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Airway and lung in sepsis

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Introduction

The development of respiratory dysfunction in patients with sepsis presents a myriad of complex interactions, which are yet to be completely understood. Similar to sepsis itself, the respiratory dysfunction that accompanies sepsis lies on a continuum from subclinical disease to overwhelming organ dysfunction. The most dreaded respiratory complication of sepsis is the acute respiratory distress syndrome (ARDS) – a severe form of acute lung injury (ALI) at the end of the spectrum of respiratory dysfunction.

Sepsis itself encompasses an entire range of host inflammatory responses, most frequently generated in humans by an infectious source. As the criteria defining the sepsis syndrome have become more established, the ability to determine specific epidemiological information associated with the syndrome has become more feasible. Recent compilations suggest a rising incidence of sepsis, likely resulting from advancing age of the population, potent immunosuppressive medications, and increasing numbers of invasive procedures [1]. In addition, data compiled by the Centers for Disease Control indicate that the incidence of sepsis increased more than 100% from 1979 to 1987, although the lack of contemporaneous standardized definitions may make this statistic exaggerated. The sepsis syndrome remains one of the most commonly recognized predisposing conditions for ALI, accounting for approximately 40% of cases [3, 4]. Pulmonary and intra-abdominal infections are the most commonly associated sites of infection identified in patients suffering ALI related to sepsis [5]. The development of ARDS in patients with sepsis is reported to occur in 25–42% of patients, increasing with persistent arterial hypotension [6].

Since its description in 1967, the defining criteria of ARDS have varied. Most physicians include the presence of bilateral pulmonary infiltrates on frontal chest radiography, impaired gas exchange, and the absence of cardiac dysfunction. Many investigators believe reduced respiratory system compliance, increased extravascular lung water, or other biochemical markers of inflammation should be included [7]. The American-European Consensus Conference on ARDS created a uniform definition for ALI and ARDS in 1994, outlined in Table 1. These criteria have allowed more precise epidemiological estimates to be made, although the incidence has been reported to vary from 5 to 71 per 100000 persons in the United States [8, 9]. Imprecision in these statistics makes quantification of the financial burden of this disorder difficult, although rational yearly estimates approach $5 billion in the United States alone. Broad, cooperative studies to obtain more precise estimates are underway.

The morbidity and mortality associated with ALI and ARDS may be declining slowly, although it is widely considered to remain in excess of 40%. Mortality is most often due to unresolved sepsis or multisystem organ failure (MOF) as opposed to progressive respiratory failure [5]. A recent review based on data from the period 1983–1993 in Seattle suggests that mortality rates have declined slowly over time, particularly in young patients with lung injury related to sepsis [10]. Several factors have been consistently found to affect mortality in patients with ALI, including age, severity of illness, cause of lung injury, presence of MOF, and preexisting comorbid conditions [11]. The degree of initial hypoxemia is not a reliable prognostic indicator, although changes in oxygenation over the first 48 h appear to dis-

Table 1 Definitions of acute lung injury *(ALI)* and acute respiratory distress syndrome *(ARDS)* (adapted from the American-European Consensus Conference)

	Timing	Degree of oxygenation defect	Radiographic appearance	Hydrostatic component
ALI	Acute	$PaO_2/FIO_2 \leq 300$	Bilateral infiltrates	PAOP < 18 mmHg
ARDS	Acute	$PaO_2/FIO_2 \leq 200$	Bilateral infiltrates	PAOP < 18 mmHg

Table 2 Calculation of the Lung Injury Score: the total number of points is divided by the number of components used

Points	0	1	2	3	4
Chest radiography	No infiltrates	1 quadrant	2 quadrants	3 quadrants	4 quadrants
PaO_2/FIO_2 ratio	> 300	225–299	172–224	100–174	< 100
PEEP (cmH_2O)	5	6–8	9–11	12–14	15
Cstat (ml/cmH_2O)	80	60–79	40–59	20–39	19

criminate eventual outcomes. In 1988 the publication of the lung injury score (LIS, Table 2) provided a method of grading the severity of lung injury – a system that has been validated prospectively for prognostic purposes. An initial LIS higher than 3.5 has been observed to be correlated with a survival rate of 18%, while a score of 2.5–3.5 corresponds to a survival rate of 30%, a score of 1.1–2.4 with a 59% survival, and a score below 1.1 with a 66% rate of survival [12].

This contribution addresses the respiratory system complications encountered in patients with sepsis, with a focus on clinically relevant diagnostic methods and management options for the practicing critical care physician.

Methods

A computer-based review of the literature was undertaken using Medline from 1993 to the present as the primary database. The specific subject heading keywords defined for each question were combined with the following general sepsis-related subject heading keywords: infection, sepsis, sepsis syndrome, septic shock, multiple organ failure, critical care, intensive care. An additional manual retrieval of pertinent cited articles from the retrieved literature was performed.

Pathophysiology

Biochemical and cellular mediators

The hallmark of ALI/ARDS is alveolar epithelial inflammation, airspace flooding with plasma proteins and cellular debris, surfactant depletion and inactivation, and a loss of normal endothelial reactivity [13]. This article is not intended to serve as a reference for the biochemical and cellular mediators of sepsis-induced respiratory dysfunction, although their interplay is indisputably critical to the pathophysiology common to the syndrome. The pathogenesis of ALI/ARDS is complex, with a consistently observed broad activation of the host inflammatory response. A well described pathophysiological model of ALI/ARDS is one of acute lung inflammation mediated by neutrophils, cytokines, and oxidant stress [14]. Bronchoalveolar lavage fluid from patients with ALI contains increased quantities of neutrophils and their enzymes, both of which are correlated with the severity of lung injury [15]. While it is clear that neutrophils exert a critical role in the evolution of the host inflammatory response, neutropenic patients can develop ALI, thus supporting a pivotal role for other effector cells such as alveolar macrophages [16]. Both of these cell types produce inflammatory mediators, catalyze the generation of reactive oxygen species, and encourage lipid peroxidation through arachidonic acid metabolism pathways. Persistent plasma elevations in the proinflammatory cytokines such as tumor necrosis factor-α and interleukins (ILs) 1, 6, and 8 are correlated with reduced survival, while increases in the bronchoalveolar lavage fluid anti-inflammatory cytokines such as IL-10 are correlated directly with survival [17, 18, 19, 20].

