Acute Respiratory Distress Syndrome in the Burn Patient

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1 Introduction and Historical Background

It may seem unusual to include a chapter on the acute respiratory distress syndrome (ARDS) in a textbook on wounds. However, patients with burn wounds are clearly at risk of developing this life-threatening complication. While ARDS is most typically seen in patients following major burn injuries, we know that it sometimes occurs even in patients that have relatively small burn wounds. The development of ARDS after a thermal injury is not overly surprising since many of the known risk factors for ARDS, in addition to the burn wound itself, such as smoke inhalation, pneumonia, sepsis, and blood transfusion all commonly occur with burns. As is the case among critically ill patients without burns, ARDS contributes significantly to heightened morbidity and mortality following burn injury.

The first published report of what we now refer to as ARDS appeared in 1967 [1]. In that report Ashbaugh et al. described a syndrome which featured severe respiratory distress, hypoxemia, stiff non-compliant lungs, and the presence of extensive bilateral infiltrates on the chest radiograph. The twelve adult patients in that report suffered from various insults such as multiple trauma, pancreatitis, and pulmonary infections. While none had sustained burns or smoke inhalation, the same syndrome was almost certainly being recognized around the same time in patients that had suffered burn injuries. Dr. Pruitt, in 1970 [2], along with Nash et al., in 1974 [3], reported the autopsy findings of burned adults that had died from pulmonary complications. Extensive diffuse interstitial lung edema and alveolar hyaline membranes—now widely recognized as pathognomonic features of ARDS [4]—were clearly described.

Among critically ill but unburned patients, there was an evolution during the late 1980s and early 1990s of stricter diagnostic criteria and definitions for ARDS, such as a lung injury severity score [5] and the American-European Consensus criteria [6]. This was followed over the ensuing two decades by a massive output of research on ARDS in the critically ill. Most recently, newer diagnostic criteria for ARDS—referred to as the Berlin definition—have been adopted. In parallel but at a slower and delayed pace, the ARDS was also being increasingly recognized and more accurately diagnosed among the burn injured [7–11]. However, relative to the extensive body of research that includes several landmark randomized controlled trials in non-burn patients with ARDS, there has been very little published on ARDS in burn patients. Thus, it must be stated at the outset that almost all our understanding of

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ARDS in burn patients comes from translation of research conducted in the non-burn population.

While most of this translation is entirely appropriate, burn patients are a unique subpopulation of the critically ill, and important differences do arise. This chapter will review the epidemiology, pathogenesis, clinical features, and management of ARDS in the burn patient. Important distinctions and areas of controversy that arise because of the unique nature of the burn injury will be emphasized.

2 Pathogenesis

ARDS can be triggered by a wide variety of primary disease processes, which may be classified as pulmonary (i.e., originating in the lung) and extrapulmonary (i.e., originating outside the lung). Pulmonary causes most commonly include pneumonia and gastric aspiration and less commonly lung contusion, near-drowning, and smoke inhalation. The most frequent extrapulmonary causes are sepsis and severe trauma with shock and less frequently multiple blood product transfusions, drug overdose, and pancreatitis [4, 12]. While burns are usually not identified as a specific predisposing condition for ARDS, many of the risk factors such as pneumonia, smoke inhalation, sepsis, shock, and blood product transfusion may occur, often in combination, following thermal trauma. We also make the assumption that the burn wound itself is a rich source of inflammatory mediators which can likely injure the lung secondarily, leading to ARDS. It is not entirely clear how these diverse predisposing conditions ultimately lead to the final pathological and clinical picture of ARDS. What is important is that the insult induces a set of common pathological changes in the lung, regardless of the cause.

The primary change is a breakdown of the pulmonary microvascular endothelial lining and the alveolar epithelial surface—together referred to as the alveolar-capillary barrier. Injury to the alveolar-capillary barrier appears to be mediated by activated neutrophils and a complex bombardment of cytokines and inflammatory mediators including interleukin (IL)-8, tumor necrosis factor α, and various oxygen-free radicals and proteases. These pro-inflammatory mediators probably play a role not only in the initiation of the injury but also in amplification of the local inflammatory process. The net result of the alveolar-capillary disruption is that the interstitial and alveolar spaces are flooded with protein-rich fluid, neutrophils, fibrin, and fibroblasts. Protein-laden hyaline membranes are deposited on the denuded alveolar basement membranes. Normal transport of fluid out of the alveolar space is compromised by injury to the type I epithelial cells that normally predominantly line each alveolus, while injury to the smaller population of type II epithelial cells results in loss of surfactant production, and importantly, disruption of the ability of these cells to differentiate into type I cells which is an important part of the repair process after injury [4]. Following this acute inflammatory phase which can last up to 5–7 days, the lungs of some patients begin to show resolution of the process with resorption and mobilization of the fluid, reduction of inflammation, and repair of the alveolar epithelial lining by the type II cells. Such patients show rapid clinical recovery. Other patients' lungs progress to a fibroproliferative phase in which mesenchymal cells, neovascularization, and procollagen are deposited in the alveolar space. This development of fibrosing alveolitis is a poor prognostic sign and is associated with an increased risk of death [13]. Resolution of this phase is prolonged but again involves mobilization of fluid and protein and restoration of the normal alveolar lining of type I cells through proliferation and differentiation of the type II cells [4].

