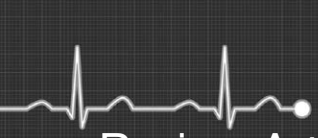

Review Article

Mechanisms of Acute Respiratory Distress Syndrome in Children and Adults: A Review and Suggestions for Future Research

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Objectives: To provide a current overview of the epidemiology and pathophysiology of acute respiratory distress syndrome in adults and children, and to identify research questions that will address the differences between adults and children with acute respiratory distress syndrome.

Data Sources: Narrative literature review and author-generated data.

Data Selection: The epidemiology of acute respiratory distress syndrome in adults and children, lung morphogenesis, and postnatal lung growth and development are reviewed. The pathophysiology of acute respiratory distress syndrome is divided into eight categories: alveolar fluid transport, surfactant, innate immunity, apoptosis, coagulation, direct alveolar epithelial injury by bacterial products, ventilator-associated lung injury, and repair.

Data Extraction and Synthesis: Epidemiologic data suggest significant differences in the prevalence and mortality of acute respiratory distress syndrome between children and adults. Postnatal lung development continues through attainment of adult height, and there is overlap between the regulation of postnatal lung development and inflammatory, apoptotic, alveolar fluid clearance, and repair mechanisms. Therefore, there is a different biological baseline network of gene and protein expression in children as compared with adults.

Conclusions: There are significant obstacles to performing research on children with acute respiratory distress syndrome. However, epidemiologic, clinical, and animal studies suggest age-dependent differences in the pathophysiology of acute respiratory distress syndrome. In order to reduce the prevalence and improve the outcome of patients with acute respiratory distress syndrome, translational studies of inflammatory, apoptotic, alveolar fluid clearance, and repair mechanisms are needed. Understanding the differences in pathophysiologic mechanisms in acute respiratory distress syndrome between children and adults should facilitate identification of novel therapeutic interventions to prevent or modulate lung injury and improve lung repair. (*Pediatr Crit Care Med* 2013; 14:631–643)

Key Words: acute lung injury; acute respiratory distress syndrome; children; lung inflammation; lung repair; mechanical ventilation

> …[T]here is no such thing as an immovable lung morphology with a stable and/or quantitatively constant tissue framework. …[L]ung development blends imperceptibly into growth and growth blends into aging (1).

Acute respiratory distress syndrome (ARDS) was originally described in adults and children, yet children have been excluded from many clinical and interventional studies of ARDS. ARDS is difficult to study in humans because of a variable latent interval following a variety of insults that result in the acute onset of severe respiratory failure associated with significant morbidity and mortality. Ethical and logistical issues make studies in children more difficult than adults. Although the clinical pattern of hypoxemic respiratory failure with restrictive lung physiology is similar across all ages, there are factors unique to children that are likely to influence the development, severity, and resolution of ARDS.

The purpose of this review is to summarize current knowledge about ARDS in children and adults, and then to identify future research directions that are needed to understand how the pathophysiology of ARDS may differ across the spectrum of ages. Although there is a new 2012 Berlin definition of ARDS, the majority of published studies used the 1994 American-European Consensus Conference definition (2, 3). The 2012 Berlin definition of ARDS has not yet been tested in children; however, an international group has been assembled to develop a consensus statement addressing pediatric ARDS (4).

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In this review, the discussion of the epidemiology of ARDS is followed by a brief examination of lung morphogenesis and postnatal lung development, innate immunity in the lungs, and alveolar epithelial and endothelial injuries in order to understand the similarities and differences in the pathophysiology of ARDS between children and adults. The conceptual approach is divided into alveolar fluid transport, surfactant, apoptosis, coagulation, and ventilator-associated lung injury (VALI). Interactions between the immune system and VALI are examined, followed by key repair mechanisms and long-term outcomes. Each section concludes with a discussion of how the gaps in knowledge between adults and children can guide future studies of ARDS.

EPIDEMIOLOGY

The quality and quantity of information about the epidemiology of ARDS is improving. Population-based studies in the United States, Europe, and Australia, published in 1997 and 2008, indicate that the prevalence of ARDS in adults has ranged from 17.9 to 81 per 100,000 person·years (5–8). In contrast to adults, the prevalence of ARDS in United States, European, and Australian children is 2–12.8 per 100,000 person·years (9–12).

Although the mortality of ARDS appears to be decreasing in clinical trials, population-based studies suggest that the overall mortality of ARDS in adults is 27–45% (5–8, 13). Several studies suggest that ARDS attributable mortality in children is lower than in adults (18–27%); however, data from Australia suggests that pediatric mortality from ARDS may be similar to adults (35%) (12, 14–17). The only study that stratified the prevalence and mortality of ARDS by age did not include patients under 15 years old (8). However, data from the same network of hospitals and patient catchment area (King County Lung Injury Project, WA) supports the conclusion that the prevalence and mortality of ARDS is lowest in children and increases with advancing age (8, 12).