Evidence of lipid peroxidation and oxidant stress is uniformly present in patients with sepsis, with reported elevations in hypoxanthine and numerous arachidonic acid metabolites (e.g., isoprostanes) [21, 24]. Plasma thiol levels have been found to be correlated with survival in patients with ARDS, while lipid peroxidation products are correlated with severity of disease and survival [25]. Cytokine expression has been known to be regulated by oxidative stress mechanisms; antioxidants such as *N*-acetylcysteine and tocopherol derivatives have been shown experimentally to reduce the expression of proinflammatory cytokines [26, 27, 28]. Recent evidence exists that mechanisms independent of oxidant control also contribute to cytokine expression [29, 30]. In addition, endogenous (e.g., transferrin and ceruloplasmin) and exogenous substances (albumin) with the ability to

chelate iron have been shown effectively to suppress proinflammatory cytokine production in vitro [31, 32]. Unfortunately, the endogenous antioxidants have been shown to be either insufficient or inactive, rendering the natural oxidant stress defense mechanisms ineffectual. As the lung functions to filter nearly the entire cardiac output, it may thus be injured as a passive participant in the systemic inflammatory cascade.

Gas exchange

The principal cause of hypoxemia associated with sepsis is extensive right-to-left intrapulmonary shunting of blood flow. Intrapulmonary shunting is normally limited to less than 5% of the total cardiac output, whereas in ARDS it may consume more than 25% of the total cardiac output. In ARDS, shunting is due to persistent perfusion of atelectatic and fluid-filled alveoli. Ordinarily, compensation occurs through hypoxic pulmonary vasoconstriction to limit the amount of shunt by reducing perfusion to poorly ventilated lung units. In states of lung injury, however, hypoxic pulmonary vasoconstriction may be ineffective or absent, thereby increasing the magnitude of the intrapulmonary shunt. After the initial insult to the lung, gradients appear along a gravitational axis, in which the dependent lung is extensively consolidated and the main source of venous admixture [33]. Another factor affecting the ability to compensate for intrapulmonary shunting may be differences among patients in the mixed venous oxygen concentration of blood perfusing the injured lung regions as a result of differences in cardiac output or tissue oxygen consumption. Shunting of blood through nonventilated lung units accounts for the relative refractory nature of hypoxemia in ARDS. As a means to improve oxygenation, manipulation of airway pressure is often required to restore ventilation to nonventilated lung units.

Lung mechanics

Decrements in lung compliance (the change in lung volume for a given change in transpulmonary pressure) related to small airway and alveolar collapse are nearly universal in patients with ALI/ARDS. When delivered by mechanical ventilation with no end-expiratory pressure, the static inflation pressure for typical tidal volumes of 8 ml/kg may exceed 25 cmH_2O. This implies lung compliance approaching 20 ml/cmH_2O, or less than one-fourth that of normal. To reflect the actual intrinsic elastic properties of lung tissue, compliance should be calculated with the quantity of lung participating in gas exchange. In early ARDS the volume of aeratable lung is reduced by alveolar edema and surfactant dysfunction. These changes account for the need for higher inflation pressures, exclusive of any change in the intrinsic elastic properties of lung. As such, the inflation pressure may function as an estimation of the amount of edema and atelectasis early in the course of ARDS. This is reflected in the concept of a "small" lung early in ARDS versus a "stiff" lung later in the course. Only if fibrosis develops in the later phases do increases in inflation pressures reflect true changes in lung compliance. In a person with normal lungs, a transpulmonary pressure of 30 cmH_2O is sufficient to achieve total lung capacity – thus the recommended pressure limit for mechanical ventilation adopted by the American College of Chest Physicians Consensus Conference [34]. Interestingly, this level of airway pressure has also been shown to induce lung injury in some animals [35].

Whereas the static inflation pressure is the best index of transalveolar pressure during mechanical ventilation, the mean airway pressure is the best predictor of an overall effect on oxygenation or hemodynamics. As the mean airway pressure increases, progressively greater amounts of potentially recruitable lung are recruited. Unfortunately, at the same time venous return can be impeded and cardiac output depressed. Because volume-related alveolar overdistension is now recognized to play a major role in airway pressure associated injury in ARDS, the term "volutrauma" (instead of barotrauma) has been coined.

At times, peak airway pressures during mechanical ventilatory support of patients with ARDS are increased out of proportion to the increase in static inflation pressures. This finding suggests an increase in airway resistance. Airway secretions, edema, mediators that provoke bronchospasm, narrow endotracheal tubes, etc. can all increase airway resistance. Airway resistance, as with compliance, should be normalized for the amount of aeratable lung volume available and, although abnormal in part due to bronchoconstriction, the extent to which airway resistance is increased in ARDS is not completely known [36].

Work of breathing

Because these changes in mechanical properties increase the airway pressure necessary to achieve a given tidal volume, the work of breathing (measured as the pressure-volume product during spontaneous breaths) is also increased in ARDS – an effect that is multiplied by coincident tachypnea. One cause of increased dead-space ventilation is hyperventilation of still normal or relatively normal alveolar units, a process exaggerated by differences in the distribution of ventilation with mechanical ventilatory support and by overinflation of normal lung units when mean airway pressure is increased by positive end-expiratory pressure (PEEP) or other maneuvers. Normally, the dead space-to-tidal volume

ratio (Vd/Vt) is 0.3, but in severe ARDS as much as 90% (Vd/Vt = 0.9) of each tidal volume may fail to participate in effective gas exchange. As a consequence minute ventilation greater than five times normal may be necessary to maintain normal arterial CO_2 concentrations.

The increases in work of breathing are multifactorial, including hypoxemia, dead-space ventilation, and increased airflow resistance from bronchoconstriction. Although normal work of breathing accounts for only a small percentage of the body's overall oxygen consumption, the work of spontaneous breathing in patients with ARDS may require nearly 50% of the body's total oxygen consumption. To supply the energy necessary to sustain this level of work, resources (i.e., relative blood flow) may have to be diverted from other vital organ systems.

Patients with lung injury related to sepsis demonstrate heightened airway resistance, as least partially mediated by bronchoconstriction, although this phenomenon has not been shown to exist specifically in sepsis (see "Lung mechanics," above). The combination of altered airflow and abnormal pulmonary vascular perfusion (with loss of hypoxic pulmonary vasoconstriction) contributes to dramatic alterations in ventilation – perfusion matching, which may lead to clinically disproportionate hypoxemia relative to radiographic changes.