3 Defining ARDS

Following Ashbaugh et al.'s [1] description of ARDS, the American-European Consensus Conference (AECC) developed clinical diagnostic criteria for the definition of ARDS in 1994 [6]. This AECC definition of ARDS included acute hypoxemia with an arterial partial pressure of oxygen to fraction of inspired oxygen ratio

(PaO_2:FiO_2 ratio) ≤200 mmHg, bilateral infiltrates on chest radiograph, and no clinical evidence of left atrial hypertension or a pulmonary artery wedge pressure (PAWP) measured by the Swan-Ganz catheter of ≤18 mmHg. The AECC definition also identified a condition called acute lung injury (ALI) which had the same features of ARDS but which had milder hypoxemia with a PaO_2:FiO_2 ratio ≤ 300 mmHg. The AECC definition was highly important because it provided a common set of definitions that allowed researchers to study the epidemiology and clinical care of patients over nearly two decades. Several landmark randomized clinical trials including the famous ARDS Network low tidal volume ventilation (ARMA) trial [14] occurred, in part, because uniform definitions could be used to identify and recruit subjects.

However, in 2011, a panel of experts convened in Berlin to address deficiencies of the AECC definition and to develop an updated set of diagnostic criteria [15]. The main concerns with the AECC definitions included an unspecified timing of ARDS onset, misinterpretation of PaO_2:FiO_2 ratio and classification of ALI vs. ARDS, low reliability of the chest radiograph interpretation, inconsistent consideration of positive end-expiratory pressure (PEEP) levels, and the use of the PAWP in the definition.

A revised definition (the Berlin definition) was developed and validated and is shown in Table 1. The key features are (1) elimination of the term ALI and stratification of all ARDS as mild, moderate, and severe based on PaO_2:FiO_2 ratios of 200 to ≤300, 100 to ≤200, and ≤100, respectively, on at least 5 cm H_2O of PEEP, (2) clarified definitions of bilateral infiltrates on chest radiograph and origin of edema, and (3) specification of acute onset within 1 week of a known clinical insult. One of the most important components of the Berlin definition of ARDS is the emphasis on training to improve chest radiograph interpretation and diagnosis of hydrostatic pulmonary edema using a series of clinical vignettes and sample radiographs included in the supplement to the publication (Fig. 1, Table 1) [15].

The Berlin ARDS definition has now been applied to intubated and mechanically ventilated civilian and military burn patients [10, 11, 16–18]. One problem that arises in application of the Berlin ARDS definition to burn patients is the requirement to eliminate "fluid overload" as a possible origin of the pulmonary edema. Most patients with major burns have received substantial amounts of resuscitation fluid by 48–72 h post-injury and have considerable generalized

Table 1 The Berlin definition of ARDS, adapted from Ranieri et al. [15]

Timing	Within 1 week of known clinical insult or worsening respiratory symptoms
Chest radiograph	Bilateral opacities that are not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure is not fully explained by cardiac failure or fluid overload. An objective assessment (e.g., by echocardiography) is required to exclude hydrostatic edema if no risk factor is present
Oxygenation	Mild ARDS, 200 mmHg < PaO_2/FiO_2 ≤ 300 mmHg with PEEP ≥5 cm H_2O; moderate ARDS, 100 mmHg < PaO_2/FiO_2 ≤ 200 mmHg with PEEP ≥5 cm H_2O; severe ARDS, PaO_2/FiO_2 ≤ 100 mmHg with PEEP ≥5 cm H_2O

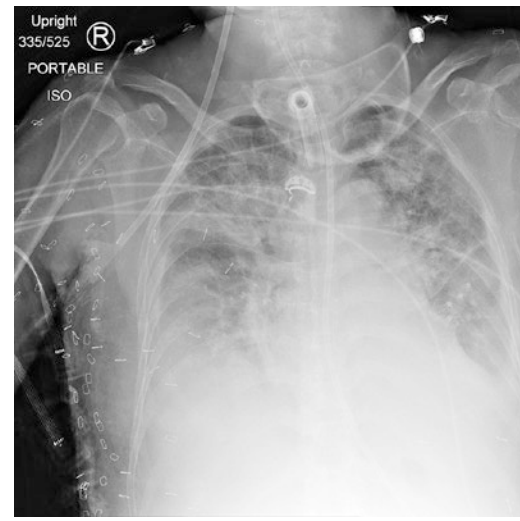

Fig. 1 Typical radiograph from an ARDS patient showing diffuse bilateral infiltrates

edema. Technically, these patients could be considered "volume overloaded." One study in burn patients [10] attempted to address this problem by using the clinical vignettes provided with the ARDS definition [15] and by making specific evaluations of clinical descriptions, use of diuretics, and echocardiography reports to rule out "volume overload" and hydrostatic pulmonary edema. That study found no difference in 24- and 48-h fluid resuscitation volumes between patients with no ARDS and those with ARDS [10]. Another study involving both combat casualty burns as well as civilian burns also was not able to identify any independent relationship between very high resuscitation volume (≥250 mL/kg/24 h) and the development of moderate or severe ARDS [11]. Thus, while it appears that resuscitation fluid volumes are not a cause of ARDS in burn patients, the clinician must be exceedingly careful to ensure that respiratory distress from suspected ARDS is not simply due to hydrostatic pulmonary edema from liberal fluid resuscitation.