The reasons for the differences in the epidemiology of ARDS between children and adults are unclear, raising important questions about the clinical risk factors and pathophysiologic mechanisms of ARDS in children and adults. The infrequent use of arterial blood sampling in pediatric patients and the failure to recognize ARDS in children with lower respiratory tract infections are possible reasons for underestimating the prevalence of ARDS in children, but there may be a similar underestimation of the prevalence of ARDS in adults (9, 18–20). Most pediatric and adult studies report increased prevalence of ARDS in males versus females, but male gender does not seem to associate with increased mortality (5–7, 10, 12–14, 21–23). Erickson et al (24, 25) showed significant differences in the mortality of black and Hispanic as compared to Caucasian pediatric ARDS patients, and it appears that the increased morbidity of African-American ARDS patients may be due, in part, to a common polymorphism of the Duffy minor blood group type. The percentage of pediatric and adult ARDS patients with preexisting illness appears to be similar (21–33% and 12–34%, respectively), but the studies by Santchi et al and Lopez-Fernandez et al reported that 65–74% of pediatric ARDS patients had a preexisting illness (7, 10, 12, 13, 17, 22, 26, 27). Immunodeficiency is a common preexisting condition in both pediatric and adult patients in whom ARDS develops, and most studies show increased mortality among immunodeficient patients in whom ARDS develops (5, 7, 10, 12, 13, 21, 22). Although there may be differences in the type and severity of preexisting comorbidities, and there may be age-dependent differences in the risks of developing extrapulmonary organ failure, there are currently no validated scoring systems to make reliable comparisons between pediatric and adult patients. Age-dependent differences in respiratory viral infection rates may contribute to differences in outcome between children and adults, but pneumonia, sepsis, aspiration, and trauma account for 63–92% of ARDS in adults and children (5, 8, 10, 12–14, 17, 22). There may be differences in the rates of pulmonary and extrapulmonary sepsis between children and adults, but the lack of uniformity in the reporting of pulmonary and extrapulmonary etiologies and mortality in ARDS patients makes direct comparison difficult (28, 29).

Future studies of the epidemiology of ARDS in children and adults will benefit from iterative improvements in definition that will facilitate capturing the prevalence of ARDS. In order to better understand the risks of developing and dying from ARDS, future definitions of ARDS may need to recommend criteria to uniformly describe the etiologies and comorbidities of patients with ARDS. Since increasing age is a risk factor for developing and dying from ARDS, future studies should consider including stratification of age in the description and analyses of data. The apparent similarities in etiology of ARDS between children and adults suggest opportunities for collaboration between adult and pediatric ARDS investigations.

LUNG MORPHOGENESIS AND POSTNATAL DEVELOPMENT

An important difference between children and adults with lung injury is that the lungs are developing and growing in children but not adults. Most information about human lung development is extrapolated from animal studies, but there is a good correlation with humans (30–32). The major stages of postnatal lung development, alveolarization, microvascular maturation, and normal growth occur simultaneously, but the peak rates at which each stage occurs are different. Human newborns have approximately 50 million alveoli, and postnatal alveolarization culminates in roughly 300 million alveoli in adults (1). Alveolarization is generally complete by 18 months old, but it probably continues through puberty (1, 32). The second stage of postnatal lung development, microvascular maturation, is characterized by a rapid increase in alveolar surface area and slowing of cell proliferation (1). There is also a decrease in mesenchymal and interstitial tissue mass and a change from the double alveolar capillary network in the newborn lung to the single capillary network of the adult lung. Alveolar epithelial cell proliferation and differentiation, septation of alveoli, and increases in the

luminal diameter of conducting airways continue until adult height is reached.

Several important regulators of lung morphogenesis overlap with inflammatory, apoptotic, and repair mechanisms. Fibroblast growth factors (FGFs) regulate branching morphogenesis of the lung, activate epithelial cell proliferation and differentiation, induce surfactant protein expression, and increase expression of aquaporins and alveolar fluid clearance (33). Nuclear factor kappa B (NF-κB, a central transcription factor in innate immunity) blocks FGF-10 expression in the embryonic chick lung, thereby inhibiting growth and budding of the respiratory epithelium, and increased NF-κB expression accelerates lung maturation in mice (34, 35). Chorioamnionitis causes decreased alveolar septation and vascular injury in animal models, and there is a strong association between prenatal inflammation and development of bronchopulmonary dysplasia (36, 37).

Transforming growth factor beta (TGF-β) has been widely studied in lung morphogenesis as well as in lung repair following injury. TGF-β is required for normal lung development; however, increased levels of TGF-β are associated with development of bronchopulmonary dysplasia in premature human infants (31, 38). TGF-β is present and maintains homeostasis in normal adult lungs and is required for normal repair after injury (39). Increased levels of TGF-β have been associated with worse fibrosis and mortality in adult patients with ARDS (40, 41). The requirement of TGF-β for regulation of normal postnatal lung development as well as maintenance of homeostasis in the quiescent adult lung suggests that unraveling the role of TGF-β in ARDS in children and adults will require carefully designed studies across the age spectrum.

The pathophysiological responses to infection and injury are likely to be different in the developing lungs of children, in whom there is a different biological network of gene and protein expression as compared with adults. In a murine model of lung injury, there were age-dependent differences in the expression of genes that regulate cell cycle, FGF, and TGF-β signaling (42). These data suggest that the inflammatory and repair mechanisms are likely to be different in the growing lung as compared to the quiescent adult lung, and applying data extrapolated from adult studies to children is likely to lead to incorrect conclusions.