Extravascular lung water

The equation described by Starling in 1896 characterizes fluid flux across a semipermeable membrane and has been applied both experimentally and clinically to predict pulmonary edema formation in humans. The prime factors in this equation are the hydrostatic and oncotic gradients between the vasculature and interstitium coupled with the degree of capillary permeability. When fluid deposition exceeds the capacity of the lung to remove such fluid (i.e., lymphatic flow), accumulation of extravascular water occurs. Patients with sepsis demonstrate variable degrees of capillary permeability, increasing the effect of the hydrostatic pressure gradient relative to the oncotic pressure gradient as molecules responsible for maintaining oncotic pressure may be allowed freely to cross such leaky barriers. Accumulation of extravascular lung water and exudation of plasma proteins into the alveolar space creates the interstitial edema recognized as a complication of sepsis (i.e., ALI/ARDS).

Pulmonary hemodynamics

Increased pulmonary artery pressure is common in patients with ARDS, but pulmonary vascular resistance is usually only mildly to moderately elevated as a consequence of increased cardiac output. The prognosis of patients with significant elevations in pulmonary vascular resistance is worse, whether related to depressed cardiac function or worsening pulmonary hypertension. The cause of pulmonary hypertension in ARDS is multifactorial [37]. Vasoconstriction caused by alveolar hypoxia or other vasoactive mediators such as thromboxane and endothelin and intravascular obstruction from platelet thrombi or perivascular edema probably dominate initially. Later, sustained or worsening pulmonary hypertension probably reflects the degree to which fibrosis is responsible for obliteration of the vascular bed. Thus the poor prognosis associated with late pulmonary hypertension in ARDS may simply reflect the severity of fibrosis.

Pathology and lung repair

The pathological hallmark of ALI/ARDS, diffuse alveolar damage, changes dynamically as ARDS evolves [38, 39]. This occurs gradually over days to weeks, depending on the severity and resolution of the insult, and may not resolve for months or may result in chronic fibrotic changes along the alveolar interstitium. The changes that develop are conveniently divided into three phases: the early exudative phase (days 1–5), the fibroproliferative phase (days 6–10), and the fibrotic phase (after 10 days). These times are approximate, and the characteristic features in each phase often overlap. The initial pathological abnormalities are interstitial swelling, proteinaceous alveolar edema, hemorrhage, and fibrin deposition. Basement membrane disruption and denudation, especially of alveolar epithelial cells, can be seen with electron microscopy. After 1–2 days hyaline membranes (sloughed alveolar cellular debris mixed with fibrin) are commonly observed by light microscopy. Cellular infiltrates may be minimal or may be dominated by neutrophils. Fibrin thrombi can be seen in some of the alveolar capillaries and small pulmonary arteries.

Although type I alveolar epithelial cells cover 95% of the alveolar surface, they are terminally differentiated cells that cannot regenerate. Instead, several days after the onset of ARDS type II cells (the cell responsible for surfactant production) proliferate and then differentiate into new type I cells to reline the alveolar walls.

After approximately 1 week most of the alveolar edema has resolved, hyaline membranes are much less prominent, mononuclear cells have replaced the neutrophilic infiltrate, and fibroblasts are proliferating within the interstitium and depositing new collagen. Pulmonary fibrosis in ARDS is often referred to as "interstitial" because structures between airspaces appear to be markedly widened by fibrotic material. Detailed inspection has revealed, however, that this fibrosis is often the

result of either alveolar collapse or intra-alveolar fibrosis in which the proteinaceous edema and cellular debris of the exudative stage have been incorporated into the alveolar wall. Actual deposition of new collagen within the interstitial space appears to be relatively uncommon [40]. Eventually this healing of injured tissue may result in lung fibrosis, but the extent to which scarring develops is enormously variable. When parenchymal fibrosis does develop, intimal fibrosis and medial hypertrophy of pulmonary arterioles, along with complete obliteration of portions of the vascular bed, are also common.

Clinical presentation

Initial signs and symptoms

When clinical manifestations of sepsis first appear, between 28 % and 33 % of patients meet the criteria for ARDS [41]. Few data exist regarding respiratory abnormalities prior to this time, although progression through a clinical spectrum of dysfunction is likely the case. Patients may experience severe dyspnea, tachypnea, and unremitting hypoxemia prior to meeting all the criteria for ALI/ARDS. Hypoxemia results from myriad causes, including cardiocirculatory dysfunction affecting global oxygen delivery and shifts in the oxyhemoglobin dissociation curve. Respiratory dysfunction contributes to hypoxemia as well, with increased work of breathing. The multifaceted increase in work of breathing is easier to recognize than to quantify. Changes occur through increased dead space ventilation, related to ventilation-perfusion mismatching, respiratory muscle dysfunction, decreased thoracic compliance and increased airway resistance (bronchoconstriction). Both increased physiological dead-space ventilation and intrapulmonary shunting are responsible for the tachypnea and elevated minute ventilation required to achieve effective CO_2 excretion in patients with ARDS. Patients may also experience altered mental status or extrapulmonary organ failure confounding their respiratory dysfunction.

These physiological changes in pulmonary and cardiocirculatory function are most often radiographically inapparent. In practice, the radiographic findings associated with sepsis vary widely [42]. During the course of sepsis pulmonary edema may develop as a combination of increased pulmonary vascular permeability as described earlier, increased hydrostatic pressures related to resuscitation efforts, and/or lowered oncotic pressure gradients from any cause. During this time bilateral infiltrates may appear on the chest radiograph without overt evidence of fluid overload (i.e., increased vascular pedicle width or cardiothoracic ratio). When combined with appropriate thresholds of hypoxemia, the diagnosis of ALI or ARDS is secured. Unfortunately, standard chest radiographs are poor predictors of the severity of oxygenation defect or clinical outcome. Although the classic pulmonary parenchymal changes associated with ALI are diffuse, bilateral, peripheral, and interstitial in nature, they may be asymmetric or even patchy and focal.

Clinical course

The natural history of ALI/ARDS tends to be dominated by the inciting event rather than the lung injury itself. As such, treatment of the underlying cause and support of the respiratory system remains the standard of care. Death from refractory respiratory failure is unusual, with the most common cause of death being from the development of multiple organ failure or (recurrent) sepsis [5].