4 Epidemiology

ARDS remains an epidemiologic challenge despite the various advances in developing a definition of ARDS [12]. There is no diagnostic test for ARDS such as a blood test or a biopsy. The PaO_2:FiO_2 ratio—essential to the diagnosis and determination of ARDS severity—can fluctuate substantially in the same patient on the same day just with changes in FiO_2 or positive end-expiratory pressure (PEEP) settings. The interpretation of the chest radiograph is fraught with difficulty and unreliability [12, 19]. Notwithstanding these important limitations, the reported incidence of ARDS in all patients over the past half century has ranged between 3.65 and 81.0 new cases per 100,000 person-years [12, 20, 21]. The recent Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG-SAFE) used the Berlin definition and found that the prevalence of ARDS was 10.4% of all ICU admissions and 23.4% of those that were mechanically ventilated [22]. This study showed that across all critically ill patients, ARDS is a global problem which is probably under-recognized. The most important risk factors appear to be pneumonia, non-pulmonary sepsis, aspiration, and trauma [12]. The mortality rate may be as high as 40% as reported in LUNG-SAFE22.

In the scenario of patients with burns that have been mechanically ventilated for at least 24–48 h, two studies found that the prevalence of ARDS using the Berlin definition ranges between 34% [11] and 43% [10]. The prevalence of moderate to severe ARDS was 29% in both studies [10, 11]. Older studies that used the AECC definitions found that the prevalence of ARDS in mechanically ventilated burn patients ranged between 40% 9 and 54% [8]. It is important to note that patients with ALI (PaO_2/FiO_2 200–300 Hg) were not included in those studies meaning that those prevalences represent what would be considered moderate to severe ARDS by the Berlin definition. This suggests that the prevalence of moderate to severe ARDS in burn patients has dropped over the past 15–20 years. One possible explanation, to be discussed under mechanical ventilation, may be the widespread adoption of strict lung-protective ventilation strategies, which were not in use during the earlier studies. The factors that have been identified as significant independent predictors for the development of moderate to severe ARDS in mechanically ventilated burn patients include the extent of full-thickness burn [10], as well as age, injury severity score, the presence of acute kidney injury, and pneumonia 11. Surprisingly, inhalation injury did not turn out to be a significant independent predictor of development of moderate or severe ARDS [10, 11]. The onset of ARDS usually takes place within the first week after the burn injury and occurred at a median of 4 days in the most recent studies on ARDS in burn patients [10, 11]. One study specifically examined the precipitating risk factor prior to onset of ARDS and found that the burn injury either alone or with inhalation injury preceded the onset of ARDS in 66% of cases, while ventilator-associated pneumonia (24%), sepsis (9%), and gastric aspiration (1%) were identified as the likely preceding primary event [10]. The mortality rates for burn patients that develop moderate

or severe ARDS have been reported at 21–44% and 50–60%, respectively [10, 11]. Increasing severity of ARDS is associated with prolonged duration of mechanical ventilation as well as increased mortality [10, 11, 16].

5 Management Strategies for ARDS in the Burn Patient

The management of ARDS in any patient, including those with burns, is entirely supportive. At the present time there are no treatments that will halt or reverse the onset and progress of ARDS. Nevertheless, a variety of strategies to optimize the supportive care of patients with ARDS have been developed over the past two decades. Many of these approaches are guided by evidence from large high-quality randomized controlled trials (RCTs).

5.1 Conventional Mechanical Ventilation

The great paradox in mechanical ventilation of the patient with ARDS is that while mechanical ventilation is almost always needed, and is at times lifesaving, the process of mechanical ventilation inflicts further damage to the lungs affected by ARDS. This process is referred to as ventilator-induced lung injury (VILI). Thus, all current approaches to mechanical ventilation of patients with ARDS revolve around the goal of reducing VILI and in turn diminishing morbidity and mortality related to VILI while still providing life-sustaining oxygenation and gas exchange. One aspect of VILI occurs because large regions of the dependent portions of the lungs are unexpanded and not aerated, leaving only a small portion of remaining aerated lung (the "baby lung") [23] to receive the entire tidal volume of each mechanical breath. If large tidal volumes are used, alveoli in this region of the lung are subjected to repetitive and injurious cyclical stretch and over-distention, referred to as "volutrauma" [24]. Ventilation with high lung volumes can also produce gross barotrauma including pneumothoraces and pneumomediastinum. Another aspect of VILI occurs in other regions of the lung, especially at the interface between aerated and atelectatic lung, where alveoli are unstable and not held open through the tidal breath cycle. Here, low tidal volume ventilation exposes alveoli in these regions to repetitive cyclic opening and closing with each breath. This produces mechanical stress and strain forces that damage the alveoli, a process referred to as "atelectrauma" [24]. The injury produced by these various mechanical forces generates the release of pro-inflammatory mediators that inflict not only an additional traumatic insult to the alveolar-capillary units (referred to as "biotrauma") but also systemic translocation of these mediators as well as bacteria from the lung, leading to multiple organ damage [24].

Lung-protective ventilation strategies (LPVS) are used to limit VILI and have three key elements: small tidal volumes to limit volutrauma, the use of higher PEEP levels to reverse low lung volume atelectrauma, and the use of recruitment maneuvers (sustained application of high airway pressure) to open or "recruit" collapsed regions of the lung to make the lung more homogeneous. However, application of these principles is hampered by the heterogeneous nature of ARDS. The lung pathology not only may vary from patient to patient but also varies tremendously within the lungs of an individual patient. Some regions of the lung (typically the upper non-dependent portions) remain open, some areas may intermittently open and close, while other regions (typically the inferior-posterior dependent portions) remain closed and never receive any ventilation. Heterogeneity of the pathology leads to regional heterogeneity in the ventilation. For example, a lower tidal volume and lower PEEP strategy may reduce volutrauma to the open aerated regions of the lung but could contribute to atelectrauma in the unstable areas. Conversely, the use of a higher PEEP setting might reduce atelectrauma in one region while producing over-distention and tidal hyperinflation in another.