INNATE IMMUNITY IN THE LUNGS

Pneumonia and sepsis are the most commonly identified etiologies of ARDS in children and adults, and the innate immune system has been the focus of many ARDS studies. The innate immune system is highly conserved, and although its function is not dependent on prior exposure to pathogens, it is not fully functional at birth. Infants are more susceptible than adults to a wide variety of infectious agents. Neonatal neutrophil responses are limited by reduced granulocyte colony-stimulating factor production, combined with a limited neutrophil storage pool (43). There is also evidence that neutrophil demargination and migration to sites of infection are decreased. Lower neonatal polymorphonuclear (PMN) cell chemotactic activity as compared with adults may be due to differences in complement activation, collectins, and fibronectin concentrations (43). The decreased chemotactic responses of human neonatal PMN may persist for as long as 1–2 years before reaching full adult levels of responsiveness. Plasma levels of soluble intercellular adhesion molecule-1, a molecule involved in neutrophil adhesion and migration, have been associated with worse clinical outcome in children and adults with ARDS (44, 45).

Neonatal inflammatory responses to bacterial products, such as lipopolysaccharide (LPS), are reduced as compared with adults. In vitro studies of neonatal PMNs, monocytes, and whole cord blood stimulated with LPS have shown that infants have lower tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, and IL-12 responses as compared with adults (46–48). Adult PMNs up-regulate membrane CD14 (an important coreceptor for toll-like receptor (TLR)4-dependent recognition of LPS) in response to LPS, whereas similarly treated infant PMNs do not significantly change membrane CD14 expression (49). Lower infant TNF-α responses as compared with adults have also been correlated with lower expression of myeloid differentiation primary response protein 88 (MyD88, a necessary intracellular adaptor protein for most TLR signaling) levels in mononuclear cells (50).

Little is known about lung macrophages in the human neonate, but the alveolar macrophages of neonates of many species have reduced microbicidal activity. Macrophage chemotaxis in children is thought to be reduced until 6–10 years old, and cytokine production in neonatal macrophages treated with TLR2 and TLR4 agonists is only 25–75% of that seen in adult macrophages (43). Although the developmental changes in monocyte expression of TLR3 receptors or responses to TLR3 agonists are not known, the responses of neonatal macrophages to viral pathogens are impaired, with interferon (IFN)-α/β production as low as 10–30% of the values of adult macrophages (43).

NF-κB is a transcription factor present in almost all mammalian cells, and NF-κB regulates cell differentiation and organ morphogenesis as well as inflammatory and apoptotic responses to external and internal stimuli (51, 52). The canonical pathway involves phosphorylation of IκB proteins, releasing cytosolic NF-κB dimers (predominantly p65p50) to translocate into the nucleus (52). Under resting conditions, p50 and p65 subunits are abundant, with p65p50 heterodimers bound to IκB in the cytoplasm and unbound nuclear p50p50 homodimers (51). In studies by Yang et al (53), neonatal but not adult mice were shown to activate NF-κB in the lungs in response to hyperoxia, and p50 null mutant neonatal mice treated with hyperoxia developed increased lung inflammation and apoptosis and lowered survival as compared with age-matched wild-type mice. Age-dependent differences in NF-κB were also found in studies by Alvira et al (54), in which the dimerization of NF-κB subunits was shown to differ in the lungs of neonatal and adult mice treated with LPS. Interestingly, the formation of p50p50 homodimers

in the lungs of adult mice was associated with increased inflammation and apoptosis in the lungs as compared with neonatal mice, in which p65p50 heterodimers predominated. Age-dependent mechanisms regulating NF-κB dimerization and the age-dependent transcriptional responses to the NF-κB dimers are poorly understood.

IL-1β has been associated with lung injury in rodents and humans (55, 56). Polymorphisms in the IL-1 receptor antagonist gene have been associated with the systemic inflammatory responses in adults and the development of ARDS in children with community-acquired pneumonia (57, 58). In an experimental model of ARDS, the combination of LPS and mechanical ventilation caused synergistic increases in the amount of IL-1β in adult but not juvenile mice (42).

There are many important intersections between the regulation of innate immunity and lung growth, development, and repair. A balanced pro- and anti-inflammatory response resulting in rapid clearance of pathogens is necessary to survive a severe infection. Infants appear to be at one end of the spectrum of innate immune function, such that they lack injurious proinflammatory responses, but pathogen clearance is impaired. Adults appear to be at the other end of the spectrum of innate immune function, as they are able to clear pathogens rapidly, but often succumb to their own proinflammatory responses. Translational studies are needed to understand how the apparent balance in inflammatory responses differs across the spectrum of age. The results of these studies have potential to lead to novel therapeutic approaches to balancing the inflammatory responses in patients of all ages.

ALVEOLAR EPITHELIAL AND ENDOTHELIAL INJURIES

Disruption of the alveolar epithelial and endothelial barriers is a pathological hallmark of ARDS and leads to accumulation of protein-rich alveolar edema fluid. Chemicals and toxins, proteolytic enzymes, shear stress from mechanical ventilation, inflammatory cascades, and viral or bacterial infections may directly injure alveolar epithelial and pulmonary endothelial cells. Injury to the alveolar epithelium may disrupt surfactant production, impair alveolar fluid clearance, and expose the alveolar epithelial basement membrane. Injury to pulmonary endothelial cells may activate coagulation and inflammatory cascades, promote vascular leak, disrupt regulation of oxidant balance and pulmonary vascular resistance, and initiate systemic inflammatory responses that contribute to remote organ dysfunction (59).

Sepsis and pneumonia are the most common risk factors for all patients to develop ARDS. Although there appear to be physiologic differences in adult patients with pulmonary versus extrapulmonary ARDS, a meta-analysis of mortality in adult patients with pulmonary versus extrapulmonary ARDS has not shown differences in mortality between these two groups (28, 60). Interestingly, a subsequent study showed lower mortality in adult patients with pulmonary sepsis versus extrapulmonary sepsis, but after correcting for severity of illness, there was no difference in the predicted mortality of patients with pulmonary versus extrapulmonary sepsis (29).