In patients who resolve ARDS relatively rapidly (over a period of 10–14 days), minute ventilation and dead-space ventilation both decrease in tandem with improvements in oxygenation. Given the substantial delay to peak incidence of pneumothorax, the lung appears to withstand exposure to somewhat higher forces in the earliest phase of human ARDS without radiographically evident barotrauma [43, 44]. After this time further improvements in oxygenation depend on whether the fibroproliferative response can restore the normal lung architecture for gas exchange. In patients with more severe ARDS, i.e., those in whom significant lung fibrosis eventually develops, minute ventilatory requirements stay high even as oxygenation improves. As fibrosis develops, progressive amounts of the vascular bed are obliterated, which contributes to the increase in dead-space ventilation even as alveolar edema and the intrapulmonary shunt resolve.

Prognostication

As discussed above, respiratory dysfunction related to sepsis exists on a continuum from subclinical aberrations to overt respiratory failure. Quantifying the severity of respiratory system involvement has been of keen interest for more than a decade. To streamline the ability to conduct research in this area, a clinical definition of lung injury was proposed and adopted in 1994 (Table 1). The Consensus Conference definition of ARDS emphasizes the spectrum of abnormalities present from ALI to ARDS, using readily available clinical criteria to make the necessary distinction. Although the exact role of respiratory failure in multiple organ failure is not clear, it has been demonstrated that potentially injurious modes of mechanical ventilation can produce cytokine release in humans and end-organ damage in animal models [45].

A number of detailed models have been created in an attempt to accurately predict the clinical outcomes in respiratory failure and/or sepsis (Acute Physiology and

Chronic Health Evaluation, Multiple-Organ Dysfunction Syndrome, Sequential Organ Failure Assessment, Injury Severity Score). Unfortunately, the prospective ability to recognize those patients who will survive is much closer to being an art than a science. Survival in sepsis appears to be slowly improving over the past 30 or more years, with a coincident decrease in the mortality associated with ALI/ARDS [11]. For most of the first two decades since ARDS was first reported, mortality remained relatively constant at 60–70 %. More recent reports, however, suggest that mortality has declined to roughly 40 % [11]. The explanation for this apparent improvement in patient outcomes is not clear but could be due to differences in patient populations, changes in ventilator support strategies, greater attention to fluid management, improved hemodynamic and nutritional support, improved antibiotics for nosocomial infection, corticosteroid use later in ARDS, or the potential benefits of protocol-driven patient management systems now implemented in many ICUs.

General scoring systems provide an estimate of the probability of mortality on admission to the ICU [46]. A specific scoring system for ARDS has been developed; however, its predictive accuracy is debated [47]. The number of acquired organ system failures is often the most important prognostic indicator for patients requiring intensive care, including patients with ARDS. Not surprisingly, patients developing fibrosis have a poorer outcome than do patients in whom fibrosis does not develop. In addition, liver failure in association with ARDS carries a particularly poor prognosis.

More specific predictors of outcome for patients with ARDS have been sought from measurements of various serum and lung lavage factors. As discussed above, concentrations of proinflammatory cytokines are correlated with outcome. The concentrations of von Willebrand factor antigen in serum and neutrophil-activating factor type 1, IL-8, and procollagen peptide in airspace lavage fluid are correlated with outcomes or progressive disease in some but not all studies. Increases in unsaturated serum acyl chain ratios appear to discriminate severity of illness and may serve as a marker of those most at risk of developing ALI/ARDS [48].

The integrity of the epithelial barrier in relation to resolution of alveolar edema also appears to be a determinant of outcome in patients with ARDS [49]. Patients who can concentrate the protein in the edema fluid during the first 12 h of illness (indicating an intact epithelial barrier with the ability to actively transport fluid out of the alveoli) are more likely to recover than those who cannot do so. Similarly, the change in the $PaO_2 2/FIO_2$ ratio following initial treatment of ARDS can discriminate between survivors and nonsurvivors [50]. At the present time none of these markers has been validated as an accurate method for predicting outcome in individual patients with ARDS.

The long-term functional outlook for survivors of ARDS is generally good [51]. Long-term abnormalities in pulmonary function are more common if lung function is impaired for more than a few days after the onset of ARDS. Most of the improvement in pulmonary function and perceived health occurs in the first 3 months following an episode of ARDS. Recently more complete data concerning long-term outcomes in patients suffering severe respiratory complications suggest a reduction in the quality of life relative to their premorbid level of function, often attributed to objective or subjective declines in pulmonary function [52].

Management options

No therapeutic intervention has been proven effective in reducing the incidence of respiratory failure in sepsis or its attributable mortality. Prevention of complications is of utmost importance while general supportive measures (e.g., antimicrobial therapy, nutrition) are undertaken. Control of the upper airway and consideration of the need for ventilatory assistance is an important first step in the management of patients with respiratory dysfunction related to sepsis. Although limited data exist, which are somewhat conflicting, noninvasive positive-pressure ventilation has not clearly been shown to be effective in this clinical circumstance [53, 56]. In addition, it is critically important to not impede the timing of other appropriate respiratory interventions, such as institution of mechanical ventilation, regardless of the availability and/or seeming adequacy of noninvasive positive-pressure ventilation (NIPPV).

Given our knowledge of fluid flux in states of altered capillary permeability (i.e., complete equalization of oncotic forces with attendant magnification of effective hydrostatic forces predicted by Starling's equation), it seems prudent to advocate judicious fluid resuscitation and/or fluid restriction when possible in this condition [57]. Recently investigators have shown that improvements in physiology and outcome occur in patients who lose weight or whose microvascular pressures fall as a result of diuresis or fluid restriction [58, 59]. These improvements can be produced by strategies employing fluid restriction without any higher incidence of complications such as renal failure or hemodynamic compromise [60]. The intravenous solution of choice (i.e., crystalloid versus colloid) is still unclear despite years of detailed investigation. In hypo-oncotic patients with established lung injury, treatment with the combination of albumin and furosemide appears to improve physiology and may reduce the duration of mechanical ventilation, although evidence of improved outcomes requires further investigation [61].