5.1.1 Low Tidal Volumes

This approach is designed to minimize over-distention of the open aerated parts of the lung affected by ARDS. The landmark ARMA trial by

the ARDS Network Investigators found that the use of a 6 mL/kg predicted body weight (PBW) tidal volume (Vt) led to a significant 9% absolute reduction in mortality (40–31%) compared to the use of a 12 mL/kg PBW Vt in adults with ARDS [14]. Plasma levels of inflammatory biomarkers were reduced in the low Vt group, which suggested that less pulmonary biotrauma had occurred. Consequently it is recommended to maintain Vt as close to 6 mL/kg PBW as possible, during mechanical ventilation. Plateau pressures also should be kept <30 cm H_2O since this was a consistent intervention in the low Vt arm.

5.1.2 Higher PEEP

This approach is designed to keep unstable alveoli open and to avoid cyclic atelectrauma. Three large RCTs have been conducted to compare higher vs. lower PEEP settings while using a low tidal volume ventilation strategy [25–27]. These studies each used somewhat different approaches to determine higher vs. lower PEEP, and none individually showed any significant reduction in mortality with higher PEEP. However, a recent patient data level meta-analysis of these three trials found that in the subset of patients with moderate and severe ARDS ($PaO_2/FiO_2 \leq 200$ mmHg), higher PEEP settings (approximately 15 cm H_2O on day 1) were associated reduced time on the ventilator and improved survival [28]. The lowest acceptable limit of PEEP is probably 5 cm H_2O. Levels below this result in underinflation of the lung and are probably harmful. Several approaches have been described to determine the PEEP level. These include the use of a table that arbitrarily dictates PEEP based on the FiO_2, the use of the highest PEEP setting that optimizes oxygenation while still allowing an acceptable Vt and keeping the PPLAT within acceptable limits (generally ≤30 cm H_2O), and bedside manual titration of the PEEP based on assessment of compliance and "recruitability" of the lung.

5.1.3 Recruitment Maneuvers

During a recruitment maneuver, a higher than normal inflation pressure (usually ≥35 cm H_2O) is briefly applied to the lungs, typically for 20–40 s. This is done to "open the lung" and recruit atelectatic regions and lessen the overall heterogeneity of the ventilation. We do not know if the use of recruitment maneuvers leads to a better outcome from ARDS, and the intervention carries risks of causing hemodynamic compromise and barotrauma [24] .

5.1.4 Special Considerations in the Burn Patient

Burn patients were not included in the major trials on ventilation during ARDS. Several unique characteristics of the major burns patient may affect the application of currently accepted lung-protective ventilation approaches. One is the reduced chest wall compliance that results from soft tissue edema from fluid resuscitation, restrictive eschar, or even tight skin grafts on the chest and abdomen. Another is inhalation injury which features narrowing or obstruction of the conducting airways and loss of surfactant in the alveoli. Yet another is the hypermetabolic response that is accompanied by a profound increase in minute ventilation. Notably, a small RCT involving burn patients with ARDS found that inadequate oxygenation and ventilation occurred in a large proportion of patients, especially those with an inhalation injury, when currently accepted low tidal volume ventilation strategies were employed [29] .

The use of low tidal volumes in a burn patient with ARDS that has poor chest compliance and/or an inhalation injury with airway narrowing could contribute to the development of atelectasis from underinflation. One retrospective study spanning a 30 year period in pediatric burn patients with inhalation injury found that low tidal volume ventilation (mean 9 mL/kg) was associated with more atelectasis, longer periods of mechanical ventilation, and a higher incidence of ARDS than a higher tidal volume approach (mean 15 mL/kg) [30]. In our experience, in hypermetabolic burn patients with ARDS that already have abnormally high minute ventilation requirements, strict application of a 6 mL/kg PBW tidal volume sometimes leads to what appears to be "air hunger," dyssynchrony with the ventilator, and hypercapnia. While hypercapnia may be tolerated to an extent ("permissive

hypercapnia"), adjustments to the ventilator mode and increases in inspiratory flow rate are often needed.

The altered chest wall mechanics in a burn patient with an edematous or eschar-restricted thorax or abdomen may affect the interpretation of plateau pressure and the setting of a PEEP level. The work of Talmor et al. [31] using trans-esophageal pressures to measure transpulmonary pressure is particularly important in this regard. The transpulmonary pressure (PTP) is the opening or distending pressure required to inflate the lung and is calculated as the difference between the alveolar pressure (PALV) and the surrounding pleural pressure (PPL), hence PTP = PALV—PPL.

PALV is easy enough to estimate during mechanical ventilation as the pressure in the proximal airway during an end-inspiratory pause in flow (i.e., the plateau pressure). Measurement of PPL on the other hand is problematic but can be approximated by measuring the pressure in the mid-esophagus using a specialized nasogastric tube with a pressure transducer.

It is conceivable that a burn patient on mechanical ventilation with a stiff chest wall from edema and eschar or intra-abdominal edema from large volume fluid resuscitation might have a PPL of approximately 25 cm H_2O. In this case, a plateau pressure of 30 cm H_2O, which otherwise would be considered at the upper limit of being acceptable, may not be that concerning because the PTP is only 30–25 = 5 cm H_2O. Recognition of this might allow more leeway with plateau pressure limits. Similarly, as was shown by Talmor et al. [31], the transpulmonary end-expiratory pressure in this case might be considerably lower than that set and recorded at the airway opening, meaning that a much higher PEEP setting is required.

