ARDS and Ventilator-Associated Events

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LEARNING OBJECTIVES

1. Using the definitions for acute respiratory distress syndrome (ARDS), classify a patient's pulmonary morbidity.
2. Analyze available data to design an appropriate pharmacotherapy plan, including exogenous pulmonary surfactant or the use of corticosteroids, for pediatric patients with ARDS.
3. Analyze the current definition of ventilator-associated pneumonia to determine the need for surveillance, and measure quality of care in pediatric ICU patients.
4. Evaluate deficiencies in current surveillance definitions and justify expanded surveillance in pediatric units to include other ventilator-associated conditions.
5. For ventilator-associated infections in the pediatric ICU, design antimicrobial therapy plan that uses the narrowest-spectrum antibacterial agents for a duration that minimizes antibacterial exposure.
6. Justify a prevention strategy for ventilator-associated events in the pediatric ICU including, but not limited to, implementation of a ventilator-associated pneumonia bundle.

ABBREVIATIONS IN THIS CHAPTER

ALI	Acute lung injury
ARDS	Acute respiratory distress syndrome
IVAC	Infection-related ventilator-associated condition
MDRGN	Multidrug-resistant gram-negative organisms
OI	Oxygenation index
PALICC	Pediatric Acute Lung Injury Consensus Conference
PARDS	Pediatric acute respiratory distress syndrome
PF ratio	Ratio of Pao_2 to Fio_2
PVAP	Possible ventilator-associated pneumonia
SF ratio	Ratio of saturation of arterial oxygen to fraction of inspired oxygen
SRMD	Stress-related mucosal disease
VAC	Ventilator-associated condition
VAE	Ventilator-associated event
VAP	Ventilator-associated pneumonia

MECHANICAL VENTILATION

Invasive positive pressure ventilation is used in the treatment of critically ill pediatric patients for a variety of indications that may arise from a pulmonary, cardiac, neurologic, or neuromuscular condition. Respiratory failure, either from inadequate oxygenation or inadequate ventilation, may be caused by pulmonary or extrapulmonary conditions. Patients with significant cardiovascular dysfunction may benefit from mechanical ventilation, which may decrease both the work of breathing and the myocardial oxygen demand. Neurologic and neuromuscular disorders can result in loss of ventilatory drive, ventilatory muscle weakness, loss of protective reflexes, and need for induced hyperventilation, all of which may be supported by positive pressure ventilation (Venkataraman 2011).

Treatment of the Mechanically Ventilated Patient

One pharmacist role in the treatment of mechanically ventilated patients is the management of pharmacotherapy used to facilitate patient-ventilator synchrony and optimize patient comfort. Pediatric patients requiring mechanical ventilation generally need some degree of pain and sedation management. Agents such as benzodiazepines, opioids, and dexmedetomidine may facilitate comfort, but their use must be balanced with minimization of the associated adverse events. This is usually achieved by identifying patient-specific goals

VAT	Ventilator-associated tracheobronchitis
VTE	Venous thromboembolism

Table of other common abbreviations.

and using a standardized approach to drug therapy that is based on the predefined goal. Although the only randomized controlled trial of protocolized sedation in mechanically ventilated, critical care pediatric patients found no difference in duration of mechanical ventilation, several secondary outcomes were improved with this approach, including fewer episodes of skin breakdown, fewer days of opioid exposure, fewer sedative class exposures, and more study days awake and calm (Curley 2015). Although no guidelines exist for treating the pain, agitation, and delirium of pediatric patients, the tenets of the adult guidelines can be generally applied to the care of critically ill pediatric patients to optimize therapy with these agents (Barr 2013).

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- Basic ventilator terminology, including settings and monitoring parameters
- Concepts and management of pain, agitation, and delirium in the critically ill patient
- Knowledge of the pharmacology of pulmonary surfactants and corticosteroids
- Knowledge of the organisms commonly associated with health care–associated pneumonia and ventilator-associated pneumonia and appropriate empiric therapy
- Knowledge of antibiotic therapy including spectrum of activity and dose-optimization strategies
- Knowledge of prophylactic strategies for both stress-related mucosal bleeding and venous thromboembolism

Table of common pediatric laboratory reference values.

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- CDC. National Healthcare Safety Network [homepage on the Internet].
- Institute for Healthcare Improvement. How-to Guide: Prevent Ventilator-Associated Pneumonia [homepage on the Internet].

In addition to facilitating patient comfort and the pharmacologic management of the primary disorder resulting in the need for positive pressure ventilation, pharmacists have a role in preventing health care–associated conditions. This includes infection prevention as well as prevention of stress-related mucosal disease (SRMD) and venous thromboembolism (VTE).

Stress-related mucosal disease may develop in acutely ill patients secondary to an inflammatory, erosive insult to the upper GI tract. Of most concern is the development of overt, clinically significant GI bleeding, which may worsen patient outcomes. Box 1-1 lists risk factors for SRMD identified in adult and pediatric hospitalized patients.

