Length of Stay

LOS in the ICU or in the hospital is a unique indicator in that it may not only reflect the quality of patient care but also the efficient use of potential resources, which can be translated into revenue generated by the ICU or hospital. In the systematic review by Pronovost and colleagues, there were 18 studies that analyzed data on ICU LOS.<sup>2</sup> Seventeen of the 18 studies (94%) demonstrated either no change (6 studies) in ICU LOS or a 14% to 51% reduction (11 studies) in ICU LOS when a high-intensity staffing model was used.<sup>2</sup> One study (6%) demonstrated a longer ICU LOS with a high-intensity staffing model.<sup>8</sup>

Although 18 studies reported on ICU LOS, only 13 included data on hospital LOS. Twelve of the 13 (92%) demonstrated either no change (6 studies) in hospital LOS or a 14% to 42% reduction (6 studies) in hospital LOS when a high-intensity staffing model was used.<sup>2</sup> The study that reported longer ICU LOS also reported longer hospital LOS.<sup>8</sup>

The one study that demonstrated longer ICU and hospital LOS compared high-intensity staffing in a neurologic-neurosurgical specialty ICU to that of low-intensity staffing in a general ICU and focused on the subpopulation within this general ICU of patients with neurologic or neurosurgical diagnoses. This study did not adjust for severity of illness, thus limiting its interpretation. Furthermore, the authors of this report attributed the longer ICU and hospital LOS to the lack of a stepdown unit for the specialty ICU and to more aggressive treatment in the specialty ICU. Other published studies that evaluated the association between LOS and staffing models in neuroscience ICUs have demonstrated 12% and 17% reductions in ICU LOS, similar to those in the systematic review.<sup>3,4</sup>

#### **Health Care Cost**

Reduced morbidity and mortality and LOS are important clinical outcomes. However, given the present health care cost crisis, these improvements also need to be affordable. This is particularly important in light of the high cost of ICU care, which has been estimated to be 1% of the gross domestic product of the United States.<sup>9</sup> The cost of implementing a high-intensity physician staffing model needs, to some extent, to be recouped from benefits of such a model. Importantly, the benefit may result from either hospital or physician payments.

Intensivists have been shown to reduce unnecessary admissions to the ICU.<sup>10</sup> This opens beds for other patients and typically leads to an increase in the severity of illness of the ICU. This may, in turn, translate into higher physician billing. Appropriately placing a patient in a lower-intensity setting also may save cost and thus improve margin in a capitated environment. The financial benefit of shorter ICU LOS and lower resource use with the high-intensity staffing model reduces the risk for canceled surgeries and refusal of requests for ICU transfers. This has the potential to further generate hospital revenue while preserving the mission of many institutions.

In a study comparing the high-intensity physician staffing model to a low-intensity staffing model in a single academic medical center, the high-intensity ICU staffing was associated with lower costs (34.500 versus 47.500; P < .01), fewer complications, and shorter LOS.<sup>11</sup> In a study that evaluated the effect of intensivist consultations using remote monitoring technologies such as video conferencing and computer-based data transmission allowing 24-hour intensivist oversight, the authors found a 33% to 36% reduction in ICU costs along with decreases in hospital and ICU mortality, complications, and LOS.<sup>12</sup> The benefits of reduced complications cannot be underestimated in today's world of pay for performance and restriction of payment for hospital-acquired complications. Another study that investigated the effect of daily ICU rounds by an intensivist on costs in patients undergoing esophageal resection revealed a 61% increase in hospital costs associated with lack of daily rounds.<sup>13</sup> In other words, high-intensity physician staffing, which includes daily rounds, was associated with significant financial benefits. Mirski and coworkers demonstrated an average cost saving of \$5900 per case when patients diagnosed with intracranial hemorrhage were treated by a neuroscience ICU team compared with being treated in medical or surgical ICUs of the same institution.<sup>1</sup>

In response to the evidence favoring high-intensity physician staffing, the Leapfrog group established a standard for physician staffing in the ICU. This standard stated that a compliant ICU would include (1) ICUs managed or comanaged by intensivists, (2) continuously present intensivists assigned duties only in the ICU during daytime hours, (3) responses to pages during "off" hours from the ICU within 5 minutes 95% of the time, and (4) availability of a qualified physician-extender to reach the ICU patient within 5 minutes when the intensivist is not present. A recent study has used published data to examine a financial model evaluating the revenue and expenses associated with implementing the Leapfrog standards. This financial model used conservative estimates and also assessed the effect of the size of the ICU. The variables included in the financial model were mean occupancy rate and mean LOS, salary and benefits of intensivists and physician-extenders, hospital net income from displacement of nonintensivist physicians, hospital revenue from intensivist billings, and costs associated with ICU admission and stay. The analysis demonstrated cost savings ranging from \$510,000 to \$3.3 million dollars per year for 6- to 18-bed ICUs that were directly proportional to the size of the ICU.<sup>15</sup>

### Educational Outcome and Consultation Rate

Manthous and associates evaluated the impact of implementation of a high-intensity physician staffing model on educational outcomes. This study compared medical residents' critical care in-service examination scores in a community teaching hospital. Despite otherwise similar levels of training, examination scores improved after implementation of a high-intensity staffing model.<sup>16</sup>

Physicians providing subspecialty consultation have raised the concern that implementation of a high-intensity staffing model might affect consultation volume. To address this, Reynolds and colleagues compared high-intensity staffing to low-intensity staffing in a medical ICU and noted that the number of consultations was unchanged.<sup>17</sup> Conversely, Hanson and colleagues showed a 43% decrease in consultations when comparing high-intensity staffing to low-intensity staffing in a university surgical ICU.<sup>11</sup> Importantly, consultation volume was not reduced to zero, and back-fill work by consultants was not assessed.