If patients cannot adequately protect their airway, placement of an endotracheal tube is indicated. Based

on increased rates of sinusitis, orotracheal intubation is the preferred route [62, 63]. Mounting evidence implicates nosocomial sinusitis in the development of ventilator-associated pneumonia (VAP) – an entity with a significant independent contribution to mortality [64, 65, 66]. Once endotracheal tube placement has occurred, institution of mechanical ventilation is almost universally indicated due to coincident respiratory failure (i.e., severe hypoxemia and increased work of breathing). For this reason one of the chief benefits of mechanical ventilatory support in ARDS is to reduce the patient's work of breathing so that blood flow may be redirected to other vital organs. Commonly accepted indications for institution of mechanical ventilation from other causes of respiratory failure apply equally to this patient population, including refractory hypoxemia ($PaO_2 < 60$ despite high flow oxygen), respiratory rate of more than 35 breaths/min, and vital capacity below 15 ml/kg, among others.

Mechanical ventilation is not a *therapeutic* option in patients with respiratory failure, and thus the goal is to support the individual respiratory requirements until the indication(s) requiring mechanical ventilation have reversed. No mode of ventilation has been proven superior to others in terms of outcomes in patients with sepsis-related respiratory failure, although complete ventilatory support is appropriate immediately after institution of mechanical ventilation. For this reason, volume-cycled ventilation using the "assist-control" mode (controlled mandatory ventilation) is an appropriate mode to choose at the outset. Similar degrees of respiratory support can probably be achieved with intermittent mandatory ventilation or pressure-regulated volume-controlled ventilation.

Inhaled oxygen requirements are dictated by the degree of hypoxemia, with arterial oximetric saturations of approx. 90 % (an approximate pO_2 of 60 mmHg) being desirable. To ameliorate the changes in closing volume and lung derecruitment, application of PEEP is appropriate and may provide dramatic improvements in PaO_2. Although some data suggest that levels of PEEP should be chosen based on respiratory system pressure-volume curves, to select the level of PEEP above the lower inflection point of the curve and thus prevent cyclic alveolar collapse, this is impractical in current clinical practice [68]. Prone positioning has been shown to be safe and to result in improvements in oxygenation in approximately 65 % of patients with ALI/ARDS, although no data exist to predict which patients will respond in this manner [68, 69] Those who do respond (defined as an improvement in $PaO_2 > 10$ % from baseline) often maintain higher oxygenation levels for up to 18 h after resuming supine positioning and are more likely to respond to subsequent attempts at prone positioning [70].

Tidal volume should be chosen based on *ideal* body weight [men = 50+2.3 (height, in.)–60; women = 45.5 +2.3 (height, in.)–60)], and should be targeted to prevent end-inspiratory plateau pressures from exceeding 30 cmH_2O whenever possible. Permissive hypercapnia, the method of allowing pCO_2 to rise while reducing tidal volume and minute ventilation to prevent alveolar overdistension or propagation of lung injury, has been shown to be safe and effective at reducing mortality without adverse consequences (noted increases in QS/QT and mean pulmonary artery pressure) in small nonrandomized series [71, 72, 73]. In this era of reduced tidal volumes based on the recent National Institutes of Health sponsored ARDS network trial, permissive hypercapnia has become accepted as a secondary phenomenon associated with the primary goal of avoiding dangerous airway pressures [73, 74, 75]. Gradual increases in pCO_2 are generally well-tolerated, particularly if significant acidosis does not occur, although the reduction in mean airway pressure may adversely affect indices of oxygenation [77]. In cases of severe acidosis, intravenous bicarbonate or extracorporeal removal of CO_2 may be employed.

No trials have been conducted to specifically define the most effective method of liberating septic patients from mechanical ventilation, although it is reasonable to presume that the literature addressing discontinuation of mechanical ventilation in other patient populations would apply equally. In patients with significant hemodynamic instability or altered mental status, attempts at discontinuing mechanical ventilation are not recommended. Thus a two-step method of identifying patients ready to discontinue mechanical ventilation is required. A daily screening test (consisting of a brief evaluation of the resolution of the primary indication for mechanical ventilation and adequate oxygenation and ventilation) is the most efficient way to identify those patients potentially capable of breathing spontaneously [78]. This screening tool is intended to identify patients in whom the primary indication for mechanical ventilation has reverted, using data such as frequency-to-tidal volume ratio, oxygenation (PaO_2/FIO_2 ratio), maximal inspiratory pressure, maximal expiratory pressure, airway occlusion pressure, and vital capacity [79, 80]. Patients with adequate respiratory recovery according to the screening information should progress to a simple spontaneous breathing trial to assess the true ability of an individual patient to be liberated from mechanical ventilation. To that end, daily attempts at spontaneous breathing (through a T-piece connection or with minimal ventilatory support such as flow-by with PEEP of 5 cmH_2O) should be offered to all hemodynamically stable patients with adequate mental status who pass the daily respiratory screening instrument. This simple assessment may be as short as 30 min, although roughly half of patients may fail such a trial after that time, suggesting 60–120 min as the appropriate duration [81]. In some circumstances pressure support

may help "bridge" patients in the weaning process, by slow reductions in the applied level of support to determine the ability of the patient to effectively breath spontaneously before a trial with minimal support as described above.

Experimental options

It is a well-known fact that numerous agents have challenged the unyielding morbidity and mortality of ALI/ARDS associated with sepsis in well-designed clinical trials, only to be added to the growing list of failed therapies. Use of systemic corticosteroids has been thoroughly tested for both prevention of lung injury as well as treatment of early phase ALI/ARDS and found to not be efficacious in either setting with possible increased mortality in patients with established ALI/ARDS [82, 83, 84]. Uncontrolled or small randomized trials have suggested benefit to intravenous corticosteroid therapy in patients with prolonged (fibroproliferative phase) ALI/ARDS (Late Steroids Rescue Study. http://hedwig.mgh.harvard.edu/ardsnet/ards02.html.), with a large scale trial underway to definitively answer this important question [85]. Ketoconazole, having demonstrated potential benefit in the prevention of sepsis-induced lung injury [86] was intensely evaluated in a multicenter trial supported by the National Institutes of Health sponsored ARDS network in the United States and found to lack efficacy in treating established ARDS [87] Intravenous prostaglandin E1 [88, 89, 90, 91] and aerosolized prostagladin I_2 (prostacyclin) [92, 93] have been shown to improve pulmonary physiology without improving outcome. Also completely tested has been intravenous lisofylline and strategies to achieve supranormal oxygen delivery DO_2 [94, 95]. Incompletely tested strategies include antioxidants such as *N*-acetyl cysteine [98], blocking of tumor necrosis factor, IL-10 therapy [97], and platelet-activating factor antagonists. There are a few experimental options worthy of discussion based on promising clinical or preclinical data.