Box 1-1. Risk Factors Associated with Upper GI bleeding

Independent Risk Factors

Pediatric:

- Coagulopathy[a]
- PRISM score ≥ 10
- Respiratory failure[b]
  - In mechanically ventilated pediatric patients:
    - High pressure ventilation (positive inspiratory pressure ≥ 25 cm H_2O)
    - Organ failure

Adult:

- Coagulopathy
- Respiratory failure
- Shock
- Multiple trauma

Factors Contributing to Cumulative Risk[c]

Acute hepatic failure
Acute renal failure
Anticoagulation
Burn injury (> 35% total body surface area)
High-dose corticosteroids (> 250 mg/day of hydrocortisone)
History of GI bleed
Hypotension
Low intrinsic gastric pH
Major surgery (> 4 hr)
Sepsis
Severe head or spinal cord injury

[a]Studies have used several definitions of coagulopathy, including prolonged PTT, prolonged PT, INR > 1.5, and Plt < 100,000/mm^3.

[b]Need for mechanical ventilation.

[c]Identified in adult and/or pediatric studies.

Information from: ASHP Commission on Therapeutics. ASHP therapeutic guidelines on stress ulcer prophylaxis. Am J Health Syst Pharm 1999;56:347-79; Chaibou M, Tucci M, Duga MA, et al. Clinically significant upper gastrointestinal bleeding acquired in pediatric ICU: a prospective study. Pediatrics 1998;102:933-8; and Reveiz L, Guerrero-Lozano R, Camacho A, et al. Stress-ulcers, gastritis, and gastrointestinal bleeding prophylaxis in critically ill pediatric patients: a systematic review. Pediatr Crit Care Med 2010;11:124-32.

Guidelines for which pediatric ICU (PICU) patients should receive pharmacologic prophylaxis are unavailable, and adult guidelines were last published in 1999, although an update is expected in the near future. Given the available data and the adult guidelines, it is reasonable to recommend pharmacologic prophylaxis to prevent upper GI bleeding from SRMD in PICU patients who have one independent risk factor or at least two cumulative risk factors (ASHP 1999). Prophylactic strategies, including histamine-2 receptor antagonists and proton pump inhibitors, have proved useful in maintaining a gastric pH greater than 4 when compared with placebo or no treatment. However, no effect on mortality or decreased risk of clinically significant bleeding was seen in pediatric studies (Reveiz 2010). Therefore, it is important to balance the benefits of SRMD prophylaxis with the potential risks (e.g., increased risk of infection, decreased bone mineral density).

The incidence of VTE, including deep venous thrombosis and pulmonary embolism, has increased in hospitalized pediatric patients (Sharathkumar 2012). This increase is postulated to be caused by enhanced surveillance, as well as advanced management of complex medical conditions leading to improved mortality. There appears to be a bimodal distribution of pediatric age groups (i.e., infants and adolescents) at higher risk of developing VTE. Other risk factors identified in a hospitalized pediatric cohort include higher BMI, direct admission to the ICU, bacteremia, central venous access, immobilization, oral contraceptive exposure, length of stay longer than 7 days, and mechanical ventilation. According to a multiple regression analysis, the factors that continued to be significantly associated with risk were direct admission to the ICU, bacteremia, central venous access, immobilization, oral contraceptive exposure, and length of stay longer than 7 days (Sharathkumar 2012).

In adult inpatients, use of pharmacologic thromboprophylaxis with the low-molecular-weight heparins and unfractionated heparin minimizes the risk of VTE and its associated poor outcomes, and thromboprophylaxis is routinely used. However, the same supporting data do not exist for pediatric patients. Although broad-scale, systematic investigation of these prophylactic strategies is needed, it is clinically appropriate to implement a risk assessment to identify high-risk patients (Reiter 2012; Sharathkumar 2012). In most pediatric patients identified as high risk, mechanical prophylaxis of sequential compression devices can be implemented safely. Pharmacologic prophylactic strategies can be implemented according to institution-specific protocols for high-risk patients with favorable risk-benefit for prophylactic anticoagulation.

As noted previously, the need for mechanical ventilation may arise from either pulmonary or extrapulmonary conditions. Pulmonary morbidities in critically ill pediatric patients may result in the need for invasive mechanical ventilation or may be caused by this invasive supportive therapy. Two such conditions are pediatric acute respiratory distress syndrome (PARDS) and ventilator-associated pneumonia (VAP).

ACUTE LUNG INJURY AND PARDS

Pathophysiology

Acute respiratory distress syndrome (ARDS) is the clinical syndrome that occurs secondary to the development of noncardiogenic pulmonary edema. Pulmonary edema develops secondary to breakdown of the permeability barrier in the alveoli, in the setting of inflammatory and coagulation dysregulation. When functioning properly, the permeability barrier maintains separation between the fluid (capillaries) and the air (alveoli) compartments within the lung and allows for appropriate gas exchange. With dysfunction, patients develop the clinical symptoms of ARDS including hypoxemia, changes on chest radiography, increase in physiologic dead space, and decrease in functional residual capacity and lung compliance. This pathophysiology usually results in the need for respiratory support to improve both gas exchange and work of breathing (Sapura 2015).

Two phases of the syndrome have been described, given the pathologic findings during clinical progression and the changes in pulmonary pathophysiology. The exudative phase, or early phase, of the ARDS is a state of overwhelming expression of proinflammatory cytokines, neutrophil activation, and coagulation dysregulation. The irreversible fibroproliferative phase, or late phase, occurs around day 7 of illness in those who do not clinically improve. This phase is characterized by fibrosis and loss of alveolar structure (Deal 2008).

