Management of acute lung injury and acute respiratory distress syndrome in children

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**Background:** Acute lung injury (ALI) and its more severe form, acute respiratory distress syndrome (ARDS), are devastating disorders of overwhelming pulmonary inflammation and hypoxemia, resulting in high morbidity and mortality.

**Aim:** To provide the clinician with a summary of the literature on the epidemiology, diagnosis, and an evidence-base for management of ALI/ARDS in children.

**Data Selection:** PubMed search for clinical trials, selected literature review of other relevant studies on epidemiology and diagnosis.

**Data Synthesis and Recommendations:** Lower mortality combined with a relatively lower frequency of ALI/ARDS in children makes performance of clinical trials challenging. Based on expert opinion, the following are recommended: 1) avoid tidal volumes <10 ml/kg body weight; 2) keep plateau pressure ≤30 cm H2O, arterial pH at 7.30 to 7.45, and PaO2 to 80 torr (8 to 10.7 kPa) (SpO2 ≥90%); 3) provide sedation, analgesia, and stress ulcer prophylaxis; and 4) use a 10 g/dL hemoglobin threshold for packed red blood cell transfusion in unstable patients (shock or profound hypoxia). Evidence supports dropping the hemoglobin transfusion threshold to 7 g/dL once profound hypoxia and shock have resolved. Promising therapies for pediatric ALI/ARDS based on pediatric studies include endotracheal surfactant, high-frequency oscillatory ventilation, noninvasive ventilation, and use of extracorporeal membrane oxygenation as a rescue therapy. Promising therapies based on adult trials include use of corticosteroids for lung inflammation and fibrosis, use of 4 to 6 ml/kg tidal volumes and restrictive fluid management. Prone positioning, bronchodilators, inhaled nitric oxide, tight glucose control, and high-flow nasal cannula (HFNC) oxygen are therapies that require further study before they can be recommended for children with ALI/ARDS. (Crit Care Med 2009; 37:2448–2454)

**Key Words:** acute lung injury; acute respiratory distress syndrome; hypoxia; diagnosis; prognosis; management; hypoxia; infants; children; adolescents

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cute lung injury (ALI) and its more severe form, acute respiratory distress syndrome (ARDS), are devastating disorders of overwhelming pulmonary inflammation leading to hypoxemia and respiratory failure (1). The American European Consensus Conference (AECC) ALI and ARDS criteria are used most commonly to diagnose ALI and ARDS in adults and children, utilizing four clinical parameters: a) acute onset; b) severe arterial hypoxemia resistant to oxygen therapy alone (PaO2/FIO2 ratio ≤200 torr (≤26.6 kPa) for ARDS and PaO2/FIO2 ratio ≤300 torr (≤40 kPa) for ALI); c) diffuse pulmonary inflammation (bilateral infiltrates on chest radiograph); and d) no evidence of left atrial hypertension (2). ALI/ARDS are responsible for high morbidity, mortality, and financial burden in children (3–5). There are detailed overviews of the diagnosis, epidemiology, pathogenesis, and treatment of adults with ALI/ARDS (1, 3, 6, 7). This concise review is designed to focus on children, highlighting differences between children and adults in the epidemiology, diagnosis, prognosis, and evidence-base for management of pediatric ALI/ARDS.

**Epidemiology of Acute Lung Injury and ARDS in Children**

The risk factors and pathophysiology of ALI/ARDS are similar in adults and children (8). The most common trigger is infection, most commonly in the lower respiratory tract (Table 1). ALI/ARDS occurs with less frequency in children than in adults. In King County Washington, the frequency of ALI increased with age from 16 per 100,000 person-years for those 15 through 19 yrs of age (morbidity 24%) to 10–16 days) and relatively high mortality (10%–40% overall) (Table 1). The Murray Lung Injury Score is another clinical definition of ARDS that incorporates lung compliance and level of positive end-expiratory pressure on the
ventilator along with PaO2/FiO2 ratio and degree of alveolar consolidation (13). It has been used in a single center study of infants with viral lower respiratory infection (14), successfully identifying those with higher morbidity and mortality. This score may hold promise for distinguishing between ALI and bronchiolitis in young children.