Newer modes of ventilation such as pressure-controlled ventilation or airway pressure release ventilation [98] may play a role in select patients requiring high levels of ventilatory support, although no data support improved outcomes at this time. In addition, some newer modes of ventilation are potentially confusing to unfamiliar physicians, thus making it less than desirable to recommend. High frequency or oscillatory ventilation has been tested in adults with ARDS and not shown to be of any significant benefit, although trials are ongoing to determine whether certain patient subgroups may benefit from such modes [99, 100, 101, 102, 103]. In addition, liquid ventilation has been shown to result in physiological improvements in small series and animal models, and phase III trials in humans are underway to evaluate the efficacy of this agent in humans with ALI/ARDS.

Nitric oxide (either alone, or in combination with the selective pulmonary vasoconstrictor almitrine) has been shown to improve oxygenation without any reduction in duration of mechanical ventilation or mortality [104, 105, 106, 107]. Extracorporeal membrane oxygenation [108] or extracorporeal removal of CO_2 [109, 110, 111] have been shown to result in significant physiological improvements in severely ill patients with ARDS, without clear beneficial effects on the development of organ failure or survival. Liquid ventilation has been shown to improve pulmonary physiology and reduce inflammation, and is currently in phase III trials to evaluate its ability to improve outcomes [112, 113, 114]. Similarly, surfactant therapy has been shown to improve gas exchange without directly affecting days of mechanical ventilation or mortality [115]. Phase III investigations are currently in progress in North America and Europe to determine the efficacy of variations in protocolized surfactant therapy.

A number of experimental therapies exist on the horizon for patients with sepsis-induced lung injury, including gene therapy [116, 117]. Modulation of cytokines continues to be a difficult but promising area of intervention, with a preliminary randomized trial administering the anti-inflammatory cytokine IL-10 in ALI/ARDS patients demonstrating a trend towards reduced organ failure.

Other relevant respiratory issues

Despite the enormous potential of future therapies we should not ignore the simple and readily available *potentially* beneficial therapies. This includes the use of inhaled beta-agonists, which have been shown to reduce inspiratory pressure and increase lung compliance by reducing airway resistance without significant benefits in dead-space ventilation, oxygenation, or overall outcome [118]. Elevating the head of the bed at least 30 degrees at all times has been shown to reduce the incidence of gastric material migrating to the trachea [119]. Hospital beds capable of patient rotation and/or distribution of pressure points to prevent decubitus ulceration [120]. Finally, specific enteral nutritional formulae with antioxidants and amino acid compositions designed to reduce inflammatory lipid mediators have recently been demonstrated to improve gas exchange and reduce the duration of mechanical ventilation and intensive care stay in patients with ARDS [121].

Postextubation period

After removal of the endotracheal tube patients should be monitored closely for signs of respiratory compromise for a period of 6–24 h depending on the cause and severity of respiratory failure. Endotracheal intubation may cause upper airway injuries that result in immediate or delayed airway compromise. Insertion of an endotracheal tube with an internal stylet may tear the pyriform recesses beside the larynx and result in bleeding and hematoma formation [122]. Use of a tube that is too large can result in vocal cord injury, edema, and hematoma and overinflation or malpositioning of the endotracheal tube cuff can cause periglottic injury and stenosis. Prolonged intubation, coughing, or repeated endotracheal tube placements can cause the formation of obstructive arytenoid granulation tissue [123]. Stridor, related to upper airway injury or inflammation, occurs in 25–75% of pediatric extubations but is rare in adults, occurring in a small fraction of endotracheally intubated patients [124]. Although in some circumstances this may be managed expectantly, a low level of tolerance should exist before replacement of an adequate airway to prevent respiratory compromise. Flexible fiber-optic examination of the larynx before extubation is often prudent in such patients.

Typically, within a few hours, patients tolerate reintroduction of oral nutrition, although this should progress through stages demonstrating adequate swallowing and airway protective reflexes. For patients with significant respiratory secretions, assistance with "pulmonary toilet" may be required either through airway suctioning (nasotracheal or orotracheal) or chest percussion with postural drainage. A subset of patients requiring prolonged mechanical ventilation demonstrate significant respiratory muscle weakness, in which case assisted coughing and/or hyperinflation therapy (e.g., intermittent positive pressure breathing) may be of benefit.

Discussion: literature-based recommendations

To answer each of the following important clinical questions, a review of the literature was performed as previously described.

Do manipulations of airway pressure improve (a) oxygenation or (b) outcome in patients with sepsis?

Answer: (a) yes, grade C; (b) uncertain, grade B.

Recommendation

Provide adequate supplemental oxygen to maintain an oximetric saturation of approximately 90% through use of simple oxygen delivery systems (i.e., nasal cannula or face mask) if possible. For endotracheally intubated patients, use of PEEP to increase mean airway pressure may be employed to reduce concentrations of inspired oxygen below potentially toxic thresholds ($FIO_2 < 0.60$).

Rationale

The following specific subject heading keywords were used to answer this question: oxygen, oxygen inhalation therapy, anoxia, anoxemia, partial pressure, and pulmonary gas exchange. The broad spectrum of respiratory dysfunction encountered in sepsis only allows for answers in specific clinical circumstances. For instance, a significant proportion of the 60% of septic patients who never develop ALI/ARDS have normal chest radiographs, and this patient population has not been intensely studied. Although the relationship between radiographic manifestations of pulmonary dysfunction and gas exchange is poor, it is reasonable to presume that hypoxemic patients with sepsis but without radiographic pulmonary infiltrates would respond similarly to patients with visible interstitial edema (i.e., patients with ALI/ARDS). It is clear that hypoxemia is modestly correlated with prognosis in ALI/ARDS related to sepsis, and that simple methods of oxygen supplementation raise PaO_2. Raising mean airway pressure results in recruitment of additional lung units to participate in gas exchange while maintaining the patency of units once recruited and thus increases PaO_2 [125, 126, 127]. It is equally clear that application of PEEP, either with an endotracheal tube in place or through a tight-fitting face mask, has been shown to improve oxygenation in hypoxemic patients through increases in airway pressure [128, 129, 130]. The underlying goal in providing such therapy is to ensure adequate oxygen delivery to critical tissue beds in states of altered microvascular flow. Unfortunately, there is no data on which to assess outcomes through manipulations of airway pressure. Studies of mechanically ventilated patients with ALI/ARDS treated with different methods of ventilation designed to achieve different inspiratory pressures have shown differences in outcome, but attributing these improvements to the manipulation of airway pressure directly is impossible [67, 74]. Determinations made by the most routine measure of oxygenation, pulse oximetry, are correlated well with arterial oxygen saturation but may misrepresent arterial saturation by 7% in patients with extremes of heart rate, cardiac index, or pulmonary arterial wedge pressure [131]. Despite this the

use of this device is recommended to monitor arterial oxygenation in this patient population, with supplemental oxygen and PEEP administered to maintain saturation of approximately 88–90 % (approximating a PaO_2 of 60 mmHg) with nontoxic concentrations of oxygen (ideally FIO_2 2 < 0.60).