#### LIMITATIONS

There are several limitations to the published evidence that should be discussed. First, using the grading system proposed by the American College of Chest Physicians, the quality of evidence is fair to low. Nonetheless, the best available evidence evaluating virtually all measurable outcomes homogeneously favors high-intensity staffing of ICUs. Second, most of the evidence was obtained and presented by intensivists. Thus, there may be a publication bias. Third, most data come from observational cohort studies with a before-after design. These contain an inherent risk for temporal bias related to implementation of other changes in patient management. These limitations are important, but as stated earlier, the homogeneity of the data from adult and pediatric ICUs, university and community hospital ICUs, American and international ICUs, full ICU populations, subsets of ICU populations, state-level analysis using multifactorial design, and a systematic review is quite striking. Importantly, the magnitude of the clinical benefit, with a median absolute risk reduction of 10%, is greater than the benefit reported with medical and device interventions in critical illness. Finally, these important clinical benefits are mirrored by reductions in cost. Consequently, implementation of a high-intensity staffing model (e.g., closing an ICU) can be accomplished at low risk yet with high expected benefits.

#### **AUTHORS' RECOMMENDATIONS**

- Peter Safar created the first physician-staffed ICU in 1958. In 1977, Safer and Grenvik postulated that an intensivist-led ICU would translate into better patient outcomes.<sup>18</sup> The evidence now supports the concept that high-intensity physician staffing is associated with decreased ICU and hospital mortality, shortened ICU and hospital LOS, reduced costs, and enhanced education.
- Despite purported obstacles, failure to implement highintensity staffing in ICUs places patients at risk and increases health care costs. Although many individual interventions, including daily rounds by an intensivist,<sup>12,19</sup> 24-hour intensivist coverage,<sup>20</sup> pharmacist consultation on ICU rounds,<sup>21</sup> and lung protective ventilation<sup>22</sup> have been associated with improved patient outcome, staffing the ICU with intensivists appears to be the most effective way of decreasing ICU mortality and morbidity and controlling costs.<sup>23</sup> Thus, based on published evidence, policy makers should help remove obstacles and create incentives to ensure that all patients, when critically ill or injured, are cared for in a high-intensity staffed ICU.
- Compared with low-intensity staffing of ICUs, high-intensity staffing of ICUs is associated with lower mortality, shorter ICU and hospital LOS, reduced health care costs, and improvements in resident education.

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## Does Telemedicine Have a Role in the Intensive Care Unit? What Is It? Does It Make a Difference?

Yuval Bitan, Mark E. Nunnally

The modern intensive care unit (ICU) arose when physicians located intense monitoring and specialized therapeutics in one specific place. The physicians assumed that an intense level of care would improve outcomes. Many agree the assumption has been correct. Today's ICU is filled with many promising, albeit incompletely explored, innovations, some of which challenge the geographic segregation of care. None challenges the concept as directly as remote telemedical monitoring. Such an innovation has the potential to fundamentally change the way critical care is provided. Any discussion of telemedical care must consider which services can be provided remotely, which must be performed at the bedside, how remote monitoring helps or harms the patient, and how an innovation can be integrated into a system it is supposed to enhance.

Telemedicine is a system for monitoring patient status and for prescription of interventions from a remote location.<sup>1</sup> Early investigations evaluated telemedicine in the care of psychiatric patients,<sup>2</sup> primary care on Native American reservations,<sup>3</sup> and dermatologic diagnoses.<sup>4</sup> In each historical case, the premise was to extend services to people at places where services had been limited. Telemedicine information systems transmit patient information to remote monitoring displays. The telemedical ICU (tICU), a relatively recent extension of telemedicine, has evolved over a short period of time, from 1 system in the United States in 2000 to more than 30 in 2007.<sup>5</sup> Current tICU systems can now monitor 100 to 150 patients remotely.<sup>6</sup> With tICU, a high level of patient-physician interaction is possible because of improved communication and data access, replacing on-site clinicians for some care activities.

Many arguments favor the tICU. Technology assists and extends an expert's skills to more patients. Data availability aids decision making. Efficiency is improved. These arguments are easy to accept, but a balanced discussion centers on how work is performed in the ICU, and any evidence should be viewed as preliminary.

#### **CURRENT EVIDENCE**

Several studies of tICUs<sup>7–9</sup> cite improvements in length of stay, mortality, cost, and patient satisfaction. In 1997, a 10-bed surgical and trauma open-model ICU underwent

a pilot study of around-the-clock remote monitoring and virtual rounds.7 Severity-adjusted mortality, complications, and length of stay decreased, and costs were reduced as a consequence. In 2001, an off-site remote care center for monitoring and telemedical intervention produced similar findings in three ICUs in two affiliated hospitals.<sup>8</sup> Although ICU mortality was unchanged, hospital mortality, length of stay, and costs decreased. On subgroup analysis, medical ICU mortality improved, whereas surgical ICU mortality did not. Finally, in 2005 and 2006, a telemedical robotic device that moved from room to room "rounded" in a neurologic ICU.<sup>9</sup> Through the device's monitor and camera, remote intensivists observed patients in addition to other clinical images and information displayed on an integrated dashboard. The device also became a source for walkup consultations by nurses. Response times to several neurologic emergencies were improved, as were bed occupancy and costs. These three studies, all with historical controls, represent the clinical evidence of tICU capabilities. The first two chart the development of the major commercial provider of tICU services in the United States. One additional study<sup>10</sup> demonstrated a decrease in ventilator days, up to 2 days (25%), correlating with the degree of tICU intervention. Independent confirmation of these findings is limited. Table 98-1 summarizes the studies.