Prevalence in Pediatric Patients

Although less prevalent than in adults, ARDS and its associated morbidity and mortality are regularly encountered in the pediatric critical care population. The reported incidence of ARDS in pediatric patients is 2–12.8 cases per 100,000 person-years compared with the 17.9–81 cases per 100,000 person-years reported in adults. From 21% to 74% of pediatric patients are reported to have preexisting illness (commonly immunodeficiency) before developing ARDS. Mortality rates appears to be lower in pediatric patients (18%–27%), although some studies report mortality closer to the adult rate (27%–45%). Pediatric patient factors associated with an increased risk of mortality from ARDS include immunodeficiency and African American ethnicity. Although the risk of developing ARDS appears to be higher in boys, the mortality risk is no higher than in girls (Khemani 2015). The patient's age may alter long-term morbidity because of the potential impact of ARDS on lung development in children (Sapura 2015).

Underlying causes for developing this syndrome may arise from either direct injury to the alveolar epithelium or injury to the capillary endothelium from conditions such as sepsis, pneumonia, trauma, and submersion injury. In adult patients with ARDS, the most commonly associated clinical condition is sepsis; in pediatric patients it is respiratory infection. Respiratory viruses are much more likely to result in ARDS in pediatric patients than in adult; ARDS arising from this cause may have a histologic

pattern of injury different from other causes. Recent evidence suggests that the associated clinical cause alters outcomes (Sapura 2015). There are few controlled trials in patients with ARDS, and these are generally underpowered to be conclusive; however, epidemiologic studies have shown improvement in ARDS mortality rates (Bembea 2015; Randolph 2009).

Definition and Classification of PARDS

Initially reported in 1967, characterization of the "adult" respiratory distress syndrome and subsequently renamed ARDS has undergone several revisions. The American-European Consensus Conference (AECC) published the first consensus definition in 1994; it delineated requirements for defining hypoxemia by the ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (Pao_2/Fio_2, or PF ratio), the onset of hypoxemia, and chest radiographic findings. This definition also established the umbrella category of acute lung injury (ALI). Establishing a consensus definition was highly useful in advancing ARDS clinical care and research; however, there were areas for optimization within this definition.

The subsequent definition, called the *Berlin definition*, tried to address these areas. In 2012, the European Society of Intensive Care Medicine convened a task force to develop a subsequent consensus definition. The Berlin definition expanded the ARDS diagnostic criteria by clarifying the time interval for the onset of hypoxemia and minimizing the effect of other ventilator parameters on the PF ratio by including positive end-expiratory pressure (PEEP) or continuous positive airway pressure in the definition. Impaired oxygenation was further delineated as mild, moderate, or severe. The term *ALI* was removed from the definition and replaced by the mild category. In addition, in the absence of common risk factors for ARDS, the Berlin definition excludes hydrostatic pulmonary edema from causes such as heart failure and fluid management.

Risk factors for ARDS include direct lung injury such as pneumonia, aspiration, pulmonary contusions, inhalation injury, pulmonary vasculitis, and submersion injury, as well as indirect lung injury such as sepsis, major trauma, pancreatitis, transfusion-related, severe burn injury, and drug overdose (ESICM 2012; Ferguson 2012). Table 1-1 details the AECC and Berlin definitions of ARDS.

Although using the Berlin definition may be reasonable, given the lack of pediatric-specific definitions, it may fail to consider the pulmonary changes that occur throughout development or how management strategies may be altered (Sapura 2015; Yehya 2015; Cheifetz 2011). Because of the potential issues with the adult-focused definition, the Pediatric Acute Lung Injury Consensus Conference (PALICC) sought to develop a pediatric-specific definition for PARDS (Figure 1-1). This definition incorporates measures of hypoxemia including oxygenation index (OI), oxygenation saturation index (OSI), and ratio of saturation of arterial oxygen to fraction of inspired oxygen (SF ratio) as markers of oxygenation impairment.

Table 1-1. ARDS Definition Criteria

Parameter	AECC 1994	Berlin 2012
Timing	Acute	Onset within 1 wk of: • Known clinical insult OR • New/worsening respiratory symptoms
Chest imaging	Bilateral infiltrates seen on frontal view	Bilateral opacities that are not fully explained by effusions, lobar/lung collapse, or nodules
Pulmonary artery wedge pressure	≤ 18 mm Hg If not measured, no clinical evidence of left atrial hypertension	Removed from definition
Presence of risk factors	Not addressed	Use to determine need to rule out hydrostatic edema
Origin of edema	Not addressed	In the absence of risk factors, hydrostatic edema should be excluded by objective assessment (e.g., echocardiography)
ALI category	PF ratio < 300	ALI term removed
Oxygenation	PF ratio ≤ 200	Mild: PF ratio 201–300 AND PEEP or CPAP ≥ 5 cm H_2O Moderate: PF ratio 101–200 AND PEEP ≥ 5 cm H_2O Severe: PF ratio ≤ 100 AND PEEP ≥ 5 cm H_2O

ALI = acute lung injury; ARDS = acute respiratory distress syndrome; CPAP = continuous positive airway pressure; PEEP = positive end-expiratory pressure; PF ratio = Pao_2/Fio_2.

Information from Ferguson ND, Fan E, Camporota L, et al. The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. Intensive Care Med 2012;38:1573-82; and ESICM. ARDS Definition Task Force. Acute respiratory distress syndrome: the Berlin definition. JAMA 2012;307:2526-33.