Sepsis is the most common risk factor in adults in whom ARDS develops, whereas pulmonary infections are the most common risk factor in children (8, 22). However, reports of direct versus indirect causes of ARDS in adults vary, and pneumonia is the commonest cause of sepsis in adult ARDS patients (8, 13). There are likely to be differences in the infectious organisms causing pneumonia and sepsis between adult and infant patients with ARDS, but nothing is known about whether the infections differ between older children and adults or whether specific infections result in differences in morbidity and mortality.

Smith et al (42) found significant differences in vascular endothelial derived growth factor protein expression and transcriptional biological ontologies of cell migration, apoptosis, and organ morphogenesis between adult and juvenile mice treated with inhaled LPS and mechanical ventilation. Future translational studies of age-dependent alveolar epithelial and pulmonary endothelial injury and repair mechanisms are needed to understand important pathophysiologic differences between children and adults with ARDS. Important opportunities exist for collaborative efforts between ARDS and sepsis as well as pediatric and adult investigators. Improved understanding of these differences has potential to lead to new collaborative studies of therapeutic approaches to patients with ARDS.

ALVEOLAR FLUID TRANSPORT

Injury to the alveolar epithelium and/or endothelium results in the accumulation of protein-rich edema fluid in the alveolar air spaces, which inactivates surfactant and increases the diffusion distance for gas exchange. Clearance of fluid from the alveolar airspace requires an intact alveolar epithelial barrier, and adult patients with low alveolar fluid clearance rates had a longer duration of mechanical ventilation, worse oxygenation, and higher mortality as compared with adults who had normal to maximal alveolar fluid clearance rates (61, 62). Although cumulative fluid balance has been shown to correlate with mortality in pediatric and adult ARDS patients, alveolar fluid clearance does not equate with fluid balance (63, 64).

Epithelial sodium channels, the cystic fibrosis transmembrane conductance regulator, Na^+-K^+-ATPase, and aquaporins (cell membrane water channels) are involved in the clearance of fluid from the distal airspaces into the interstitium of the lung. Salt and water transport is regulated by catecholamines, glucocorticoids, mineralocorticoids, growth factors (epidermal growth factor, TGF-α, keratinocyte growth factor [KGF], or FGF-7), FGF-10, NF-κB, and serine proteases (65).

Male gender has been associated with low alveolar fluid clearance in adult patients with ARDS, whereas premenopausal women were more likely to have high alveolar fluid clearance. These findings are supported by animal data showing that progesterone and estrogen increased expression and function of the epithelial sodium channel (62, 66). Beta-adrenergic

agonists up-regulate alveolar fluid clearance in human lungs (67). However, two randomized placebo-controlled trials of treatment with IV salbutamol did not show a reduction in ventilator-free days or mortality in adults with ARDS (68, 69). Animal studies of KGF therapy for acute lung injury have suggested that pre- but not postinjury treatment is protective, but there is an ongoing trial in the United Kingdom investigating the effect of treatment with KGF in adult patients with lung injury (http://www.controlled-trials.com/ISRCTN95690673/) (70).

Children have not been included in studies of alveolar fluid clearance in patients with ARDS, and nothing is known about the rate of alveolar fluid clearance in children with ARDS as compared with adults. However, experimental models of alveolar fluid clearance may provide clues to mechanisms by which alveolar fluid clearance in children with ARDS could be different from adults. KGF/FGF-7 increases clearance of alveolar fluid, and it is an alveolar cell mitogen that is up-regulated in injured lungs (70). Pretreatment with KGF before lung injury preserves alveolar fluid clearance, is protective in several models of lung injury, and it is not clear why treatment with KGF after injury in animal models has not been beneficial (70). KGF is an important mediator of postnatal lung morphogenesis. Therefore, throughout childhood, the lung may be "pretreated" with KGF before any insult actually occurs.

Future studies of the rate of alveolar fluid clearance in children and adults with ARDS are necessary in order to determine whether alveolar fluid clearance is better preserved in children with ARDS versus adults. Since preservation of alveolar fluid clearance has been associated with decreased mortality in adults with ARDS, identifying a population with higher alveolar fluid clearance may lead to identification of therapeutic interventions that are beneficial for all patients with impaired alveolar fluid clearance.

SURFACTANT SYSTEM

Pulmonary surfactant is composed primarily of lipids (90%) and proteins (10%). The primary functions of surfactant are to provide variable surface tension at the air-liquid interface of the alveoli and contribute to innate immune function as collectins by enhancing opsonization of pathogens (71). Surfactant proteins A (SP-A) and D (SP-D) have important roles in the inflammatory responses to microbial pathogens, including lung remodeling after resolution of infection (72). Surfactant may also contribute to the function of the mucociliary escalator, improving clearance of debris (73). Additionally, SP-A also plays a role in regulating apoptosis of lung fibroblasts and type II epithelial cells (74).

Dilution of alveolar surfactant by pulmonary edema fluid, injuries to type II epithelial cells, and leakage of surfactant from the alveolar compartment into the vascular compartment are conventional but inadequate explanations for the loss of alveolar surfactant during ARDS. Inflammation also changes the expression of surfactant proteins and lipid composition. TNF-α and LPS decreased expression of SP-A but not SP-D, whereas IFN-γ increased SP-A but not SP-D in human fetal lung (75). The quality of surfactant may also be altered in lung injury as evidenced by increased nitration of SP-A and increases in the relative amounts of dysfunctional small aggregates compared to functional large aggregates of surfactant (73, 76).