### IS THE TELEMEDICAL INTENSIVE CARE UNIT NEEDED?

It has been argued that intensive care is best provided by specialized intensivists.<sup>11</sup> It is estimated, however, that only about one third of ICU patients are cared for by intensivists.<sup>12</sup> Such a shortage of available specialists mandates novel solutions. The tICU extends the expert care of an intensivist to a large number of patients, including those in rural or underserved hospitals.

Intensive care is an expensive part of an expensive health care industry.<sup>13</sup> Many patients make the largest health care expenditures at the end of their lives, especially if terminal illness brings them to the ICU. For those who believe tICUs can increase the providerto-patient ratio, telemedicine may spread the costs of

Table 98-1 Overview of Study Design and Findings of Major Studies Involving Telemedical Intensive Care Unit Care								
Study	Design	Intensive Care Unit (ICU) Type	No. of Patients Studied	Intervention	Key Findings	Notes		
Rosenfeld et al, 2000 <sup>7</sup>	Observational triple cohort	10-bed surgical ICU, open unit	201: intervention 225, 202 in control groups	Round-the-clock monitoring in intensivists' homes	Adjusted mortality ↓ 68% and 42% ↓ Complications ↓ LOS 26% and 35% ↓ Costs 25% and 31%	Formal video rounds about 50% of days Twice-daily discussions with bedside nursing 45% of control patient outliers, who ↓ from 8.2% to 4.5% of population with intervention		
Breslow et al, 2004 <sup>8</sup>	Observational before-after trial	10-bed medical ICU, 8-bed surgical ICU, mostly open model	1396 baseline, 744 intervention	Remote ICU in dedicated facility; variable intervention level	↓ Hospital mortality Significant ↓ medical ICU mortality ↓ ICU LOS ↓ Costs	Virtual rounds every 1 to 4 hr Remote intensivists involvement in all codes ↓ LOS outliers in surgical ICU Variability in autonomy given to remote team		
Cowboy et al, 2005 <sup>10</sup> ( <i>abstract only</i> )	Retrospective before-after study	3 ICUs, details not specified	2745 preintervention, 1872 postintervention	Remote ICU care program	<ul> <li>Ventilator days: 25%, 18%, 2% in 3 groups (significance not specified).</li> <li>Significance correlation with degree of intervention</li> </ul>	Addressed ventilation days only; authors concluded remote ICU team increased implementation of best practices		
Vespa et al, 2007 <sup>9</sup>	Observational before-after study	Neurologic ICU	578 preintervention, 640 postintervention	Nighttime robotic rounds	<ul> <li>↓ LOS by 0.5 days</li> <li>↓ Attending physician response latency</li> <li>↓ Costs attributed to ↓ LOS</li> </ul>	Robot facilitated remote examination, discussions with nurse Nursing walkups accounted for 54% of pages Visual information judged to be 67% of critical data		

specialty care across a larger pool of patients. Proponents of the tICU suggest that, by promoting "best practices," telemedical oversight can optimize resource use by both evidence-based allocations and shorter patient stays.<sup>5</sup> For some, the inconsistency of practice and reluctance of practitioners to adopt evidence-based standards impede the quality of care. Concentrating specialist care in large entities makes it is easier to standardize intensivist care. If standardization is a metric of quality, telemedical intensive care can raise care to a higher level.

#### WHAT POSITIVE RESULTS MIGHT THE TELEMEDICAL INTENSIVE CARE UNIT PRODUCE?

The forces driving the demand for telemedical services do not necessarily represent the areas in which telemedicine might produce the greatest benefit. Remote monitoring technologies could improve the process of care now. Data processing and display might make it easier to monitor patients with complex medical conditions. Virtual rounds could enhance the feedback intensivists need to adapt to a patient's changes in physiologic status. Telemedical workstations could enhance bedside care because they combine and display data in formats that facilitate diagnosis and treatment. With technologies assembled ad hoc around the critically ill patient, data integration in critical care lags behind that in many other domains. For example, no "dashboard" replicates the central display and record of information found in transportation.<sup>14</sup> The developments that make the tICU possible could help improve the portability of patient data. Unified and reconciled databases potentially simplify care. This long-elusive goal was most famously popularized by the ill-fated initiative for a national patient medical record.<sup>15</sup> Telemedical monitoring not only supports better displays and logical combinations of data, it also requires them.

Rather than replacing bedside care, telemedical systems bring a new level of monitoring to critical care. Vigilance may improve with the "virtual" presence of an additional provider. By bringing critical data to one location, telemedical providers can round on their patients continuously, assessing changes and responses to therapy in real time. Impressions based on changing patient data can be brought to the bedside team to inform care. In this way, the teleintensivist becomes the ultimate "smart" monitor. Ideally, teamwork between the bedside practitioners and remote intensivists would optimize this feature. The role of social factors in this kind of vigilance is not described.