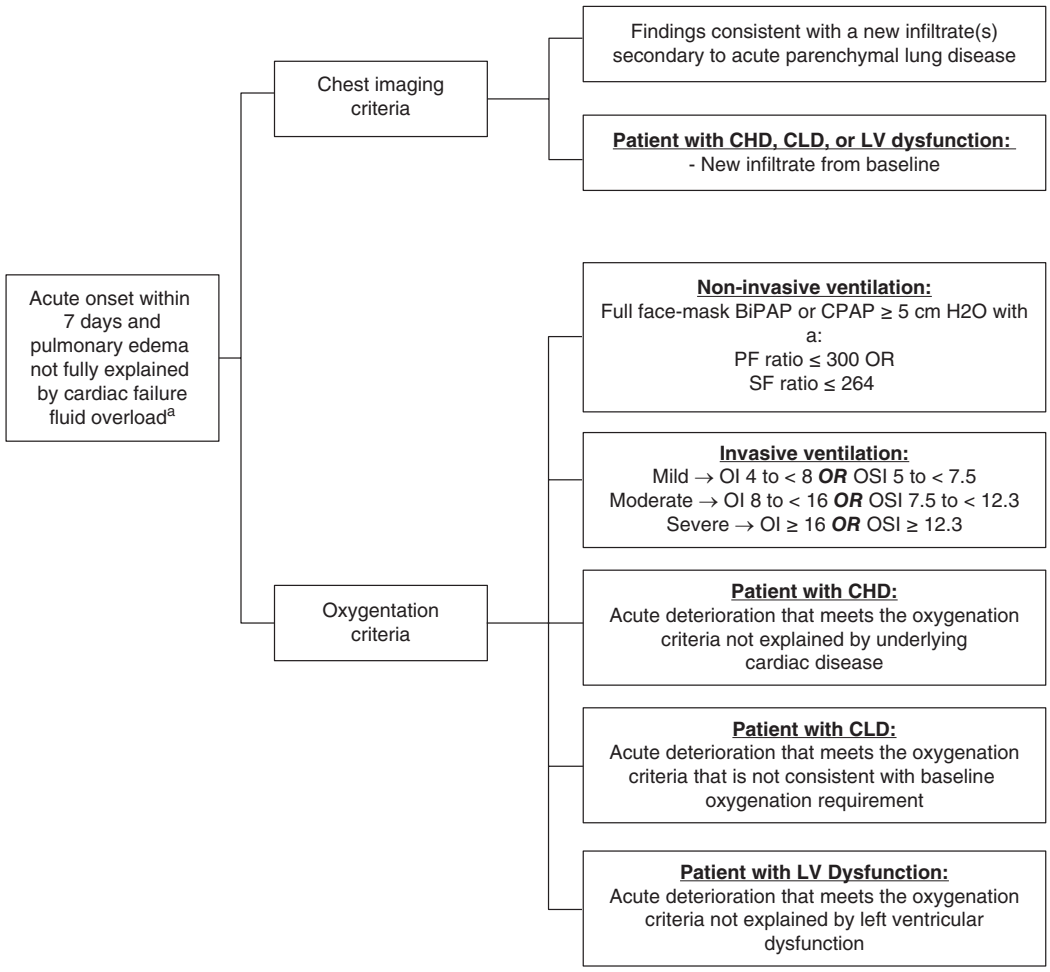

Figure 1-1. Pediatric ARDS definition.

[a]Excludes patients with lung disease unique to the perinatal period such as surfactant deficiency, meconium aspiration, and congenital diaphragmatic hernia.

BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; CHD = cyanotic heart disease; CLD = chronic lung disease; LV = left ventricular; OI = oxygenation index [(FiO_2 × mean airway pressure × 100)/PaO_2]; OSI = oxygen saturation index ([FiO_2 × mean airway pressure (Paw) × 100)/SpO_2]; PARDS = pediatric ARDS; PEEP = positive end-expiratory pressure; PF ratio = PaO_2/FiO_2; SF ratio = SaO_2/FiO_2.

Information from Khemani RG, Smith LS, Zimmerman JJ, et al. Pediatric acute respiratory distress syndrome: definition, incidence, and epidemiology: proceedings from the pediatric acute lung injury consensus conference. Pediatr Crit Care Med 2015;16:S23-S40.

There are several reasons to use OI and OSI rather than PEEP in the definition of PARDS. First, there is known variability in clinical ventilator management. Second, pediatric intensivists may be less likely to use higher PEEP than their adult colleagues. Third, PEEP is unavailable in high-frequency oscillatory ventilation, which is commonly used in PARDS. In addition, the OI may better delineate the mortality risk in pediatric patients than the PF ratio. The OSI and SF ratio are offered as alternatives to the OI and PF ratio, respectively, when pulse oximetry is available but an arterial blood gas is not. There is no clearly defined upper age limit for when the PARDS definition versus the Berlin definition should be applied, but neither definition should be applied to patients with perinatal-related respiratory failure (Khemani 2015).