Can noninvasive positive-pressure ventilation be safely and effectively used in ALI/ARDS related to sepsis?

Answer: no, grade B.

Recommendation

Avoid the use of NIPPV in sepsis-related ALI/ARDS patients.

Rationale

The following specific subject heading keywords were used to answer this question: positive pressure respiration, artificial respiration, intermittent positive pressure ventilation, adult respiratory distress syndrome. There has been a surge of interest in applying noninvasive positive-pressure ventilation to all patients with respiratory failure, although it appears that patients with ALI/ARDS are more likely to fail this therapy [53]. It is clear that NIPPV is most effective in selected patients (normal or near normal mental status without significant respiratory system secretions) with expected resolution of respiratory failure within 72 h – a rare situation in ALI/ARDS [55]. Although NIPPV may avoid the use of mechanical ventilation (and its attendant risks) in a small population of ALI/ARDS patients [54], the delay in institution of mechanical ventilation may be equally likely to result in untoward complications in the majority of patients.

Does (a) placement of an endotracheal tube or (b) institution of mechanical ventilation improve outcome in respiratory failure related to sepsis?

Answer: (a) no, grade E; (b) yes, grade E.

Recommendation

Early placement of an endotracheal tube and institution of mechanical ventilation in patients with sepsis is appropriate based upon standard clinical criteria heralding the onset of respiratory failure to avoid the recognized complications associated with respiratory failure and/or acute respiratory arrest. Indications for institution of mechanical ventilation include severe tachypnea (respiratory rate > 40 breaths/min), muscular respiratory failure (use of accessory muscles), altered mental status, and/or severe hypoxemia despite supplemental oxygen.

Rationale

The following specific subject heading keywords were used to answer this question: intubation, intratracheal intubation, respiratory insufficiency, artificial respiration, positive-pressure respiration, and adult respiratory distress syndrome. For ethical reasons there are no randomized trials evaluating the use of endotracheal intubation in critically ill patients. It is important to recognize that placement of an endotracheal tube is not a therapeutic maneuver. This step carries the attendant risks of anesthesia for the procedure and subsequent morbid events such as VAP and thus by itself does not improve outcome in this clinical circumstance. In addition, mechanical ventilation (independently of airway protection, etc.) has not been shown to improve outcome in patients with sepsis and respiratory failure, although this has not been studied in depth. In comparison with historical controls (i.e., the polio epidemic), mechanical ventilation does indeed provide significant tangible clinical benefits [132]. Alternatively, discontinuation of mechanical ventilation by removing an endotracheal tube in terminally ill patients results in more rapid expiration than simply withholding therapy, thus providing indirect evidence of clinical benefit from endotracheal intubation with mechanical ventilation [133].

The greatest morbidity associated with endotracheal tube placement relates to risk of VAP, which is increased in patients with burns, trauma, central nervous system disease, respiratory disease, cardiac disease, and witnessed aspiration [134]. Potentially VAP may be decreased by use of orotracheal intubation, subglottic secretion drainage, kinetic hospital beds, and increased by heated respiratory circuit humidifiers and histamine-2 receptor antagonists [135, 136]. It is well recognized that mechanical ventilation possesses the potential to initiate or propagate lung injury, and thus can be considered an independent source of patient morbidity.

Is normalization of (a) pH or (b) pCO_2 necessary in ALI/ARDS?

Answer: (a) no, grade D; (b) no, grade D.

Recommendation

Implement permissive hypercapnia through reduced tidal volume ventilation in mechanically ventilated ALI/ARDS patients with high inspiratory pressures or otherwise at risk for barotrauma/volutrauma.

Rationale

The following specific subject keyword headings were used to answer this question: hypercapnia, artificial respiration, positive pressure respiration, adult respiratory distress syndrome. Permissive hypercapnia, the method of allowing pCO_2 to rise while reducing tidal volume and minute ventilation to prevent alveolar overdistension or perpetuation of lung injury has been shown to be safe and effective at reducing mortality without adverse consequences in small nonrandomized series [75, 76, 77]. The upper limit for pCO_2 has not been established, although arterial pH should be maintained at a level higher than 7.20. Based on these data, normalization of arterial blood gas values is not considered a valuable therapeutic maneuver.

Does the use of (a) small tidal volume ventilation or (b) pressure limited ventilation strategies affect outcome in ALI related to sepsis?

Answer: (a) yes, grade A; (b) uncertain, grade A.

Recommendation

Mechanical ventilation of patients with ALI should be conducted with small tidal volumes (approximately 6 ml/kg ideal body weight) with the goal to maintain end-inspiratory plateau pressures at levels less than 30 cmH_2O.

Rationale

The following specific subject heading keywords were used to answer this question: tidal volume, lung compliance, positive pressure respiration, intrinsic positive pressure respiration, mechanical ventilator, adult respiratory distress syndrome. Well-designed large scale randomized trials designed to alter inspiratory pressure through variations in tidal volume have been conducted, with varying results [137, 138, 139, 140]. It is not completely understood why the results of these well-designed trials conflict, although the intergroup differential in airway pressure is a likely contributor. In a recent trial in the United States, absolute all-cause mortality was reduced by 10 % in ALI patients receiving mechanical ventilation with tidal volumes of 6 ml/kg ideal body weight [74]. This topic has also been recently reviewed by an international expert consensus conference [141].

Does prone positioning affect (a) gas exchange or (b) outcome in sepsis-related ALI?

Answer: (a) yes, grade C; (b) uncertain, grade C.

Recommendation

Prone positioning *may be considered* in patients requiring high levels of inspired oxygen ($FIO_2 > 0.60$) in whom positional changes are not contraindicated, and who are cared for at facilities experienced in the management of critically ill mechanically ventilated patients.