5.2 Unconventional Mechanical Ventilation

Various unconventional modes of mechanical ventilation have been evaluated for patients with ARDS. The most widely known is high-frequency oscillatory ventilation (HFOV), in which very small, sub-dead space tidal volumes are delivered at high frequency (between 6 and 15 Hz) while maintaining a constant sustained mean airway pressure. HFOV can dramatically improve oxygenation and was found to significantly reduce mortality in a meta-analysis of eight RCTs, (total of 419 patients) [32], but two recent large RCTs both found that HFOV did not improve survival and may have contributed to worse outcomes among adult patients with ARDS [33, 34]. Consequently, HFOV is not recommended as part of the primary ventilation strategy in ARDS, but it is sometimes considered as a "rescue approach" for patients with refractory oxygenation failure. In the burn patient with ARDS, there are two unique considerations surrounding the use of HFOV. The first is that HFOV is generally unsuccessful in improving oxygenation when the patient has had a preceding inhalation injury [35]. This is probably because effective lung recruitment, which is the physiologic basis of HFOV, is impaired by narrowing or obstruction of the conducting airways. The second is that the recent large RCTs on HFOV did not include burn patients and enrolled large numbers of subjects with ARDS related to pneumonia [33, 34]. In many instances ARDS follows the burn injury itself rather than developing from pneumonia. Hypothetically, the lungs affected by burn-related ARDS may differ in terms of "recruitability" from the lungs where ARDS arises from pneumonia, based upon our understanding of ARDS heterogeneity and possible differences between "pulmonary" and "extrapulmonary" ARDS [36]. Thus we do not have a complete answer on whether HFOV may be suitable in some cases of burn-related ARDS.

High-frequency percussive ventilation (HFPV) using the volume diffusive respirator (VDR) delivers very small high-frequency tidal breaths with cyclic variations in mean airway pressure and regular passive exhalation to a predetermined baseline continuous positive airway pressure. This mode is a mainstay in the ventilatory care of patients with inhalation injury, but it has also been applied to burn patients with ARDS. A randomized controlled trial comparing HFPV to protective low tidal volume (LTV) conventional ventilation in burn patients with ARDS, found

that a significantly higher proportion of patients in the LTV arm had inadequate oxygenation and ventilation and required "rescue" by crossover to HFPV [29]. This difference was even more pronounced in patients that had also sustained an inhalation injury.

Airway pressure release ventilation (APRV) is a mode in which patients breathe spontaneously at regularly fluctuating high and low levels of continuous positive airway pressure. The major benefit of this approach is that patients are less heavily sedated and breathe spontaneously, which appears to confer benefit to lung opening, maintenance of diaphragmatic activity, and hemodynamics. However, the use of spontaneous breathing modes such as APRV and pressure support ventilation during ARDS has not been extensively studied, and concerns surround the potential of generating very high transpulmonary pressures and tidal volumes with strong spontaneous breathing on these modes.

5.3 Prone Position

When a patient with ARDS is repositioned from supine to prone, the posterior and inferior lungs are freed from the weight of the heart and mediastinum, the lungs more naturally fill the thoracic cavity, the overall end-expiratory lung volume is increased, and there is an overall improvement in homogeneity of ventilation. This usually produces an increase in oxygenation by improving matching of ventilation and perfusion to the dorsal lung regions [24]. The most recent RCT found that >16 h/day of prone positioning in adults with severe ARDS (PaO_2:FiO_2 ratio <150 on a FiO_2 >0.6) led to significant reductions in 28- and 90-day mortality [37]. A 2015 Cochrane systematic review of RCTs on prone positioning in ARDS concluded that three groups of patients were most likely to derive a survival benefit from prone positioning (PP): those with severe hypoxemia, those where PP was instituted early, and those where PP was used >16 h/day [38]. PP is not without risk, and important potential complications include displacement, obstruction or loss of the airway, anterior pressure sores especially on the face, dislodgement of vascular access lines and chest tubes, and external pressure on the eyes with the risk of orbital compartment syndrome.

Special consideration must be given to prone positioning in a burn patient with ARDS. Loss of the airway in a patient with significant facial and/or neck edema with a difficult airway could be catastrophic. The same concern applies to loss of an indwelling vascular catheter in an edematous major burn patient with difficult vascular access. Anterior burns and recent skin grafts may be harmed during PP. The act of turning a massively burned and edematous patient prone is itself a difficult challenge. Undoubtedly PP in the burn patient with ARDS should only be considered in more extreme cases of oxygenation failure and only after due consideration of the above risks. Several experienced personnel under careful direction are needed to perform this intervention safely. One retrospective study has evaluated prone positioning in a cohort of burn patients and found that oxygenation was improved compared to baseline prior to being positioned prone. No airway dislodgements were reported though it should be noted that nearly 60% of the patients already had tracheostomies [39].

5.4 Neuromuscular Blocking Agents ("Paralytics")

Neuromuscular blocking agents (NMBAs) are sometimes used to paralyze the patient during severe ARDS to allow more precise delivery of low tidal volume ventilation and achieve better control over airway pressures and synchrony with the ventilator. There is no specific evidence to guide the use of NMBAs in burn patients with ARDS. In other critically ill patient populations with moderate to severe ARDS (i.e., a PaO_2:FiO_2 ratio <150), a meta-analysis of data from three RCTs found that initiation of a 48-h continuous infusion of cisatracurium within 36–48 h of ARDS diagnosis led to a significant reduction in 28-day mortality [40]. There does not appear to be any long-term risk of weakness from neuromyopathy from this intervention [41]. Thus, it is probably reasonable to consider a short course of pharmacological paralysis in

burn patients early during severe ARDS, to facilitate strict adherence to protective low tidal volume and pressure-limited ventilation.