TOWARD EVIDENCE-BASED PHARMACOTHERAPY MANAGEMENT OF ALI AND ARDS

Using an evidence-based approach to managing ARDS can be difficult. Contradictory results among studies with small sample sizes for this heterogeneous syndrome make it difficult to discern which pharmacologic therapies, if any, should be used in these critically ill patients. Although the pathophysiology

of ARDS is likely similar between adults and children, there are also likely subtle differences because of the developmental changes that occur in the lung parenchyma and immune system. These differences may be behind the variability in treatment outcomes between these two patient populations.

Many pulmonary-specific and nonpulmonary-specific therapies for managing ARDS have been evaluated; this chapter focuses on exogenous surfactant and corticosteroids. Much clinical controversy exists concerning the use of these therapies (Tamburro 2015). The proceedings from the PALICC, convened in October 2012, address in further detail additional pulmonary-specific and nonpulmonary-specific pharmacotherapy, as well as ventilator management strategies. A complete review of the PALICC is beyond the scope of this chapter. For further details regarding the nonpharmacologic and pharmacologic management options (e.g., inhaled nitric oxide, inhaled prostacyclins, bronchodilators, diuretics, neuromuscular blocking agents) see the published proceedings (PALICC 2015).

Exogenous Surfactant

Direct injury to the alveoli, together with the intrusion of fluid into the alveolar airspace, is likely to result in pulmonary surfactant dysfunction or washout. The success of exogenous pulmonary surfactant in respiratory distress syndrome of the perinatal period has fueled interest in its use in ARDS. Many studies have attempted to delineate surfactant's benefit in ARDS, with underwhelming results. Despite some positive outcomes reported in the literature (Table 1-2; Table 1-3), surfactant investigations have varied greatly in surfactant product, dose, routes of administration, population studied, and ARDS definition used. In addition, although most studies have shown improvements in oxygenation, improvements in clinical end points have been inconsistent. Pharmacologic differences in phospholipid and surfactant protein composition of the different surfactant products make comparing the results between studies difficult. The pulmonary-specific therapies group at the PALICC reached strong agreement that routine use of surfactant therapy cannot be recommended (Tamburro 2015).

Future Directions and Ongoing Research

Much investigative effort has been placed into evaluating exogenous surfactant in ARDS, with little identified benefit. Potential reasons for failure to produce positive outcomes include surfactant product, nonstandardized doses, preparation techniques, administration methods, and heterogeneity of the ARDS population. Despite this extensive effort, the pulmonary-specific therapy subgroup of the PALICC recommended that future investigations focus on the populations most likely to benefit from surfactant therapy, although the specific groups this might include were not described (Tamburro 2015).

Secondary to the lack of identified survival benefit, a pooled analysis of five multicenter investigations of recombinant surfactant protein C (rSP-C) in adults sought to identify which patient populations with ARDS to focus on in future investigations. Subgroups with decreased mortality included those with direct lung injury, including lung injury secondary to pneumonia or aspiration, and those with severe direct lung injury, defined as having a mean baseline PF ratio of 100 ± 29.4 (Taut 2008). Subsequent prospective clinical trials of both adult and pediatric patients have failed to achieve mortality benefit in patients with direct lung injury using either rSP-C or calfactant, though the calfactant study was discontinued secondary to slow enrollment before reaching the predetermined sample size (Willson 2015, 2013; Spragg 2011).

A review of clinicaltrials.gov shows no actively enrolling or ongoing investigations into the use of pulmonary surfactant in ARDS. One pediatric investigation of calfactant evaluated all-cause mortality, duration of mechanical ventilation, PICU and hospital length of stay, and effect on oxygenation in patients with hematopoietic stem cell transplantation and acute leukemia and lymphoma with ALI; this study is complete, but results have not yet been reported (PSU 2015). Pending these data, and using results from previous investigations, patients with immunocompromise may be a reasonable group in which to attempt pulmonary surfactant.

Pharmacoeconomic Considerations

To date, no pharmacoeconomic evaluations of surfactant therapy in ARDS have been published, but cost must be considered when contemplating the use of this therapy for this indication. Of the surfactants investigated for this use, only beractant, calfactant, and poractant alfa are commercially available in the United States. However, the calfactant product used in the most recent adult and pediatric study is not the commercially available product (Willson 2015, 2013). Table 1-4 estimates the cost of this therapy using doses from the published literature and a PICU patient of moderate size.

Even in the absence of a positive effect on mortality, the additional drug cost may be justifiable if surfactant therapy minimizes mechanical ventilation or length of stay. However, because data to support clinical benefit are currently lacking, it is difficult to justify the increased cost of therapy.

Corticosteroids

Inflammation, endothelial damage, and altered coagulation caused by an uncontrolled innate defense response result in the potentially reversible pathology of ARDS. However, in some instances, this initial injury is followed by an irreversible fibroproliferative phase. Interest in corticosteroids arises from the ability to protect patients from the uncontrolled inflammatory response leading to ARDS and potentially irreversible fibrotic changes. In addition, relative adrenal insufficiency can occur in patients with ARDS (MacLaren 2002).