Bronchoalveolar lavage (BAL) fluid obtained from adult patients with ARDS has fewer surfactant lipids, fewer surfactant-associated proteins, and impaired surface tension reducing capacity as compared to normal patients (77). Increased concentrations of surfactant proteins A, B, and D are detectable in the serum of adult patients with ARDS versus normal patients suggesting leakage of surfactant proteins through the damaged alveolar epithelium (77). SP-B polymorphisms have been associated with an increased risk of ARDS in adults and an increase in the 60-day mortality of adult patients with ARDS (78, 79). Exogenous surfactant therapy for adult patients with ARDS has been shown to improve oxygenation, but it has not reduced mortality or mechanical ventilator days (80). However, a post hoc pooled analysis suggested that treatment of adult patients with ARDS from direct lung injury (pneumonia or aspirated gastric contents) with exogenous recombinant surfactant protein C may decrease mortality (81).

In a study of surfactant content in children, children with ARDS were found to have abnormal surfactant composition but, in contrast to adults, normal amounts of surfactant A and B proteins (82). However, similar to adult studies, SP-B polymorphisms were associated with worse lung injury in African-American children with community-acquired pneumonia (83). In contrast to adults, exogenous surfactant therapy has improved oxygenation and reduced mortality in children with ARDS (84, 85). Although exogenous surfactant provided a survival benefit to children with ARDS, there was an imbalance in baseline immunodeficiency in the study groups, and treatment with surfactant was not associated with an improvement in ventilator-free days as compared with placebo (85).

The efficacy of exogenous surfactant therapy in pediatric but not adult patients with ARDS suggests that there might be important differences in the injuries to the alveolar epithelium in children versus adults. This hypothesis is supported by findings in children and adults showing that exogenous surfactant is beneficial for patients with direct (pneumonia) but not indirect (sepsis) lung injuries. Because pulmonary infections are the most common cause of ARDS in children, whereas sepsis is the most common cause of ARDS in adults, it is possible that the apparent age-dependent benefit of exogenous surfactant is not due to an intrinsic age-dependent difference, but rather due to the cause of the lung injury.

Future studies of the effect of exogenous surfactant in children and adults with ARDS should use the same surfactant and include a study design that can stratify direct versus indirect lung injury. Future studies should also consider investigating the role of exogenous surfactant in immunodeficient ARDS patients. The apparent discrepancy between the improvement in mortality but not ventilator-free days in children with ARDS treated with surfactant may also be important to consider in the design of future studies. Previous investigations have been

designed to detect changes in ventilator-free days, but with improvements in mortality it is possible that sicker patients are surviving and, subsequently, requiring longer support with mechanical ventilation. Another important factor in the detection of ventilator-free days in multicenter studies is the use of careful design and application of ventilator weaning protocols, extubation criteria, and noninvasive support. As progress is made in the determination of differences between the degree of alveolar epithelial injury, inflammatory and innate immune function, as well as differences between the regulation of apoptosis in the lungs of children and adults, it is possible that intrinsic age-dependent differences in the response to treatment with exogenous surfactant will become apparent.

APOPTOSIS

Cellular death occurs primarily by lysis of the cell membrane (necrosis) and spillage of cytoplasmic and nuclear contents or by a controlled process of cell shrinkage, chromatin condensation, and DNA degradation (apoptosis) (67). Apoptosis signaling pathways are important in the pathogenesis of ARDS, and the relevance of apoptosis varies by cell type. Recruitment of activated neutrophils to the lungs is necessary to eradicate most pathogens, but delay in the clearance of activated neutrophils from the lungs could prolong ARDS. Surprisingly, increased granulocyte macrophage colony-stimulating factor (which delays apoptosis of alveolar neutrophils) concentrations in BAL fluid have been associated with improved survival in adult patients with ARDS (86). However, sustained inflammation in the lungs has been associated with worse outcome, and once pathogens have been eradicated, induction of neutrophil apoptosis is essential for the resolution of alveolar inflammation (87, 88).

The Bcl2 family and Fas signaling have been shown to be important in the development of alveolar epithelial cell apoptosis in animal models of ARDS as well as in adults with ARDS (89, 90). Increased concentrations of soluble Fas ligand (sFasL) in the BAL fluid of adult patients with ARDS have been associated with increased mortality, and BAL fluid from adult patients with ARDS causes apoptosis of cultured human distal lung epithelial cells (90, 91). These studies have generated interest in therapies that modulate apoptotic pathways (92–94).

Apoptotic signaling is modified by coregulation of Fas and TLR4 pathways by Fas-associated death domain as well as activation of both Fas and Bcl2 pathways by inflammatory signaling (95–98). Surfactant proteins have been shown to modulate apoptosis of alveolar epithelial cells and pulmonary fibroblasts as well as macrophage clearance of apoptotic cells (99–101). The renin-angiotensin system also modulates apoptosis in the lungs. Angiotensin II has been shown to be important to LPS, Fas, and surfactant depletion models of lung injury, and blockade of the renin-angiotensin system has therapeutic benefit in models of ARDS (102, 103). Oxidative stress is another modulator of apoptosis in the lungs, in part, by modifying the structure and function of sFasL (104, 105). Oxidative stress results from oxidants produced in the alveolar microenvironment by neutrophils and other cells by high concentrations of inhaled oxygen. Oxidative lung injury has been widely studied, and there are possible therapeutic interventions for oxidant-induced apoptosis (106, 107).