To summarize, the benefits of telemedical intensive care include a format for sharing medical information across institutions, integration of diverse technologies to improve diagnosis and treatment, a new level of vigilance with a virtual presence, and new opportunities for coordination of insight and technology. Evidence for these benefits thus far is circumstantial.

#### WHAT ARE THE POTENTIAL DISADVANTAGES OF THE TELEMEDICAL INTENSIVE CARE UNIT?

Health care, like many complex domains, is made and broken in systems. Telemedical services add another layer of complexity to a system that must manage multiple simultaneous concerns, large volumes of data, resource allocation, and even political conflicts. Potential disadvantages lie in the difference between real and virtual bedside presence, excessive influence of third parties, and the need to facilitate, rather than confound, the work being performed on-site.

Although some cognitive activities may be manageable remotely, physical aspects of care require proximity. Moreover, management of intensive care through a virtual presence is not bedside management; it risks ignoring or losing bedside expertise. The flexibility of local experts helps a complex system to function properly. Experienced ICU nurses are often able to predict when a patient's status might decline. Expert practitioners develop an instinctive sense of problems based on previous experiences.<sup>16</sup> How telemedical care can integrate bedside expertise is an open question currently better explored in nonmedical systems. In unmanned aircraft systems, pilots have been reluctant to trust automated remote systems and were most comfortable putting decisions in the hands of the on-site pilot.<sup>17</sup> Research with decision aids<sup>18</sup> suggests that the process of assisting human expertise is hard to study and intrinsically prone to mistakes. With telemedicine, the duties of the bedside clinician might change. Telemedical supervisors might reduce the local clinician to a simple monitor. In such a role, humans who feel threatened by their loss of productive orientation<sup>19</sup> may abandon their decision-making responsibility.<sup>18</sup>

Telemedical services can be harnessed for other purposes. The benefits of standardization and cost containment may conflict with local clinical care. Central oversight can restrict care and police for best practices. Centralized ICU care may be leveraged for financial interests. Agencies and hospitals are contending with rising costs, and their containment and ICU care are particularly expensive. Intensivists could become *gatekeepers*, a term used during the health care debates of the early 1990s to describe persons who allocate health care resources. With the wrong mission, telemedical systems begin to resemble Orwell's "Big Brother."<sup>20</sup>

Practitioners must bridge the gaps that develop when technologies do not fit perfectly into the working system they are meant to supplement.<sup>21</sup> Complex technologies require both central and local maintenance. Tasks, ranging from data entry to equipment checks, confront those taking care of patients. These tasks increase the workload of already overburdened practitioners, especially when they interrupt or disrupt workflow.<sup>22,23</sup> In one study of a physician order entry system, the technology made the process of order entry more difficult and prone to failure.<sup>24</sup> Given that systems tend to have local irregularities, standardized technology can be an awkward fit. Proponents of telemedical care point out that technology should supplement, not replace, bedside care; technology's practitioners should not become its servants.

A potential disadvantage of the tICU rests in control. Telemedicine is and should remain a tool. Its success should be measured by its usefulness to those who wield it. For the foreseeable future, these users are most likely to be the bedside practitioners. The future of the tICU depends on its ability to assist practitioners while minimizing the risks for inappropriate oversight, replacement of bedside expertise, or the further complication and disruption of workflow.

#### HOW CAN THE TELEMEDICAL INTENSIVE CARE UNIT SATISFY THE NEEDS WHILE MINIMIZING DISADVANTAGES?

Most importantly, telemedicine should concentrate on partnering with existing ICU systems. Monitoring and data integration, two areas in which telemedical ICU services already lead in medicine, could continue to improve. Better understanding of alarms and how they help or hinder patient care could spur the evolution of new systems that might reduce unnecessary distractions. Multiple forms of advanced technology already surround critically ill patients. These are often assembled ad hoc. Seamless integration of advanced technologies is difficult in the presence of different hardware and software platforms. Technologic standardization is not likely in the near future, nor may it be completely desirable, as evidenced by the slow adaptation of a communications standard in health care.<sup>25</sup> Higher-order monitoring systems must not only integrate the data but also manage the conflicting signals from multiple autonomous sources and present them clearly for the system operator in real time with a low probability of system breakdown. Studies have explored the trade-offs between alarm sensitivity and specificity and how these change with expertise.<sup>26</sup> Further research describing the partnership of provider expertise and monitoring technology could inform debates about how to filter and integrate data.

Methods to trace the decision-making process exist in other domains.<sup>27</sup> They analyze workflow to integrate, coordinate, and improve systems. Workflow modeling is one way to understand complex decision making in terms of time, space, and cognition.<sup>28</sup> The process by which teams of practitioners resolve complex data into a common concept and care plan is called *sensemaking*. Telemedicine should improve, not detract from, local sensemaking.<sup>29,30</sup>

Like a consultation, telemedicine constitutes a request for services that enhance the care given by the primary service. Effective consultants are available and cooperative. One experience with a telemedical "robot"<sup>9</sup> suggested that walkup consultation from nurses represented 54% of the robot's pages, evidence that availability may be one of the greatest benefits of telemedical consultation. In the setting of telemedical oversight, however, bedside care shouldered increased coordination loads,<sup>23</sup> and communication with bedside staff was not always congenial.<sup>31</sup> This drawback powerfully signals a need for improvement. The tICU should continue to serve the right customer: the bedside clinician.