Evidence for Use, Dosing Regimen, and Timing for Initiation

Investigations of corticosteroid use in adults with ARDS span almost 30 years, a broad range of dosing strategies,

Table 1-2. Pediatric Evidence for Surfactant Use in Acute Hypoxemic Respiratory Failure

Reference	Study Details	End Point/Intervention	Results	Comments
Willson 1996	Open-label, multicenter, observational n=29 • Mean age 4.7 yr • Acute hypoxemic respiratory failure • OI ≥ 7	• ≥ 25% improvement in OI • Calfactant 80 mL/m^2; endotracheal instillation in four equal aliquots • Up to four doses, depending on initial improvement, followed by deterioration	≥ 25% improvement in OI • First dose (n=29): 83% • Second dose (n=17): 59% • Third dose (n=10): 60% • Fourth dose (n=4): 50% 4 of 29 patients died Complications: • Bronchospasm (1) • Pneumothoraces (2) • Pneumopericardium (1) • Unrelenting hypoxia (2) • Multiorgan failure (1) • Pneumopericardium (1)	• Ventilator management algorithm used • Improvement in oxygenation and ventilator parameters in the 24 hr after surfactant administration • Development of air leaks should be monitored for after administration • Effect on outcome cannot be assessed because of lack of a control group
Luchetti 1998	Randomized, single center n=10 • PPV + surfactant • Mean age 10.4 mo n=10 • PPV only • Mean age 11.2 mo Severe bronchiolitis requiring: • PPV • PF ratio < 158 mm Hg	• Surfactant treatment effect on gas exchange, PIP, duration of PPV and PICU stay • Poractant alfa 0.625 mL/kg administered in two or three aliquots	• No difference in baseline characteristics or MV parameters • Surfactant vs. control: • PF ratio improved significantly at 1, 3, 12, and 24 hr after surfactant • $Paco_2$ improved significantly at 12 and 24 hr after surfactant • PIP improved significantly at 3, 12, and 24 hr after surfactant • Duration of PPV and ICU length of stay decreased significantly • No adverse effects noted	• Viral etiology only known in four patients (all RSV) • Gas exchange, pulmonary mechanics, and clinical outcomes improved in surfactant group • Other medications used in both groups including bronchodilators, corticosteroids, and aminophylline, none of which is considered standard of care in bronchiolitis
Willson 1999	Multicenter, prospective, randomized, unblinded n=21 surfactant group n=21 control group • Acute hypoxemic respiratory failure • OI ≥ 7	• Surfactant treatment effect on OI and clinical outcomes • Calfactant 80 mL/m^2; endotracheal instillation in four equal aliquots • Up to four doses – retreatment criteria varied	• No difference in baseline characteristics Surfactant vs. control • Acute sustained improvement of a 50% decrease in OI from baseline at 24 hr after surfactant • Duration of PPV and ICU length of stay decreased significantly • No significant difference in mortality Complications with surfactant administration: • Bronchospasm (1) • Air leaks (1) • Pulmonary interstitial emphysema (1)	• Ventilator management algorithm used • Criteria for retreatment changed during the study. Subsequent criterion was retreatment in all patients unless a significant adverse event during previous administration or OI improved to < 7 • With the exception of bronchospasm, complications in the surfactant group were noted in a similar number of children in the control group

(*continued*)

Table 1-2. Pediatric Evidence for Surfactant Use in Acute Hypoxemic Respiratory Failure (*continued*)

Reference	Study Details	End Point/Intervention	Results	Comments
Lopez-Herce 1999	Open-label, single-center, observational n=20 • 1 mo – 16 yr • Acute pulmonary disease with severe hypoxemia • PF ratio < 100 mm Hg	• > 20% improvement in PF ratio within 4 hr of administration • Poractant alfa 0.625 mL/kg (n=14) and 2.5 mL/kg (n=6) given in two equal aliquots • Number of repeat doses (0–5) varied	• No significant difference in PF ratio improvement based on dose Pulmonary or systemic pathology (n=13) • > 20% improvement in PF ratio in 10 patients • 4 of 13 patients died CCHD pathology (n=7) • > 20% improvement in PF ratio in two patients • Six of seven patients died	• Uncontrolled study • Heterogeneous population • High overall mortality
Herting 2002	Retrospective report n=8 • 1 mo – 13 yr • PF ratio < 100 mm Hg • Pneumonia	• Poractant alfa given in two equal aliquots. Dose not standardized (median dose 1.625 mL/kg) • Repeat doses given, depending on favorable response	• Significant improvement in PF ratio within 1 hr of first administration • Repeat dose in seven of eight patients • Significant, but less pronounced improvement in PF ratio with second administration • Four of eight patients died • Pneumothorax (2)	• Rescue therapy • iNO or prostacyclin used in two patients • All patients had severe impairment of oxygenation • High overall mortality
Luchetti 2002	Multicenter, randomized controlled n=20 • CMV + surfactant • Mean age 8.7 mo n=20 • CMV only • Mean age 7.4 mo RSV-induced severe respiratory failure: • PF ratio < 150 mm Hg	• Surfactant treatment effect on gas exchange, respiratory mechanics, need for retreatment, duration of CMV, PICU stay, and mortality • Poractant alfa 0.625 mL/kg administered in two aliquots	• No difference in baseline characteristics or MV parameters • Surfactant vs. control • PF ratio improved significantly at 1, 3, 6, 12, 24, and 48 hr • $Paco_2$ improved significantly at 1, 3, 6, 12, 24, and 48 hr • PIP improved significantly at 1, 3, 6, 12, 24, and 48 hr • Duration of PPV and ICU length of stay decreased significantly • No adverse effects noted • All patients survived	• Nasotracheal intubation used in all patients – associated with increased risk of VAP • Ventilator management algorithm used • Prior treatment with β_2-agonist, corticosteroids, and epinephrine in all patients • Unusually low mortality rate