### Predictors of Mortality in Pediatric ALI/ARDS

In contrast to adults, severity of hypoxia at presentation is a fairly strong predictor of mortality in children with ALI/ARDS. As shown in Table 1, PaO2/FiO2 ratio and/or oxygenation index ((\(\text{Mean Airway Pressure} \times \text{FiO}_2)/\text{PaO}_2\)) consistently predicted mortality across five studies of the epidemiology of pediatric ALI/ARDS. In a recent randomized trial of endotracheal Calfactant (calf-lung surfactant high in surfactant protein B) for pediatric ALI, severity of hypoxia was measured by the oxygenation index ((\(\text{Mean Airway Pressure} \times \text{FiO}_2)/\text{PaO}_2\)). Average mortality in children with an oxygenation index ≥13 at study entry was 36% vs. 20% in those with an oxygenation index ≤12. Multiple organ failure (Table 1) is also a consistent mortality predictor in children with ALI/ARDS.

### Clinically Important Outcomes in Pediatric ALI/ARDS Trials

Mortality in the selected populations of children with ALI/ARDS enrolled in recent clinical trials was reported as 8% (15) and 27.5% (16). The study with higher mortality included children with ALI who had undergone a bone marrow transplant. If bone marrow transplant patients are excluded, mortality in children with ALI eligible for a clinical trial is estimated at 10% to 15%. Given this low mortality rate, it would require >2000 children with ALI per study arm to detect a moderate (25%) decrease in mortality (\(\alpha = 0.05, \beta = 0.80\)). Many more patients would be needed to detect clinically important but smaller decreases in mortality. This is not feasible given the lower occurrence of ALI in children.

Decreased duration of mechanical ventilation is an accepted measure of improved lung function resulting from decreased lung inflammation, even if overall mortality is only minimally altered by an intervention. Ventilator-free days (VFDs) is a composite rank-scored end point that incorporates duration of mechanical ventilation in survivors with mortality (17), giving mortality the highest rank. VFDs was the primary outcome used in the last two ALI/ARDS trials performed by the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network (15, 16), although one trial actually showed a mortality difference and not a difference in VFDs (16). Adult survivors of ALI/ARDS have reported decreased muscle mass, chronic hypoxia, weakness, decreased quality of life, and cognitive deficits, including marked impairment in executive function (18–21). Data on long-term outcomes in pediatric ALI/ARDS are lacking.

### Management of Pediatric ALI and ARDS

A search of PubMed for “acute lung injury” or “acute respiratory distress syndrome” or ARDS, limited to child (ages = 0–18 yrs) and human, using the evidence-base recommended search strategy for treatment articles (22) yielded 742 citations (searched 1.13.09). In addition, a search of the reference lists of published studies and solicitation of input from experts in the area was performed. The following sections review the evidence supporting management recommendations for children (ages = 0–18 yrs, excluding perinatal respiratory distress syndrome in neonates) with ALI/ARDS (Table 2).

Untreated infection, necrosis of tissue, pancreatitis, and other persistent triggers of the inflammatory cascade will lead to unrelenting escalation of ARDS (1). Identification of the ARDS trigger source and achievement of source control are essential to optimize clinical outcomes. Because sepsis is commonly the trigger for ALI (Table 1), early antibiotic therapy is recommended in those suspected of being infected (23).

Therapies for ALI/ARDS are targeted at decreasing mortality and morbidity, hastening recovery, and optimizing long-term cognitive and respiratory function. It is important to minimize profound hypoxia that leads to cell death and is damaging to the developing brain, and to minimize secondary damage to the injured lung and other organ systems that could prolong recovery (1, 3, 6, 7).

### Respiratory Support in Children With ALI and ARDS

The National Institutes of Health ARDS Clinical Trials Network (ARDSNet) published ventilator management protocol for adults (http://www.ardsnet.org/) uses a PaO2 target of 55 to 80 torr (7.3 to 10.7 kPa) (\(\text{SpO}_2\) target 88%–95%). The effect of tolerating lower levels of oxygenation for prolonged periods on the developing brain is unknown; long-term follow-up studies in
pediatric ALI/ARDS that evaluate neurologic function have not been performed. Maintenance of a PaO2 of 60 to 80 torr (—kPa) (or SpO2 ≥90%) is usually considered safe in children with ALI/ARDS; however, there are no studies supporting the safety of this therapeutic target. If achievement of a normal pH and normal PaCO2 requires respiratory support strategies that are potentially damaging to the lung, lower pH and higher PaCO2 levels should be tolerated (24). It is believed that very high PaCO2 levels are not damaging to the brain, but rigorous long-term outcome studies in children with ALI/ARDS have not been performed. Optimally, the target arterial pH levels in children with ALI/ARDS is the same as in adults (pH 7.30 to 7.45) (1, 25).