Future considerations for telemedicine include issues of staffing, location, and reimbursement. Because it is a new innovation, the effects of provider expertise are not well understood. The major U.S. provider of tICU care uses trained intensivists and experienced ICU nurses for its monitoring. What skill sets are most important to virtual care and how these might be identified is a subject for future research. At the local level, consideration might also be given to facilitators who could maintain and service the information technologies. Clinicians may benefit from the availability of local tICU workstations. Finally, financial competition must be avoided between local clinicians and telemedical intensivists to prevent the drain of resources from conventional ICU care in a "zero sum" reimbursement system such as Medicare. Like any monitoring system, telemedical care should be used within the existing reimbursement model rather than in competition with it.

#### CONCLUSION

Telemedicine could reorganize intensive care. To maximize its benefits while minimizing adverse consequences, efforts must be devoted to studying the processes of care and how to enhance them. Some areas for study are the types of care best provided at the bedside, how remote monitoring may conflict or supplement bedside care, how telemedicine changes the work performed at the bedside, and how remote caregivers can be integrated into the health care team. The tICU is a complementary tool for the traditional ICU; its successful integration requires innovation and an attention to local factors.

#### **AUTHORS' RECOMMENDATIONS**

- Telemedical ICU services have demonstrated cost savings, decreased resource use, and improved clinical outcomes in limited studies. Such services are a novel approach to information management, technologic integration, and monitoring. Proponents suggest benefits from improved vigilance, standardization around best practices, and the ability to extend limited specialist resources to more patients. Mechanisms of benefit and rigorous clinical data are still limited.
- Telemedical care is not bedside care. Care must be taken to avoid the professional, economic, or social conflicts that could disrupt local care. There is a need for further research looking at how care is provided, and how best to integrate telemedical services into this model.
- To bridge the gaps in care that come from adding a new level of oversight to an existing complex system, new skills will need to be developed to integrate telemedical care into traditional bedside models, possibly including new training or job positions.
- To fulfill its promise as a useful tool in the ICU, telemedicine must continue to seek ways to supplement bedside care, cooperate with local practitioners, and, above all, be viewed as useful to them. Telemedicine's strength in data and technology consolidation and integration, including comprehensive displays, is one particularly innovative feature.

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## When Is Intensive Care Unit Care Innovative Therapy and When Is It Clinical Research?

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As an attending in a trauma ICU, you are caring for several ventilated patients with pulmonary contusions. You are unsure about which of two ventilator modes works better for such patients. A brief review of the literature confirms your suspicion that there is no published research comparing volume-cycled and pressure-controlled ventilation in patients with pulmonary contusions. You decide to use pressure-controlled ventilation for some and volume-cycled ventilation for others. You make the choice based on your hunch of which will work better for a specific patient on a case-by-case basis, and you often switch modes if the initially selected mode is not working well.

After a year or so of this practice, you decide to look back and compare those who got one mode versus the other to see which group had shorter durations of ventilation. Is this an example of innovative therapy or clinical research?

Critical care physicians frequently employ innovative or unproven therapeutic strategies in the course of caring for the sickest patients. Often, these innovative therapies are employed only after patients have failed to respond to standard therapies for a given disease state. In this setting, the innovative therapy is used with the hope that it will directly benefit a particular patient in a specific and often dire—state of critical illness. In fact, the only alternative to innovative practice in such circumstances may be to employ no intervention at all.

In their book, *Innovation in Medical Technology*, Eaton and Kennedy write: "what innovative treatments have in common is that they have not been sufficiently tested to meet peer or regulatory standards for acceptance or approval."<sup>1</sup> Innovative therapies include the use of novel and untested procedures and the application of evidence-based therapeutic strategies to novel patient populations (e.g., off-label medication use). Although commonly employed when no evidence-based practices exist, innovative therapeutic strategies may also be employed when other options are established but the clinician believes the new approach will be superior. Whether used as an alternative to the standard of care or as a last resort, innovative practices are used by physicians with the goal of treating a particular patient in a specific situation.

As the above scenario suggests, there is a critical but often uncertain boundary between innovative practice and medical research. Both innovative practice and research are motivated by the desire to improve patient care. Further clouding the distinction between innovative therapy and research is that frequently what begins as innovative therapy may later become formal research. Such research may, in turn, inform evidence-based practices in the future. On the other hand, innovative practice may also become accepted practice based on experiential knowledge of safety and efficacy and through transfer of this knowledge to colleagues and trainees. When an *innovative practice* becomes *common practice* without formal research, practitioners and patients alike may be left without the data to assess the risks, benefits, and potential long-term effects of an innovative therapy.

Amid such ambiguity, some may question the value of maintaining and regulating a crisp distinction between innovative therapy and clinical research. However, failing to enforce a uniform distinction may generate substantial consequences for patients and physicians alike. Granting substantial discretion to individual clinicians to decide whether a practice constitutes innovative therapy or research would revive the potential for research subject abuses that plagued clinical research before the advent of systematic regulations. For physicians, the distinction is critical lest they be held liable for failing to obtain regulatory approval before initiating well-meaning but nonstandard treatment strategies aimed at promoting their patients' best interests.