Willson 2005	Multicenter, randomized, blinded Infants, children, and adolescents n=77 • Surfactant • Mean age 7.2 yr n=75 • Placebo • Mean age 6.7 yr Acute respiratory failure • OI < 7 • Enrollment within 48 hr of MV	• Surfactant treatment effect on clinical outcomes • Calfactant administered in four equal aliquots • < 10 kg: 3 mL/kg • ≥ 10 kg: 80 mL/m^2 • Two doses at 12-hr intervals	• No difference in baseline characteristics Surfactant vs. control • OI significantly improved at 12 hr • Significantly lower CMV failure • Significantly lower mortality • No difference in ventilator-free days Complications with surfactant administration: • Significantly greater hypotension • Significantly greater transient hypoxia • No difference in the development of air leaks	• Ventilator guidelines • Eight patients (four in each group) were protocol violations – six did not meet the OI criteria, and two received a non-protocol surfactant • High overall mortality – likely because of the number of immunocompromised patients • More immunocompromised patients in the placebo group • Mortality with placebo did not reach statistical significance when controlling for immune status
Thomas 2012	Multinational, phase II, double-blind, placebo-controlled, randomized Children 38 wk PMA to ≤ 2 yr n=84 • Surfactant • Mean age 23.1 wk PNA n=81 • Placebo • Mean age 23.4 wk PNA Acute respiratory failure • Two consecutive PF ratios ≤ 300 mm Hg (or SF ratio ≤ 250) • MV ≥ 6 hr but ≤ 48 hr on inclusion	• Duration of MV • Lucinactant 5.8 mL/kg in four equal aliquots • Repeat doses 12–24 hr after initial allowed if patient still met inclusion criteria	• Lower baseline PEEP and tidal volume in the placebo group • No other differences in baseline characteristics Surfactant vs. control • No difference in duration of MV • No difference in improvement in PF ratio • Fewer repeat doses in the lucinactant group Complications with surfactant administration: • Transient bradycardia • Transient hypoxia	• Synthetic surfactant • No longer commercially available • Ventilator management protocol • Subset of patients with ALI – shorter duration of MV with lucinactant than with placebo

(*continued*)

Table 1-2. Pediatric Evidence for Surfactant Use in Acute Hypoxemic Respiratory Failure (*continued*)

Reference	Study Details	End Point/Intervention	Results	Comments
Willson 2013	Multinational, randomized, placebo-controlled, masked Infants, children, and adolescents n=56 • Surfactant • Mean age 6.3 yr • n=53 • Placebo • Mean age 6 yr ALI/ARDS secondary to direct lung injury • PF ratio ≤ 300 mm Hg (or SF ratio ≤ 250) • Enrollment within 48 hr of MV	• Surfactant treatment effect on clinical outcomes • Calfactant in two equal aliquots • < 10 kg: 1.7 mL/kg • ≥ 10 kg: 0.5 mL/cm • Up to two repeat doses with a 25% improvement in PF ratio (or SF ratio) within 12 hr of the previous dose	• No difference in baseline characteristics Surfactant vs. control • No difference in mortality, ventilator-free days, or PICU-free days • No improvement in oxygenation • Hospital-free days significantly less Complications with surfactant administration: • Transient hypoxia • Transient bradycardia • Pneumothorax • Pneumomediastinum	• Combined adult and pediatric study (table 3 in: Willson 2015) • Study terminated at planned interim analysis for futility • More homogeneous population – direct lung injury only • Primarily infectious lung injury • Independent randomization of those with a PF ratio < 100 mm Hg, OI > 30, or immunocompromised status to ensure equal distribution • Calfactant product containing 60 mg/mL of phospholipid

CMV = conventional mechanical ventilation; CCHD = complex congenital heart disease; iNO = inhaled nitric oxide; MV = mechanical ventilation; PIP = positive inspiratory pressure; PMA = postmenstrual age; PNA = postnatal age; PPV = positive pressure ventilations; RSV = respiratory syncytial virus; VAP = ventilator-associated pneumonia.

Information from: Willson DF, Jiao JH, Bauman LA, et al. Calf's lung surfactant extract in acute hypoxemic respiratory failure in children. Crit Care Med 1996;24:1316-22; Luchetti M, Casiraghi G, Calsecchi R, et al. Porcine-derived surfactant treatment of severe bronchiolitis. Acta Anaesthesiol Scan 1998;42:805-10; Willson DF, Zartsky A, Bauman LA, et al. Instillation of calf lung surfactant (calfactant) is beneficial in pediatric acute hypoxemic respiratory failure. Crit Care Med 1999;27:188-95; Lopez-Herce J, de Lucas N, Carrillo A, et al. Surfactant treatment for acute respiratory distress syndrome. Ach Dis Child 1999;80:248-52; Herting E, Moller O, Schiffmann JH, et al. Surfactant improves oxygenation in infants and children with pneumonia and acute respiratory distress syndrome. Acta Paediatr 2002;91:1174-8; Luchetti M, Ferrero F, Gallini C, et al. Multicenter, randomized, controlled study of porcine surfactant in severe respiratory syncytial virus-induced respiratory failure. Pediatr Crit Care Med 2002;3:261-8; Willson WF, Thomas NJ, Markovitz BP, et al. Effect of exogenous surfactant (calfactant) in pediatric acute lung injury a randomized controlled trial. JAMA 2005;293:470-6; Thomas NJ, Guardia CG, Moya FR, et al. A pilot, randomized, controlled trial of lucinactant, a peptide-containing synthetic surfactant, in infants with acute hypoxemic respiratory failure. Pediatr Crit Care Med 2012;13:646-53; Willson WF, Thomas NJ, Tamburro R, et al. Pediatric calfactant in acute respiratory distress syndrome trial. Pediatr Crit Care Med 2013;14:657-65; and Willson DF, Truwit JD, Conaway MR, et al. The adult calfactant in acute respiratory distress syndrome trial. Chest 2015;148:356-64.