Although apoptosis pathways are involved in ARDS, apoptosis is also important to normal postnatal lung development (108). Growth factors that regulate lung development and repair (FGF-10, KGF, and TGF-β) modulate apoptotic mechanisms (109–111). In LPS and hyperoxia models of ARDS, neonatal mice exhibit different apoptotic responses in the lungs as compared with adults (53, 54). Furthermore, mechanical ventilation has been shown to alter the normal apoptotic programs of neonatal mice (112). These studies suggest that while postnatal lung growth continues, the development of ARDS occurs in a different background of cellular life and death responses as compared with adults, in which lung growth has ceased. Furthermore, these studies suggest that infectious stimuli, delivery of supplemental oxygen, and application of life-sustaining mechanical ventilation affect apoptotic responses differently in children versus adults. Therefore, understanding the differences in apoptotic mechanisms in ARDS in children and adults has the potential to improve our understanding of key pathophysiologic differences in injury responses in the lungs of children and adults.

COAGULATION

The coagulation system is inextricably linked to acute inflammatory responses. Endothelial cell and platelet activation may lead to a consumptive coagulopathy in patients of all ages with sepsis or ARDS (113, 114). Reduced levels of activated protein C (APC) have been associated with increased mortality in septic adult and pediatric patients. Ware et al (69, 115) have shown that APC is reduced in adult patients with ARDS; however, a randomized controlled trial of APC in adults with ARDS failed to show an improvement in outcomes. Increased von Willebrand factor antigen and plasminogen activator inhibitor-1 in plasma of adult and pediatric patients with ARDS are associated with increased mortality and fewer ventilator-free days (113, 116–118).

Although targeting the coagulation system could have significant therapeutic benefit, there are no large human studies showing that this strategy reduces morbidity or mortality in patients with ARDS. Despite the apparent similarities between children and adults, future studies need to be carefully designed to determine the pathophysiology and therapeutic efficacy of targeting the coagulation system in children and adults with ARDS.

VENTILATOR-ASSOCIATED LUNG INJURY

The introduction of mechanical ventilation heralded the modern era of intensive care and continues to be a mainstay of life-saving therapy worldwide. However, the association between positive pressure mechanical ventilation and lung injury has fostered the concepts of volutrauma, atelectrauma, and biotrauma and led to the clinical development of "lung protective ventilation." The Acute Respiratory Distress

Syndrome Network (ARDSNet) study of adult patients with ARDS using tidal volumes (V_T) of 6 versus 12 mL/kg showed a 22% relative reduction in mortality in the low tidal volume group (119). In follow-up studies, initial plasma levels of cytokines and soluble cytokine receptors (IL-6, IL-8, IL-10, and soluble tumor necrosis factor receptors I and II [sTNFRI and sTNFRII, respectively]) in adults with ARDS were associated with adverse clinical outcomes, and reducing the distending forces in the lungs by ventilating patients with 6 versus 12 mL/kg V_T resulted in a more rapid attenuation of circulating IL-6, IL-8, and sTNFRI (120, 121). Children were excluded from the ARDSNet V_T trial, so the extent to which reducing tidal volume reduces inflammation and improves mortality in children remains uncertain.

Biotrauma was coined in order to describe the association between stretching the respiratory system (tidal volume) and inflammation (122). Cyclic mechanical stretch of lungs or even isolated alveolar epithelial cells results in the release of cytokines and inflammatory mediators (123, 124). Human data comparing pediatric with adult inflammatory responses to mechanical ventilation are limited. The increased compliance of the pediatric chest wall combined with the tendency of positive pressure ventilator breaths to distribute to the most compliant areas might be expected to result in increased VALI in pediatric patients, whereas the less compliant adult chest wall should limit the amount of volutrauma that a given inflation pressure might cause (125). Plotz et al (126) found increased TNF-α in tracheal aspirates from normal human infants subjected to mechanical ventilation. Two studies demonstrated that infant rodents have lower proinflammatory responses to mechanical ventilation when compared with adults. Copland and Post (127) showed that infant rats treated with mechanical ventilation have lower and more delayed increases of IL-1β, TNF-α, IL-6, macrophage inflammatory protein-2, and IL-8 than adult rats. Kornecki et al (128) confirmed that infant rats treated with mechanical ventilation had lower TNF-α responses as compared with adults, but they also showed that infant rats had less lung injury as measured by lower wet:dry ratios and hyaline membrane scores than adults. Although the mechanisms for these differences between infant and adult animals are uncertain, FGF-10, epidermal growth factor receptor, mitogen-activated protein kinases, and NF-κB are important intersections between lung morphogenesis and the regulation of key elements of mechanotransduction pathways (33, 109, 129–132).

The size of the endotracheal tube has been an important factor limiting the feasibility of collecting lower airway samples in infants, toddlers, and small children. Future studies may benefit from the development of less invasive methods of collecting representative lower airway samples, such as exhaled breath condensate and mini-BAL (133, 134). Future studies of ARDS in children and adults should investigate the age-dependent differences between the innate immune function of infants and adults as well as the age-dependent differences in the responses to mechanical stretch that have been demonstrated in animal models of lung injury.