5.5 Inhaled Vasodilators

When a vasodilator is administered by inhalation, it selectively increases blood flow to the lung regions that are being ventilated, thus improving matching of ventilation and perfusion. The immediate effect is an improvement in oxygenation as measured by the PaO_2:FiO_2 ratio. The most widely studied agent is inhaled nitric oxide (iNO). A meta-analysis of 12 RCTs in adults with ARDS found that administration of iNO increased oxygenation but did not have any important effect on duration of ventilation or mortality [42]. Burn patients with ARDS similarly respond to iNO with an improvement in oxygenation [43], but there are no large-scale studies from which to determine any other effects on outcomes. Currently iNO is used as a "rescue agent" in patients with severe life-threatening oxygenation failure. It is usually started at 5 ppm and can be titrated up to 20 ppm. If no effect is seen after a short course, the agent is usually stopped. A newer but less well-studied agent that has similar effects on oxygenation is inhaled prostacyclin.

5.6 Other Pharmacologic Interventions

Numerous studies have attempted to alter the course and outcome of ARDS using a variety of anti-inflammatory drugs. A detailed review of this topic is beyond the scope of this chapter. However, a recent systematic review and meta-analysis of 23 RCTs conducted since 2003 in adults with ARDS found that the use of late low-dose methylprednisolone, neutrophil elastase inhibitors, *N*-acetylcysteine, granulocyte-macrophage colony-stimulating factor (GM-CSF), surfactant, or intravenous salbutamol had no effect on survival [40]. Consequently, none of these agents are recommended in the management of any patient with ARDS at this time.

5.7 Avoidance of Fluid Overload

While increased capillary permeability in the lung is a central component of ARDS, increased hydrostatic pressure can worsen extravascular lung water. Thus, there has been long-standing concern during the management of ARDS patients about avoiding fluid overload, in order to minimize deleterious hydrostatic forces. This concept was examined by the ARDS Network Investigators in a trial involving 1000 ARDS patients that were randomized to either a conservative fluid strategy (achieving approximately zero net daily fluid balance over 7 days) to a liberal fluid strategy (which achieved approximately 1 L/day positive fluid balance over 7 days) [44]. The conservative strategy led to better oxygenation and less time on the ventilator, although no significant survival benefit was identified. A subsequent meta-analysis of trials that compared fluid-conservative or "de-resuscitative" approaches to fluid liberal or "usual care" in ARDS found that fluid-conservative strategies led to significant increases in the number of ventilator-free days in hospital [45].

Translation of these findings to the burn patient is particularly difficult. We recognize that extremely large volumes of resuscitation fluid may need to be administered to a major burn patient by 48–72 h. Available studies show that ARDS onset occurs at a median of 4 days after burn injury [10, 11]. Hence, in many cases ARDS may overlap the resuscitation phase. Conservative fluid management and especially administration of diuretics have the potential to compromise burn resuscitation. Furthermore, most major burn patients have substantial insensible fluid losses from their wounds. Thus, determination of a daily fluid balance is inaccurate and often errs on the side of a falsely positive balance. Thus, application of a fluid-conservative strategy in a major burn patient with ARDS should be considered very carefully. This is not to say that there is a role for liberal fluid provision, but rather, strict attention should be given to providing the least amount of fluid that achieves adequate organ perfusion and function.

6 Managing the Burn Wound

It is axiomatic that deep partial-thickness and full-thickness burns should be excised and closed within 3–5 days of injury. The burn wound itself may be the inflammatory source that is stimulating the development of ARDS. In our experience, the median day of ARDS onset was postburn day 4, and in the majority of cases, the only identifiable risk factor for ARDS development was the burn wound [10]. Therefore, in a major burn patient, surgical debridement of the wounds should not be deferred because of respiratory deterioration related to ARDS. This approach requires an anesthesiologist that is experienced and familiar with the intraoperative and perioperative care of a critically ill patient with ARDS. We will sometimes use the patient's ICU ventilator in the OR during burn surgery, and we have gained considerable experience using HFOV as a temporary intraoperative ventilator approach in patients with moderate to severe ARDS [46]. Prone positioning in the OR to debride the large posterior surfaces is often necessary and does not need to be avoided. This often actually improves the oxygenation, which should not be surprising given our current understanding of the physiological changes induced by prone positioning in the ARDS patient.

Conclusions

Burn patients are at risk of developing ARDS. Approximately 30–40% of mechanically ventilated burn patients develop ARDS. Most of the approach to ARDS in the burn patient has been translated from an extensive body of research on ARDS in non-burn patients conducted over the last two decades. An important feature of ARDS in the burn population is that it appears to arise most often from the burn injury itself, in contrast to critically ill non-burn patients where ARDS predominantly arises from pneumonia and sepsis. Management of ARDS in the burn patient is largely supportive and includes the use of low tidal volume and pressure-limited mechanical ventilation, avoidance of fluid overload, and treatment of the primary source(s) that may be "driving" the lung process, including early excision of the burn wound and control of infective sources. Severe ARDS may require further intervention with ventilation in the prone position, short-term use of pharmacologic paralysis, and inhaled vasodilators. Burn patients that develop moderate to severe ARDS are at risk of more prolonged mechanical ventilation and higher mortality.