Although some children survive ALI/ARDS requiring only supplemental FiO2, most patients require assisted ventilatory support (26). Infants and small children are at a disadvantage compared with larger children and adults due to smaller airways with increased airway resistance, less rigid chest walls, and lower functional residual capacity, all which lead to a higher risk of respiratory failure and more rapid development of sustained hypoxia. A meta-analysis of the literature of noninvasive positive-pressure ventilation use in adults with ARDS concluded that there is no proven effect on mortality or need for intubation, although population heterogeneity limited conclusions (27). A randomized trial of use of noninvasive positive-pressure ventilation to prevent reintubation after failed extubation in a mixed population of critically ill adults concluded that noninvasive positive-pressure ventilation did not reduce the risk of reintubation or reduce mortality (28). In children, a Cochrane Collaboration review concluded that there is a lack of well-designed, controlled experiments of noninvasive positive-pressure ventilation in children with acute hypoxic respiratory failure (29). Only one small before-after study in bronchiolitis (30) and a very small randomized trial in acute hypoxic respiratory failure (31) have been published.

Heated high flow nasal cannula (HFNC) FiO2 in infants and children with ALI/ARDS has been used increasingly in neonatal and pediatric intensive care units in which continuous positive airway pressure (CPAP) may have been instituted. Three neonatal studies reported delivery of unpredictable levels of CPAP with HFNC (32–34). A randomized trial in neonates ≤1250 g showed that CPAP delivered by HFNC failed to maintain extubation status compared with conventional CPAP (35). The HFNC humidification levels can also promote bacterial overgrowth and require adherence to infection control protocols (36).

There are no clear guidelines for when endotracheal intubation and ventilatory support should be initiated in children with ALI/ARDS with the exception of loss of consciousness and inability to protect the airway. Individuals experienced in intubating pediatric airways and use of appropriate-sized equipment and endotracheal tubes are important considerations. Cuffed endotracheal tubes can be used safely in infants and young children (37), and may be optimal to ensure adequate positive end-expiratory pressure delivery in the face of low pulmonary compliance.

Although mechanical ventilatory support is lifesaving, low lung compliance and high ventilatory pressures can lead to ventilator-induced lung injury from alveolar overdistention (volutrauma), repeated alveolar collapse and reexpansion (atelectrauma), and oxygen toxicity (38). Reducing plateau pressure to ≤30 cm H2O by targeting tidal volumes to ≤6 mL/kg decreased mortality in the ARDSNet trial in adults with ARDS (25). There is much controversy over whether low tidal volumes, maintenance of plateau pressure <31 cm H2O, or both are necessary to improve outcomes in ALI/ARDS (39, 40). It has been speculated that reproduction of the pivotal ARDSNet tidal volume study would not be possible in children due to lack of clinical equipoise (41). Results of studies with historical controls suggest that use of lower tidal volumes and higher positive end-expiratory pressure levels in pediatric ALI/ARDS have become more standard over time and may explain the improvement of outcomes reported over the past two decades (41–43). One randomized trial of prone positioning in children with ALI/ARDS employed a modified ARDSNet low tidal volume ventilatory management protocol with an overall mortality rate of only 8%, the lowest reported to date (15, 44). In contrast, a recent observational study of 117 children with ALI/ARDS in Australia and New Zealand (overall mortality = 37%) showed that higher maximum and median tidal volumes were associated with reduced mortality (5).
There have been no clinical trials evaluating methods of weaning from mechanical ventilation specifically in children with ALI/ARDS. In a heterogeneous group of children with respiratory failure from pulmonary and neurologic etiologies, including ALI/ARDS, there was no difference between physician driven weaning vs. either of two different pressure support-based weaning protocols (45). Although all children did not meet the extubation criteria before randomization, the duration of time in weaning was very brief (1.6–2 days) in all three study arms. There is no evidence to support a specific mechanical ventilatory weaning method for children with ALI/ARDS (46).

Studies have reported extubation failure rates of 10% to 20%, most commonly associated with upper airway swelling, in heterogeneous populations of children with respiratory failure (46). Absence of an airleak around the endotracheal tube at 30 cm H₂O pressure, however, is not predictive of extubation failure in children (47). A recent evidence-base review concluded that there are no extubation criteria for children with ALI/ARDS that are proven more accurate than expert clinical judgment (46). The PALISI Network used three criteria: a) minimal tidal volume of 5 mL/kg exhaled measured at the endotracheal tube; b) a SpO₂ of ≥95% on positive end-expiratory pressure ≤5 cm H₂O and FiO₂ ≤50%; and c) a respiratory rate that was appropriate for age) to test a heterogeneous group of children with respiratory failure that physicians believed needed to be weaned from mechanical ventilatory support (45). Using these criteria led to an extubation failure rate of 15%. Similar outcomes were found, using a T piece trial (48). A significant proportion of children with ALI/ARDS being evaluated for weaning may actually tolerate extubation, if tested (45, 46).