In this chapter, we attempt to elucidate the complex interplay and fundamental differences between innovative practice and clinical research. Our discussions of the issues involved and concluding recommendations are intended to help practitioners answer the following questions:

- What is innovative practice and how is it different from formal clinical research?
- Because innovative practice is not externally regulated to the same extent as formal research, what ethical obligations do physicians employing innovative practices have to patients, colleagues, and the community?
- When are clinicians obligated to study or evaluate an innovative practice using a formal research protocol?

#### **DEFINING INNOVATIVE PRACTICE**

Before addressing the ethical dilemmas associated with innovative practice and medical research, we must clearly define the terms at hand. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research offers a broad definition of *innovative practice* in the Belmont Report published in 1979:

For the most part, the term "practice" refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals.... When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is "experimental," in the sense of new, untested or different, does not automatically place it in the category of research.<sup>2</sup>

Thus, innovative practice is undertaken by a clinician who, based on experience, knowledge, and judgment, believes the practice will promote the best interests of *a specific patient*. As a result, innovative practices are generally not subjected to formal external review. Whereas the fiduciary relationship between patient and clinician obligates clinicians to act in their patients' best interests, such relationships do not exist between a researcher and research subjects. Rather, investigators are charged with advancing medical science within a set of constraints designed to safeguard research participants' interests.

One consequence of this key distinction is that physicians can ethically and legally employ an experimental practice without the formal oversight and approval from an Institutional Review Board (IRB) or other regulatory body in the name of patient care. The lack of required regulatory oversight does not absolve clinicians from the responsibility to discuss with patients and their families the experimental or unproven nature of an innovative therapy. Indeed, as the risk of the therapy or the degree of departure from standard practice increases, so too should the depth of discussion with patients or their surrogate decision makers. However, whereas candid discussions of the potential risks and benefits of innovative practices with appropriate documentation of informed consent are sufficient to protect patients' autonomy and promote their best interests, distinct external safeguards serve similar purposes for clinical research.

#### **DEFINING RESEARCH**

In contrast to innovative practice, the Belmont Report defines research as "an activity designed to test a hypothesis, permit conclusions to be drawn, and thereby to contribute to generalizable knowledge."<sup>1</sup> The report acknowledges that research and practice may occasionally coexist but that "the general rule is that if there is any element of research in an activity, that activity should undergo review for the protection of human subjects."<sup>1</sup> Federal law, embodied in the Code of Federal Regulations, similarly suggests that the collection of data on human subjects for any purpose other than direct patient care may be research and should therefore trigger IRB review.<sup>3</sup> In contrast to the usual therapeutic relationship, in which the patient is the client of the physician, when a patient becomes a research subject, he or she is subject

to experimentation and observation by the physicianinvestigator. Although the physician-investigator is still obligated to protect the welfare of the patient, he or she is also obligated to the research. This dual responsibility frequently presents conflicts of interest. For example, the physician may wish to protect a deteriorating patient by removing the patient from the study, whereas the investigator may wish to keep the patient enrolled so as to avoid biasing the research results.<sup>4</sup> To avoid such conflicts, the separation of the roles of physician and investigator is ethically optimum.<sup>9</sup> However, because such separation cannot always be practically achieved, all human subject research must be submitted, reviewed, approved, and monitored by an IRB. The IRB is an external source of review designed to ensure the protection of the patients' rights to informed consent, disclosure, and withdrawal from the study at any time without recourse. IRBs also may provide ongoing monitoring of outcomes during the study, either directly or through establishment of a data safety and monitoring board. Such continued oversight enables early detection of unacceptable risk-tobenefit ratios that may require the subsequent exclusion of patients unlikely to benefit or even complete study termination.

#### FROM INNOVATIVE PRACTICE TO RESEARCH: THE PULMONARY ARTERY CATHETER IN CRITICAL CARE

The history of the pulmonary artery catheter (PAC) provides an informative example of how an innovative therapy can, and often should, evolve into formal research. The PAC was introduced as an innovative diagnostic tool in 1970. Early research showed that PACs could be used to calculate cardiac output, ventricular filling pressures, and other hemodynamic parameters. Soon thereafter, PACs were widely employed by critical care physicians in efforts to rationally guide therapeutic interventions and monitor their success. In this way, physicians were attempting to serve their patients' best interests by using PACs to clarify complex or uncertain hemodynamic derangements. Real-time physiologic feedback allowed for more timely and targeted interventions to optimize patients' physiology.

The hypothesis that continuous hemodynamic feedback would improve outcomes in critically ill patients was so compelling that PACs gained widespread use and standard of care status in a range of critical illnesses without a formal evaluation of their efficacy. By the mid-1980s, between 20% and 43% of critically ill patients in the United States had a PAC placed at some point in their hospitalization.<sup>6</sup> As a result, little was made of an editorial questioning their utility in 1985.7 Then, in 1991, a small randomized clinical trial (RCT) suggested that PACs might be associated with increased mortality.<sup>8</sup> These results were, however, of questionable generalizability because only 33 of 148 eligible patients were enrolled because many physicians felt that they could not ethically "randomize" a critically ill patient not to receive a PAC.
Widespread use of PACs thus continued until 1996, when Connors and colleagues published a multicenter observational study suggesting a trend toward increased mortality associated with use of PACs.<sup>9</sup> Since then, at least six large RCTs<sup>10–15</sup> and a meta-analysis<sup>16</sup> of PACs have been reported. None of these studies has shown any evidence of survival benefit from PAC use, and all have shown increased complications among patients receiving PACs. The findings of these studies have resulted in a significant curtailment of PAC use as standard of care in critical care medicine.<sup>6</sup>