References

1. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE (1967) Acute respiratory distress in adults. Lancet 2:319–323
2. Pruitt BA Jr, DiVincenti FC, Mason AD, Foley FD, Flemma RJ (1970) The occurrence and significance of pneumonia and other pulmonary complications in burned patients: comparison of conventional and topical treatments. J Trauma 10:519–531
3. Nash G, Foley FD, Langlinais PC (1974) Pulmonary interstitial edema and hyaline membranes in adult burn patients. Hum Pathol 5:149–160
4. Ware LB, Matthay MA (2000) The acute respiratory distress syndrome. N Engl J Med 342(18):1334–1349
5. Murray JF, Matthay MA, Luce JM, Flick MR (1988) An expanded definition of the adult respiratory distress syndrome. Am Rev Respir Dis 138(3):720
6. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, Lamy M, Legall JR, Morris A, Spragg R (1994) The American-European Consensus Conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 149:818–824
7. Hollingshead TC, Saffle JR, Barton RG, Craft BW, Morris SE (1993) Etiology and consequences of respiratory failure in thermally injured patients. Am J Surg 166:592–597
8. Dancey DR, Hayes J, Gomez M, Schouten D, Fish J, Peters W, Slutsky AS, Stewart TE (1999) ARDS in patients with thermal injury. Intensive Care Med 25:1231–1236
9. Liffner G, Bak Z, Reske A, Sjöberg F (2005) Inhalation injury assessed by score does not contribute to the development of acute respiratory distress syndrome in burn victims. Burns 31:263–268
10. Cartotto R, Li Z, Hanna S, Spano S, Wood D, Chung K, Camacho F (2016) The acute respiratory distress syndrome(ARDS) in mechanically ventilated burn patients: an analysis of risk factors, clinical features, and outcomes using the Berlin ARDS definition. Burns 42:1423–1432
11. Sine CR, Belenkiy SM, Buel AR, Waters JA, Lundy JB, Henderson JL, Stewart IJ, Aden JK, Liu NT,

Batchinsky A, Cannon JW, Cancio LC, Chung KK (2016) Acute respiratory distress syndrome in burn patients: a comparison of the Berlin and American-European definitions. J Burn Care Res 37:e461–e469
12. Pham T, Rubenfeld GD (2017) The epidemiology of acute respiratory distress syndrome: a 50th birthday review. Am J Resp Crit Care Med 195(7):860–870
13. Martin C, Papazian L, Payan MJ, Saux P, Gouin F (1995) Pulmonary fibrosis correlates with outcome in adult respiratory distress syndrome: a study in mechanically ventilated patients. Chest 107:196–200
14. Acute Respiratory Distress Syndrome Network, Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A (2000) Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 342:1301–1308
15. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS (2012) Acute respiratory distress syndrome: the Berlin definition. J Am Med Assoc 307:2562–2533
16. Belenkiy SM, Buel AR, Cannon JW, Sine CR, Aden JK, Henderson JL et al (2014) Acute respiratory distress syndrome in wartime military burns: application of the Berlin criteria. J Trauma Acute Care Surg 76:821–827
17. Waters JA, Lundy JB, Aden JK, Sine CR, Buel AR, Henderson JL, Liu NT, Lundy JB, Renz EM, Batchinsky AI, Cancio LC, Chung KK (2015) A comparison of acute respiratory distress outcomes between military and civilian burn patients. Mil Med 180:56–59
18. Bordes J, la Croix G, Esnault P, Goutorhe P, Cotte J, Dantzer E, Meaudre E (2014) Comparison of the Berlin definition with the American-European Consensus definition for acute respiratory distress syndrome in burn patients. Burns 40:562–567
19. Meade MO, Cook RJ, Guyatt GH, Groll R, Kachura JR, Bedard M, Cook DJ, Slutsky AS, Stewart TE (2000) Interobserver variation in interpreting chest radiographs for the diagnosis of acute respiratory distress syndrome. Am J Resp Crit Care Med 161:85–90
20. Li G, Malinchoc M, Cartin-Ceba R, Venkata CV, Kor DJ, Peters SG, Hubmayr RD, Gajic O (2011) Eight year trend of acute respiratory distress syndrome : a population based study in Olmsted County, Minnesota. Am J Resp Crit Care Med. 183:59–66
21. Sigurdsson MI, Sigvaldason K, Gunnarsson TS, Moller A, Sigurdsson GH (2013) Acute respiratory distress syndrome; nationwide changes in incidence, treatment and mortality over 23 years. Acta Anaesthesiol Scand 57:37–45
22. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, Gattinoni L, vanHaren F, Larsson A, McAuley DF et al (2016) Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. J Am Med Assoc 315(8):788–800
23. Gattinoni L, Presenti A (2005) The concept of "baby lung". Intensive Care Med 31:776–784
24. Slutsky AS, Ranieri M (2013) Ventilator-induced lung injury. N Engl J Med 369:2126–2136
25. Brower RG, Lanken PN, MacIntyre N, Matthay MA, Morris A, Ancukiewicz M, Schoenfeld D, Thompson BT, National Heart, Lung, and Blood Institute ARDS Clinical Trials Network (2004) Higher vs lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N Engl J Med 351:327–336
26. Meade MO, Cook DJ, Guyatt GH, Slutsky AS, Arabi YM, Copper DJ, Davies AR, Hand LE, Zhou Q, Thabane L, Austin P, Lapinsky S, Baxter A, Russell J et al (2008) Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressures for acute lung injury and acute respiratory distress syndrome; a randomized controlled study. J Am Med Assoc 299:637–645
27. Mercat A, Richard JC, Vielle B, Jaber S, Osman D, Diehl JH, Lefrant JY, Prat G, Richecoeur J, Nieszkowska A, Gervais C, Baudot J, Bouadma L, Brochard L, Expiratory Pressure (Express) Study Group (2008) Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. J Am Med Assoc 299:646–655
28. Briel M, Meade M, Mercat A, Brower RG, Talmor D, Walter D, Slutsky AS, Pullenayegum E, Zhou Q, Cook D, Brochard L, Richard JC, Lamontagne F, Bhatnagar N, Stewart TE, Guyatt G (2010) Higher vs lower positive endexpiratory pressure in patients with acute lung injury and the acute respiratory distress syndrome: systematic review and meta-analysis. J Am Med Assoc 303:865–873
29. Chung KK, Wolf SE, Renz EM, Allan PF, Aden JK, Merrill GA, Shelhamer MC, King BT, White CE, Bell DG, Schwacha MG, Wanek SM, Wade CE, Holcomb JB, Blackbourne LH, Cancio LC (2010) High frequency percussive ventilation and low tidal volume ventilation in burns; a randomized controlled trial. Crit Care Med 38:1970–1977
30. Sousse LE, Herndon DN, Andersen CR, Ali A, Benjamin NC, Granchi T, Suman OE, Mlcak RP (2015) High tidal volume decreases adult respiratory distress syndrome, atelectasis, and ventilator days compared with low tidal volume in pediatric burned patients with inhalation injury. J Am Coll Surg 220:570–578
31. Talmor D, Sarge T, Malhotra A, O'Donnell CR, Ritz R, Lisbon A, Novack V, Loring SH (2008) Mechanical ventilation guided by esophageal pressure in acute lung injury. N Engl J Med 359:2095–2104
32. Sud S, Sud M, Friedrich JO, Meade MO, Ferguson ND, Wunsch H, Adhikari NK (2010) High frequency oscillation in patients with acute lung injury and acute respiratory distress syndrome (ARDS): systematic review and meta-analysis. BMJ 340:c2327
33. Ferguson ND, Cook DJ, Guyatt GH, Mehta S, Hand L, Austin P, Zhou Q, Matte A, Walter SD, Lamontagne F, Granton JT, Arabi YM, Arroliga AC, Stewart TE, Slutsky AS, Meade MO, OSCILLATE Trial Investigators; Canadian Critical Care Trials Group (2013) High frequency oscillation in early acute respiratory distress syndrome. N Engl J Med 368:795–805