B bronchodilators are used commonly in children with ALI/ARDS but there are no clinical trials in children with ALI/ARDS. Asthma is the most common comorbid condition in mechanically ventilated children (49). Bronchodilators should be considered only in children with evidence of bronchospasm.

**Therapies That Improve Oxygenation But Not Clinically Important Outcomes**

Similar to studies in adult patients (50), a recent randomized, controlled study performed by the PALISI Network in children with ALI showed no significant benefit of prone positioning (20 hrs/day for 7 days) on VFDs despite improved oxygenation (15).

Inhaled nitric oxide is a potent pulmonary vasodilator and doses as low as 1 ppm can improve oxygenation in ALI/ARDS (51). A meta-analysis of multiple studies showed that inhaled nitric oxide improved oxygenation without improving overall clinical outcomes in children and adults with ALI/ARDS (52). Aerosolized prostacyclin also improved oxygenation in 8/14 children with ALI/ARDS (53).

**Nonrespiratory Supportive Care of Critically Ill Children With ALI and ARDS**

A restrictive fluid management protocol has been proven to increase VFDs and improve oxygenation in adults with ALI/ARDS when compared with a more liberal fluid protocol (54). Use of albumin with furosemide in hypoproteinemic adult patients with ALI may also be beneficial, although effects on mortality and duration of ventilation remain to be tested (55, 56). No association has been shown between cumulative fluid balance and duration of mechanical ventilatory weaning or extubation outcomes in children, the majority of whom were managed using ventilator management protocols (57). There is likely to be a relationship between fluid overload during the acute phase of illness and clinical outcome (58), but evidence is lacking. Fluid restriction should only be implemented after children have been resuscitated adequately from septic shock (23).

A recent clinical trial by the Canadian Critical Care Trials Group and the PALISI Network showed that a hemoglobin transfusion target of 7.0 g/dL is as safe as a target of 9.5 g/dL in stable critically ill children (59). Profound hypoxia was a reason for study exclusion. Anemia is very common in critically ill children (60). Although oxygen delivery and consumption are greater in survivors than nonsurvivors in adults with ARDS (61), there is no proof that transfusing to higher-than-normal hemoglobin levels will improve regional oxygen delivery or clinical outcome (62). Transfusion of blood products is not without risk, including transfusion-related acute lung injury (63) and fluid overload. In the absence of data, it is reasonable to maintain hemoglobin concentration within the normal range for age (≥10 g/dL [6mmol/L]) in children with profound hypoxia or shock (23).

In a randomized trial in critically ill children, delivery of feeds into the small bowel instead of the stomach resulted in a greater amount of nutrition to be delivered successfully but did not decrease aspiration of gastric contents (64). There is some supportive evidence in adult patients with ARDS that Omega 3 fatty acid supplementation improves clinical outcomes (65), but there is no evidence to support use of any specific nutritional formulas or supplements in children.

Sedative use is predictive of duration of mechanical ventilatory weaning in children (45). Intravenous infusion of lorazepam must be used carefully in children due to the risk of propylene glycol toxicity (66). Propofol is contraindicated for long-term use in children for sedation in the intensive care unit due to the risk of potentially fatal propofol infusion syndrome leading to rhabdomyolysis, metabolic acidosis, and multiple organ failure (67). Although appropriate sedation and analgesia for children who are mechanically ventilated are the standard of care, there are no data supporting any specific regimens. Prolonged muscle relaxation has been associated with development of weakness and critical illness myopathy in adult patients with ALI (68); there are no pediatric studies. Use of muscle relaxants in children with ALI/ARDS should be limited. Ensuring adequate sedation and analgesia during use is essential.

Coagulopathy and mechanical ventilation are risk factors for clinically important gastrointestinal bleeding in children, common conditions in children with ALI/ARDS (69). Clinically important gastrointestinal bleeding has been associated with high morbidity and attributable cost in children (70). There are also no data on use of heparin prophylaxis to prevent deep venous thrombosis in critically ill children before puberty. It is unclear if heparin prophylaxis prevents pediatric deep venous thrombosis associated with central venous catheters. In children in or beyond puberty, recommendations for deep venous thrombosis prophylaxis in adults may be relevant.