INTERSECTION BETWEEN INNATE IMMUNITY AND STRETCH/SHEAR

The common role of infectious stimuli in patients with ARDS combined with the proinflammatory effects of mechanical ventilation is consistent with the "two-hit hypothesis" in which two or more factors combine to cause or worsen ARDS (8, 135–137). Experimental studies suggest that important synergistic interactions exist between activation of innate immunity pathways and mechanical ventilation (123, 138–143). These studies show increases in alveolar neutrophil recruitment, proinflammatory cytokines, and lung injury when mechanical ventilation is combined with activation of the innate immune system by bacterial products, either in the lungs or the systemic circulation. However, a recent study has indicated that synergistic increases in alveolar neutrophil recruitment and production of IL-1β occur in adult but not juvenile mice treated with the combination of inhaled LPS and mechanical ventilation (42). Although the mechanism regulating the acquisition of synergistic inflammatory and injury responses to the combination of LPS and mechanical ventilation is not yet clear, the data suggest that it is the result of coordinated changes in gene expression controlling proinflammatory, apoptotic, FGF, and TGF-β pathways.

In order to better understand the pathophysiology of ARDS in adults and children, future studies will need to investigate the interactions between mechanical stretch and infectious stimuli. In order to include the effects of postnatal lung morphogenesis on these complex biological interactions, a systems biology approach will likely be required to understand the mechanisms of lung injury and repair in mechanically ventilated children and adults with severe infections (144).

FIBROPROLIFERATIVE REPAIR

> …[R]estoration of a normal pulmonary epithelium after acute injury is associated with an absence of fibrous scarring (145).

Biological reparative processes have been separated conceptually and experimentally into the inflammatory, injury (necrotic and apoptotic), and fibroproliferative phases. Although it is difficult to simultaneously investigate inflammatory, injury, and repair mechanisms, these are functionally inseparable. The fibroproliferative phase of ARDS begins at the time of intubation and initiation of mechanical ventilation, rather than after inflammation, necrosis, and apoptosis have resolved (146). Failure to resolve the inflammatory response and dysregulation of the fibroproliferative phase may result in chronic ARDS and fibrotic lung disease, which occurs in up to 30–50% of adult patients with ARDS and is associated with a mortality of up to 80% (147–151). The reasons why fibrosing alveolitis develops in some patients whereas others with seemingly equivalent degrees of lung injury resolve the inflammation and injury without evidence of fibrosis are unknown.

Alveolar epithelial repair begins with the formation of granulation tissue characterized by mesenchymal cellular proliferation and mesenchymal cell products, angiogenesis, and deposition of collagen (types I and III) and a fibrinous,

fibronectin-rich matrix (152). Fibrosis in the lungs is histologically evident as early as 5 days after clinical presentation, and type III procollagen is found within hours after intubation (153). The amount of type III procollagen in the lungs of adult patients with ARDS has been associated with increased mortality (149).

There is strong evidence supporting the importance of IL-1β in the early inflammatory responses as well as fibroproliferative processes in the lungs of adult patients with ARDS (56, 88, 154). Pulmonary edema fluid from patients with ARDS has been shown to accelerate alveolar epithelial cell repair in an in vitro model of rat alveolar epithelial cell injury (155). IL-1β has important mitogenic effects on fibroblasts and alveolar epithelial cells, and blockade of the IL-1 receptor attenuates the mitogenic effects of edema fluid from adult patients with ARDS (155–158).

The role of TGF-β in lung injury and repair is also well established (39, 159). TGF-β signaling is important in the early inflammatory phase of ARDS, and it is critical to the resolution of inflammation in the lungs (159, 160). However, excessive or prolonged TGF-β signaling causes fibrosis in the lungs of rodents, and inhibition of the TGF-β pathway prevents progression of fibrosis (161–165).

Glucocorticoids are important modulators of inflammation and fibrosis, although studies of high-dose glucocorticoid therapy for early and severe ARDS have not shown a consistent therapeutic benefit (166–168). Even though two randomized placebo-controlled studies suggest that prolonged low-to-moderate dose corticosteroids might reduce mortality in adult patients with ARDS, a controlled randomized trial of steroids in persistent ARDS did not find an overall benefit (169–171). Several meta-analyses have been published but have produced conflicting results (172–175).

Translational studies are needed to determine the rate and timing of repair and fibrosis in children who survive lung injury. The role of IL-1β and TGF-β in lung repair and fibrosis in children remains unknown. Mechanisms that regulate the resolution of inflammation and repair in ARDS patients remain poorly understood and are an area ripe for collaborative translational studies between pediatric and adult investigators.

LONG-TERM OUTCOMES

There is a growing body of information about health-related quality of life (HRQOL) of premature infant and adult survivors of lung injury (174, 175). Unfortunately, very little is known about the HRQOL of children who survive ARDS, but there is an ongoing multicenter study of the effect of sedation on the outcome of children treated with mechanical ventilation for respiratory failure (The Randomized Evaluation of Sedation Titration for Respiratory Failure [RESTORE]) (176, 177). A follow-up study of the RESTORE trial is being conducted by the Clinical Research Investigation and Systems Modeling of Acute Illness Center that will provide information about the HRQOL of children mechanically ventilated for respiratory failure.

If the prevalence and mortality of ARDS in children and adults continues to decrease, future studies will need to measure outcomes other than mortality. Improvements in the HRQOL of children and young adult ARDS patients are especially relevant given the number of potential years that they may survive and that improving HRQOL may represent the most important goal of medicine. Future studies are needed to determine the long-term effects on HRQOL of surviving ARDS during childhood. Are there times during childhood that are increased/decreased risk for worse HRQOL outcomes?