## THE LINE BETWEEN INNOVATIVE THERAPY AND RESEARCH

The cautionary tale of the PAC raises a pivotal question: Should all innovative practice be subject to regulation and oversight? Given the importance of research in determining the safety, efficacy, risk, and cost of a therapy, clinicians must always consider the need for formal study when undertaking innovative practice. The rules and regulations that govern formal biomedical research (largely the jurisdiction of the IRB) are intended to protect human subjects of biomedical research from undue risk. There is no such body overseeing innovative practice, and patients may be subjected to undue risk for unproven benefit.

It is neither practical nor necessary to subject *all* innovative therapies to formal research protocols. However, given the potential risks inherent in continuing to employ unexamined practices, guidelines are needed to clarify *when a new therapy should be subjected to the rules and regula-tions of formal research.* 

We believe that at least four issues regarding the use of an innovative therapy should be considered when determining whether such acts will be considered as research and thereby subject to formal oversight. Physician intent lies at the heart of these distinctions between innovative therapy and research. Although multiple, potentially conflicting and frequently opaque intentions commonly exist among well-meaning clinicians grappling with a variety of ethical dilemmas,<sup>17</sup> there appears to be no better criterion on which to base this critical distinction. Indeed, if clinicians recognize and accept the importance of carefully considering their own intentions in deciding whether their acts constitute innovative therapy or research, the process may become more transparent and amenable to regulation when needed.

With this caveat in mind, patterns of clinical behavior should be considered as innovative therapy when the physician's *sole* intent is to provide optimal care for a single patient in a particular clinical situation. By contrast, potentially similar practice patterns should be considered as clinical research whenever, and as soon as, the physician manifests any intention of producing *generalizable knowledge*. To distinguish between innovative therapy and clinical research, physicians should scrutinize their intent with respect to the treatments they select, how they will monitor patients' responses to therapy, how they justify the risks of the treatment approach, and their plans (if any) to publish their patients' outcomes (Table 99-1).

## Table 99-1 Innovative Therapy vs. Clinical Research

	Innovative Therapy	Clinical Research
Treatment selection	Treatments (i.e., dose adjustments, variations on surgical norms) are guided by the physician's judgment of what will best serve the individual patient	Treatments are standardized and/ or determined by protocol
Monitoring	Scheduling of follow-up and/or monitoring is tailored to the individual patient	Scheduling of follow- up and/or monitoring is standardized*
Risk	Risks of diagnostic tests must be reasonable in light of their potential to improve care and/ or monitoring of the individual patient	Risks of tests must be reasonable in proportion to their ability to produce generalizable knowledge
Publication	No prospective plans to publish results (even if ultimately published)	Prospective plans to publish and/or present at meeting

\*Exceptions may be made in the case of adverse events or for other reasons of participant safety.

## **Treatment Selection**

In innovative practice, treatment choices are guided by the physician's judgment of what will benefit their patient. In contrast, treatment decisions in clinical research are standardized according to a research protocol. Truog writes that, "what differentiates clinical research from clinical care is that trial participants must forego their right to individualized care. In other words, physicians have a duty ... to make individualized decisions for their patients. Any research that requires physicians to treat patients according to a particular approach forces physicians to violate that duty."<sup>18</sup> In an RCT, the randomization procedure means that patient care is not being determined by individual physician judgment but rather by chance.

#### Monitoring

Differences in monitoring and follow-up between innovative therapy and research logically follow from the differences in treatment choice. Monitoring and follow-up after innovative therapy are tailored to the needs of the individual patient. In research, scheduled follow-up and monitoring are generally standardized and guided by a protocol. Systematic follow-up is intended to reduce the risks for differential ascertainment of outcomes that would bias the results. Although exceptions to the monitoring protocol may be made when patient safety is compromised, such as following the development of an adverse event, this does change the activity's orientation as research.

#### Risk

In daily practice, physicians make clinical decisions based on an analysis of a risk-to-benefit ratio. The acceptable risk is determined largely by the *potential benefit*. In innovative therapy, the risk-benefit analysis applies only to an individual patient. The acceptable risk of an innovative procedure or surgery in a critically ill patient generally increases in direct proportion to the severity of patient illness. If standard therapies have failed and death appears imminent, greater risks of innovative therapies may be acceptable. In clinical research, a dual assessment of research risk is required.<sup>19</sup> The risks of therapeutic aspects of the research must be justified in relation to the potential benefits to research participants, whereas the risks of nontherapeutic aspects of the research (such as extra blood draws simply to test research hypotheses) must be justified by the value of the generalizable knowledge to be gained (i.e., the prospects of helping patients in the future). Thus, in research, the severity of illness for all eligible patients may influence the risk-benefit calculus used to determine the study's ethics, but severity of illness itself is not an adequate justification for enrolling patients in a study.