A recent randomized, clinical trial in critically ill children (75% cardiac surgical, few patients with ALI) showed that tight glucose control was associated with a statistically significant 3% reduction in mortality, reduced risk of nosocomial infection, and shorter pediatric intensive care units of stay (71).
care unit stay but a 24% higher risk of hypoglycemia (71). This trial had no long-term neurocognitive follow-up. Tight glucose control in children with ALI/ARDS should not be implemented until further trials confirm its safety and efficacy. Prolonged duration of mechanical ventilation puts children with ALI/ARDS at risk for developing nosocomial infections, including ventilator-associated pneumonia (VAP). Selective decontamination of the digestive tract has been shown to decrease mortality in adults requiring prolonged mechanical ventilation presumably by decreasing development of VAP (72, 73). There are some reports suggesting a rationale for use of selective decontamination of the digestive tract in critically ill mechanically ventilated children (74). There is no evidence that selective decontamination of the digestive tract improves clinically important outcomes in children with ALI/ARDS.

Rescue Therapies for Children With ALI/ARDS

High-frequency oscillatory ventilation uses high-frequency very-low tidal volumes and laminar air flow to protect the lung. One crossover trial comparing rescue high-frequency oscillatory ventilation with conventional mechanical ventilation in pediatric ALI/ARDS (75) showed that high-frequency oscillatory ventilation was associated with higher mean airway pressures, improved oxygenation, and a reduced need for supplemental oxygen at 30 days. Use of high-frequency oscillatory ventilation has become ingrained in pediatric practice and is used frequently in children with ARDS (49), despite lack of evidence to support it. Extracorporeal membrane oxygenation has been used as a rescue therapy for over two decades in children with ALI/ARDS, with reported survival rates of >50% (76). An attempt at a randomized trial of extracorporeal membrane oxygenation for ARDS in children failed due to a drop in baseline mortality. This was hypothesized to be associated with increased use of lung protective ventilation strategies (77). Given the need for anti-coagulation and the increased risk of bleeding in children who receive extracorporeal membrane oxygenation, its use should be limited to those patients in whom conventional therapies have failed.

Potentially Promising Therapies for Children With ALI/ARDS

Trials of endotracheal surfactant in adult patients with ALI/ARDS have been negative (78), with speculation that efficacy may be higher in patients with direct lung injury (79). A PALISI Network randomized trial of Calfactant in children with ALI/ARDS showed improved oxygenation and decreased mortality but no improvements in the course of respiratory failure (ventilator days, hospital, or intensive care unit length of stay) (16). A meta-analysis of six trials of surfactant therapy in children with acute respiratory failure including bronchiolitis and ALI showed decreased mortality, increased VFDs, and decreased duration of mechanical ventilation (80). Delivery of surfactant to children with ALI/ARDS is not without risks, including hypotension, hypoxia, and barotrauma (16), and must be done by skilled surfactant administrators. Surfactant is expensive but may be cost effective in ALI treatment (81). There are two ongoing clinical trials across the PALISI Network evaluating the effect of endotracheal surfactant (Calfactant and Lucinactant) in children with ALI.

In adults with ARDS, a recent meta-analysis of corticosteroids in ALI/ARDS (82) led to the following conclusions: a) preventive steroids (four trials) might increase the risk of adult patients developing ARDS and may increase mortality in those who develop ARDS; and b) steroids in patients with ARDS may reduce mortality and was associated with an increase in VFDs without increasing the risk of infection. There have been no studies of corticosteroids for treatment of ALI/ARDS in children.

Specific Recommendations for Hematopoietic Stem Cell Transplant (HSCT) Patients With ALI/ARDS

Adults and children who develop ALI/ARDS and respiratory failure after HSCT have a mortality rate of ≥75% (83, 84). In a case-series of ten very immunocompromised children with ARDS (six with HSCT), continuous veno-venous hemofiltration instituted at the time of intubation with tight control of fluid balance resulted in eight of ten survivors (85). Given the high mortality rate in this group, the benefit of bronchoalveolar lavage and sometimes also a lung biopsy to identify undiagnosed treatable conditions is often considered to outweigh the risks. Histopathologic analysis of open-lung biopsy determined frequently the cause of the underlying condition and led to management changes, but it failed to improve overall patient outcomes (86). In patients after HSCT, the term “Idiopathic Pneumonia Syndrome” is used for those patients who meet the AECC criteria with no identified underlying cause. Etanercept, a tumor necrosis factor-α inhibitor, has been studied in combination with corticosteroids in 15 patients (half were children), half of whom required mechanical ventilation at the onset of therapy. Ten of 15 patients responded to etanercept and were able to be weaned off oxygen support. Definitive clinical trials are desperately needed to identify therapies and supportive management strategies to decrease mortality in children developing ALI/ARDS after HSCT.

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