THE CHALLENGE OF PEDIATRIC ARDS RESEARCH

The American Thoracic Society and the Division of Lung Diseases of the National Heart, Lung, and Blood Institute have emphasized the need for research in pediatric pulmonary diseases (178, 179). The Pediatric Acute Lung Injury and Sepsis Investigators Network and the Collaborative Pediatric Critical Care Research Network have the ability to conduct studies of ARDS in children. United States 2010 census data show that there are approximately 234 million adults (≥ 18 yr old) and 74 million children (< 18 yr old) living in the United States. There are approximately 10-fold more adult ICU beds than PICU beds in the United States. The Pediatric Acute Lung Injury Ventilation (PALIVE) study assessed the feasibility of conducting multicenter clinical trials for children with lung injury in North America and Europe and optimistically concluded that it would take "over 4 years and at least 60 PICUs to enroll 800 children with ALI/ARDS in an international clinical trial aiming for a reduction in mortality as primary endpoint (22)."

The ethical issue of consent by proxy is a major challenge for clinical studies involving children. Research on human subjects may be conducted with consent by proxy, but as the potential for harm increases and therapeutic benefit declines, the "reasonableness" of the research decreases. Once conclusive studies in adults have been completed, equipoise is lost and it is often difficult to propose an unbiased, randomized, and blinded study on a younger population. Although the information is important, the interventions and treatments derived from adult medicine often creep into pediatric practice without evidence of safety or efficacy. This leads to a new standard of care for children, which is not necessarily supported by appropriate data.

Consent by proxy complicates research further when there is no potential therapeutic benefit and only a potential for harm, such as collecting BAL fluid from intubated pediatric patients with sepsis who do not have clinical evidence of pneumonia or lung injury. Performance of BAL has risk, and the therapeutic benefit is limited. The development of less invasive outcome measures is necessary to decrease the risk to patients enrolled in studies, thereby increasing the feasibility of future investigations (180, 181).

Technical considerations also make research on children difficult. For example, the technical feasibility of BAL is limited by endotracheal tube size, airway diameter, and available bronchoscope sizes. Once technologic advancements have provided the means to do procedures or obtain samples from children and infants, the question will be whether the existing

information from adults will make pediatricians unwilling to do the relevant clinical studies.

Although there are significant obstacles to performing research on children with ARDS, investigating the mechanisms of lung injury in children and identifying the mechanistic differences between children and adults are important (178, 179, 182). Although epidemiologic data suggest that the prevalence and mortality from ARDS are reduced in children as compared with adults, the frequency of pulmonary fibrosis in children who survive ARDS is not known, and the pulmonary function of child survivors is not known (8, 14). Adult survivors of ARDS have neurocognitive, emotional, and quality of life sequelae, and if these sequelae occur in children, there are likely significant lifelong personal and societal costs (183, 184). In addition, the demands for adult and pediatric intensive care resources are increasing in the United States (185–187). A recent study suggests that there is a significant additive burden on the current critical care resources by special needs children who are at increased risk for respiratory failure (188). Therefore, identification of mechanisms by which children are less susceptible and have a lower mortality from ARDS as compared with adults should have significant preventive and therapeutic benefits for pediatric and adult patients in whom ARDS develops.

Future studies of age-dependent differences in ARDS are likely to show acquisition of mechanisms that worsen lung injury as well as loss of protective mechanisms in adults as compared with children. Improved understanding of age-dependent differences in alveolar fluid clearance, innate immune and inflammatory responses to infections, regulation of apoptosis, as well as responses to mechanical ventilation combined with infectious stimuli are likely to result in therapeutic advances for the care of all patients with ARDS.

SUMMARY

Knowledge of the transcriptional control of lung morphogenesis, the activation and regulation of innate immunity, and mechanisms of lung injury and repair has increased dramatically. However, the "trickle-down" of adult data resulting in loss of equipoise for pediatric studies remains a significant barrier to conducting appropriate pediatric investigations of ARDS. There is overlap between regulation of lung morphogenesis, activation of innate immunity, and lung repair. Because lung growth and development occur throughout childhood, it is reasonable to predict that the response to and outcome from a given injury will differ for infants, toddlers, older children, and young adults. The reduced mortality seen in children with lung injury as compared with adults may be due to differences in the genetic and environmental mechanisms that regulate continued growth and development of the lungs. In order to advance the understanding and the quality of care provided to all patients with ARDS, future studies should investigate pathophysiologic mechanisms of alveolar fluid clearance, apoptosis, innate immunity, and early inflammatory responses to mechanical ventilation, as well as repair mechanisms and long-term outcomes of children and adults with ARDS. The low prevalence and mortality of ARDS in children as compared with adults and the lower population of children as compared with adults will require well-organized multi-institutional and possibly international studies (22). Multi-institutional translational studies involving laboratory-based investigators and clinical researchers are needed in order to understand the complex biological interactions between lung morphogenesis, inflammation, apoptosis, alveolar fluid clearance, and repair mechanisms. Future studies will likely require collaborations between pediatric and adult investigators to design studies that include patients across all age categories. Our greatest hope is to be able to identify characteristics that predict better responses to lung injury and develop therapies that could be individualized to provide better outcomes for patients with high morbidity and mortality from lung injury.

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