Rationale

The following specific subject heading keywords were used to answer this question: prone position and supine position. Although the evidence for prone positioning must be graded C because of the small size of randomized trials, strong data exists to confirm the physiological benefits of this intervention. Recent studies have made it clear that prone positioning of patients with ALI/ARDS results in improvements in oxygenation in approximately 65 % of patients ("responders") [68, 69, 70]. In addition, the improvements in gas exchange may persist up to 18 h, even after returning to the supine position, and such changes in position may be accomplished safely in intensive care units accustomed to managing critically ill mechanically ventilated patients. Because of the limited size of trials to date, no definitive comments can be made on the general applicability of these maneuvers to all patient care centers or their effect on overall mortality.

Does inhaled nitric oxide affect (a) oxygenation or (b) outcome in ALI/ARDS?

Answer: (a) yes, grade A; (b) no, grade A.

Recommendation

Restrict nitric oxide as an option for salvage therapy in patients with life-threatening hypoxemia not responding to traditional mechanical ventilation strategies or for evaluation in controlled clinical trials.

Rationale

The following specific subject heading keywords were used to answer this question: oxygen, nitric oxide, inhalation administration, and pulmonary gas exchange. Inhaled nitric oxide has been studied extensively in both preclinical models of lung injury and clinical trials of patients with ALI/ARDS. It has been shown to lower pulmonary artery pressures and improve right ventricular function in patients with pulmonary hypertension. Inhaled nitric oxide improves oxygenation and may reduce edema formation in patients with ALI/ARDS through effects on hydrostatic pressure. Unfortunately, it has not been found to significantly affect mortality [104, 105, 106]. These data support the observation that inhaled nitric oxide consistently improves pulmonary physiology in a large proportion of these patients, but fails to affect outcome.

Is there a defined fluid management strategy in sepsis-related ALI/ARDS?

Answer: uncertain, grade C.

Recommendation

Judicious use of crystalloid fluid administration should be practiced in patients with ALI/ARDS, with colloid solutions considered in hypo-oncotic patients with established ALI/ARDS. It is not clear if volume restriction improves outcome.

Rationale

The following specific subject heading keywords were used to answer this question: fluid therapy, resuscitation, diuresis, intravenous infusions, hypertonic saline solution, sodium chloride, colloids, plasma substitutes, hetastarch, dextrans. Optimal fluid management has been considered a critical question in patients with sepsis and ALI/ARDS since these syndromes were first described. Conflicting data exist regarding the relative benefits of crystalloid and colloid administration in these patient populations despite years of research. Use of colloids in this patient population has been advocated and debated for decades, with evidence for potential benefit appearing only recently. Similarly, only recently has fluid balance been evaluated independently with respect to its contribution to overall morbidity and mortality [59]. Prospective, randomized trials have been conducted which support improved clinical outcomes based on direct manipulation of fluid balance variables in this critically ill patient population [60]. The details of the most appropriate intravenous solution and volume of administration requires large-scale investigation.

Are corticosteroids indicated in the (a) prevention, (b) early treatment (exudative phase), or (c) late treatment (fibroproliferative phase) of ARDS?

Answer: (a) no, grade A; (b) no, grade A; (c) uncertain, grade C.

Recommendation

Do not routinely administer corticosteroids to patients at risk for, or meeting current criteria for, ALI/ARDS. Consider intravenous methylprednisolone in patients with persistent or refractory ARDS after actively excluding infection, pending the results of ongoing trials.

Rationale

The following specific subject heading keywords were used to answer this question: steroids, adrenal cortex hormones, prednisone, methylprednisolone, hydrocortisone, dexamethasone. Corticosteroids have long been considered part of an appropriate treatment plan for patients with lung injury. There have been well-designed trials that fail to demonstrate any significant benefit for corticosteroids in the prevention or early treatment of ARDS [82, 83, 84]. A recent resurgence of interest has been generated by small trials suggesting benefit in the subpopulation of patients failing to progress in the late phase of ARDS (Late Steroids Rescue Study, http://hedwig.mgh.harvard.edu/ardsnet/ards02.html). In an attempt to answer this pressing question, the National Institutes of Health have sponsored a large-scale trial in the United States randomizing patients with ARDS for more than 7 days to methylprednisolone therapy [85]. In conducting all of these trials, close attention was paid to excluding infection before or during corticosteroid therapy. Until definitive trials have been completed, a clear recommendation cannot be made regarding corticosteroid administration in patients with persistent ALI/ARDS.

Do daily spontaneous breathing trials or weaning protocols reduce the duration of mechanical ventilation?

Answer: yes, grade A.

Recommendation

It is recommended that all patients requiring acceptable levels of ventilatory support who are not overtly unstable should receive a spontaneous breathing trial on a daily basis to determine ability to breathe unassisted.

Rationale

The following specific subject heading keywords were used to answer this question: weaning, ventilator weaning, artificial respiration, and mechanical ventilator. The last 10 years has seen a surge in interest in determining the optimum method of discontinuing mechanical ventilation [142, 143, 144]. Recent large-scale trials have been conducted to demonstrate the benefits of daily trials of spontaneous breathing in reducing the duration of mechanical ventilation [78, 145, 146].

Identifying patients capable of breathing spontaneously requires a two-step process: a brief screen and a trial of spontaneous breathing. The screening procedure is designed to exclude patients requiring excessive levels of mechanical ventilatory support. Thus the following criteria may be employed to identify patients ready to accept a trial of spontaneous breathing: $FIO_2 < 0.50$, PEEP 5 cmH_2O, intact airway reflexes, hemodynamic stability and adequate mental status. The definition of spontaneous breathing trial is still a subject of debate, with both "T-piece" breathing and flow-triggered ventilation with continuous positive airway pressure of 5 cmH_2O currently being acceptable methods of achieving "spontaneous breathing." Patients who tolerate such a breathing trial for 2 h have an approximately 85% success rate with complete discontinuation of mechanical ventilation.

Conclusion

Despite significant advances in both the knowledge of sepsis-related respiratory failure and the care of critically ill patients, ALI/ARDS continues to be a complex problem with high mortality. The recommendations above represent the current state of knowledge for this condition, but equally serve to highlight the vast deficiencies of knowledge that remain. To provide our patients with the best possible outcome, a continued focus on physiological, therapeutic, and outcomes research is necessary.

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