#### Publication

Intent to publish is one of the more challenging distinctions to make between innovative practice and clinical research. When a physician first decides to use a new therapy, an important question to ask is, Do I plan to publish the results of my experience with this therapy? If a physician has no prospective plans to publish the results, the new therapy can often be considered an innovative one. However, if a novel therapy is undertaken with the intent of future publication or presentation, the therapy should be considered research. Physician intent can be a complex and moving target, especially with respect to publication and generalizability. For example, a physician may employ an innovative practice with no intention at the outset to collect data or contribute to generalizable knowledge. However, as this physician gains experience with an innovative therapy, he or she may begin to observe trends that should be shared in the form of a publication. At the moment that the physician notes such a shift in intent, the physician should formalize this innovation as a research protocol and seek IRB approval.

## CHALLENGES OF QUALITY IMPROVEMENT INITIATIVES

In most cases, analyzing plans for a novel therapy based on the foregoing criteria will lead to a clear designation as either innovative therapy or research. However, the current definitions and regulations set forth by the Code of Federal Regulations provide little guidance on how to proceed when an activity has elements of both therapeutic innovation and data gathering. Can it ever be ethical to collect data in a systematic fashion without first obtaining approval from an IRB? Is the IRB the appropriate regulatory body for all types of data collection initiatives?

Because of incomplete analysis of the meaning of experimentation in patient care, regulatory documents sometimes fail to help providers navigate the boundaries between innovative practice and research as well as the newer boundary between research and quality improvement (QI) efforts. In fact, strict interpretation of regulatory guidelines may lead to a conclusion that any deviation from standard practices should be subject to formal review as research. Agich suggests that the current paradigm of research ethics "creates the presumption that without review by an IRB, innovation cannot be conducted in an ethically defensible fashion."<sup>20</sup> Agich concludes that the regulatory ethics paradigm is insufficient to address the complex ethical standards required of innovative care. Others have made similar claims regarding the lack of a distinct regulatory standard for QI initiatives.<sup>21,22</sup>

The risks of unregulated research have a long and storied history, and the IRB was formed to protect human subjects of research. But the risks of applying a singular research standard to all data-gathering activities are beginning to surface. A recent QI initiative carried out by investigators from Johns Hopkins University provides one such example. Pronovost and colleagues implemented an evidence-based, noninvasive intervention in a cohort of ICU patients in Michigan in order to reduce catheter-related bloodstream infections among ICU patients.<sup>23</sup> Between March 2004 and September 2005, each ICU involved in the study implemented five evidencebased interventions to reduce the rate of catheter-related bloodstream infections. The recommended procedures included hand washing, use of full-barrier precautions during central line insertion, cleaning the skin with chlorhexidine, minimizing the number of femoral lines inserted, and removing unnecessary catheters as early as possible. Eighteen months after the intervention was initiated across 108 ICUs, the mean rate of catheter-related bloodstream infections decreased from 7.7 per 1000 catheter-days at baseline to 1.4 per 1000 catheter-days at 18 months of follow-up (P < .002).<sup>23</sup> Over the course of 18 months, the program saved more than 1500 lives as well as \$200 million.<sup>2</sup>

The findings of the first 18 months of the QI initiative were published in the *New England Journal of Medicine* on December 28, 2006. One year later, the Office for Human Research Protections shut the program down. The OHRP alleged that the implementation of a standardized checklist along with the tracking and publication of results constituted research and should have been regulated as such. The OHRP also alleged that the investigators and the Michigan Health and Hospital Association had violated research regulations by failing to obtain written informed consent from all patients involved in the QI initiative, although they later recanted on this position.<sup>24</sup>

Did this initiative constitute research? Clearly, this initiative met many definitions of research—data were collected prospectively and systematically, the approach was applied on a population as opposed to an individual basis, and the purpose of collecting data across multiple hospitals was to produce generalizable knowledge. Publication of the findings confirmed the authors' intentions of conducting research. The fact that this research met every criterion for waiving the requirement for informed consent does not change its classification as research.<sup>24</sup> The IRB is the body charged with determining whether such criteria are met and allowing research to proceed without informed consent.

On the other hand, categorizing all QI initiatives as research requiring IRB review would create substantial delays, costs, and conflicts.<sup>20</sup> Casarett and colleagues suggested that "ultimately, what might be needed is a system of ethical oversight that can guide institutions that engage in QI initiatives. This ethical system should begin at a local level."<sup>21</sup> In fact, many institutions are beginning to create internal committees designed specifically for the review of both innovative practice and QI initiatives. For example, the University of Pittsburgh Medical Center recently formed an Innovative Practices subcommittee that allows innovative practices within the health care system to be evaluated and monitored in a systematic fashion.<sup>25</sup> Adaptations such as these are to be applauded. To protect patients, whether within the doctor-patient relationship or as human subjects of research, our ethical and regulatory paradigm must evolve hand in hand with the practice and science of medicine.

## AUTHORS' RECOMMENDATIONS

- The advancement of the practice and science of medicine is dependent on both innovative therapies and formal research.
- Although the considerable overlap between innovative practice and human subjects research can blur the distinction, maintaining and clarifying the distinction will benefit both patients and physicians.
- Criteria for distinguishing innovative practice from research include the methods for treatment selection and patient monitoring, how the risks of treatment are justified, and whether physicians intend to produce generalizable knowledge such as through publication.
- Physicians engaging in innovative practice must vigilantly reevaluate these practices; when their activities have begun to resemble research, IRB approval should be sought.
- IRB review should not be required for all innovative practice and quality improvement initiatives; however, the development of novel review and advisory mechanisms may usefully guide clinicians engaging in these practices.

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