34. Young D, Lamb SE, Shah S, MacKenzie I, Tunnicliffe W, Lall R, Rowan K, Cuthbertson BH, OSCAR Study Group (2013) High Frequency oscillation for acute respiratory distress syndrome. N Engl J Med 368:806–813
35. Cartotto R, Walia G, Ellis S, Fowler R (2009) Oscillation after inhalation: High frequency oscillatory ventilation in burn patients with the acute respiratory distress syndrome and co-existing smoke inhalation injury. J Burn Care Res 30:119–127
36. Gattinoni L, Pelosi P, Suter PM, Pedoto A, Vercesi P, Lissoni A (1998) Acute respiratory distress syndrome caused by pulmonary and extra-pulmonary disease: different syndromes? Am J Resp Crit Care Med 158:3–11
37. Guérin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, Mercier E, Badet M, Mercat A, Baudin O, Clavel M, Chatellier D et al (2013) Prone positioning in severe acute respiratory distress syndrome. N Engl J Med 368:2159–2168
38. Bloomfield R, Noble DW, Sudlow A (2015) Prone position for acute respiratory failure in adults. Cochrane Database Syst Rev 11:CD008095
39. Hale DF, Cannon JW, Batchinsky AI, Cancio LC, Aden JK, White CE, Renz EM, Blackbourne LH, Chung KK (2012) Prone positioning improves oxygenation in adult burn patients with severe acute respiratory distress syndrome. J Trauma Acute Care Surg 72:1634–1639
40. Duggal A, Ganapathy A, Ratnapalan M, Adhikari NKJ (2015) Pharmacological treatments for acute respiratory distress syndrome: a systematic review. Minerva Anestesiol 81:567–588
41. Hraiech S, Forel JM, Papazian L (2012) The role of neuromuscular blockers in ARDS: benefits and risks. Curr Opin Crit Care 18:495–502
42. Adhikari NK, Burns KE, Friedrich JO, Granton JT, Cook DJ, Meade MO (2007) Effect of nitric oxide on oxygenation and mortality in acute lung injury. Systematic review and meta-analysis. BMJ 334:779
43. Musgrave MA, Fingland R, Gomez M, Fish J, Cartotto R (2000) The use of inhaled nitric oxide as adjuvant therapy in patients with burn injuries and respiratory failure. J Burn Care Rehabil 21(6):551–557
44. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, deBoisblanc B, Connors AF Jr, Hite RD, Harabin AL (2006) Comparison of two fluid management strategies in acute lung injury. N Engl J Med 354:2564–2575
45. Silversides JA, Major E, Ferguson AJ, Mann EE, McAuley DF, Marshall JC, Blackwood B, Fan E (2017) Conservative fluid management or deresuscitation for patients with sepsis or acute respiratory distress syndrome following the resuscitation phase of critical illness: a systematic review and meta-analysis. Intensive Care Med 43:155–170
46. Walia G, Jada G, Cartotto R (2011) Anesthesia and intraoperative high-frequency oscillatory ventilation during burn surgery. J Burn Care Res 32(1):118–123