Table 1-3. Adult Evidence for Surfactant Use in ARDS

Reference	Study Details	End Point/Intervention	Results	Comments
Weg 1994	Multicenter, double-blind, placebo-controlled, randomized, parallel n=17 • 12-hr nebulized surfactant n=17 • 24-hr nebulized surfactant n=17 • 12- or 24-hr nebulized saline Sepsis-induced ARDS • Within in 18 hr of onset	• Safety of nebulized surfactant • Surfactant treatment effect on oxygenation and clinical outcomes • Exosurf nebulized • 12-hr group: ~1.6 mL/kg per day • 24-hr group: ~3.2 mL/kg per day • Administered for up to 5 days	• Numerically more females in the placebo group • No other differences in baseline characteristics Surfactant vs. placebo • No safety issues • No significant differences in oxygenation improvements • No significant differences in mortality or hospital days	• Synthetic surfactant, contains no surfactant proteins • Product not manufactured for nebulization, intended for endotracheal administration • No longer commercially available
Anzueto 1996	Multicenter, double-blind, placebo-controlled, randomized n=364 • Nebulized surfactant n=361 • Nebulized saline Sepsis-induced ARDS • ARDS developed in the preceding 48 hr	• Surfactant treatment effect on oxygenation and clinical outcomes • Exosurf ~8.3 mL/kg per day • Administered for up to 5 days	• No differences in baseline characteristics Surfactant vs. placebo • Similar number completed 5 days of treatment • No significant differences in oxygenation improvements • No significant differences in mortality or hospital days Complications with surfactant administration: • Worsening hypoxia • Respiratory arrest • Increased PIP • Increased secretions • Hypotension (both groups) • Barotrauma (both groups)	• Synthetic surfactant, contains no surfactant proteins • Product not manufactured for nebulization, intended for endotracheal administration • No longer commercially available • Mean PF ratio for both groups < 150 mm Hg

(*continued*)

Table 1-3. Adult Evidence for Surfactant Use in ARDS (*continued*)

Reference	Study Details	End Point/Intervention	Results	Comments
Gregory 1997	Multicenter, open-label, randomized, controlled n=43 • Surfactant n=16 • Control group ARDS: • From trauma, multiple transfusions, aspiration of gastric contents, or sepsis • Age 15–70 yr • AECC definition • PEEP ≥ 5 cm H_2O	• Surfactant treatment effect on oxygenation and clinical outcomes • Safety of endotracheally administered surfactant • Beractant in four equal aliquots • 2 mL/kg of LBW for up to eight doses (n=8) • 4 mL/kg of LBW for up to four doses (n=16) • 4 mL/kg of LBW for up to eight doses (n=19) • Assessment for retreatment every 6 hr up to 96 hr • Retreatment criteria: ◦ PF ratio > 60 to < 200 mm Hg ◦ PEEP > 10 cm H_2O ◦ PF ratio ≥ 200 but ≤ 250 mm Hg AND PEEP ≥ 5 but ≤ 10 cm H_2O	• Significant differences in baseline characteristics include: ◦ Increased weight in the 4 mL/kg of LBW for up to four doses compared with control patients ◦ More patients with risk factor for multiple transfusions in the 2 mL/kg of LBW for up to eight doses and 4 mL/kg of LBW for up to eight doses compared with control patients Surfactant vs. control • Significant reduction in Fio_2 at 120 min in the 4 mL/kg of LBW for up to four doses group • Significant improvement in Fio_2 and PEEP at 7 days 4 mL/kg of LBW for up to four doses group • Significantly increased length of stay in the 4 mL/kg of LBW for up to eight doses group • No difference in mortality Complications with surfactant administration: • Oxygen desaturation • Air leak • Bronchospasm • Hypotension	• Included adolescent patients • Large volumes of surfactant generally well tolerated
Spragg 2004	Two clinical trials Multicenter, randomized, double-blind, controlled n=224 • Surfactant + standard therapy n=224 • Standard therapy only ARDS • AECC definition • PEEP ≥ 5 cm H_2O • Enrollment 48 hr (North American sites) to 72 hr (European/South African sites) from diagnosis	• Surfactant treatment effect on oxygenation and clinical outcomes • rSP-C 1 mL/kg of LBW in two aliquots intratracheal administration • Up to three repeat doses • Assessment of retreatment every 4 hr for 24 hr • Retreatment criteria: ◦ PF ratio > 60 to < 200 mm Hg AND ◦ PEEP ≥ 5 cm H_2O	• Percentage of patients with baseline APACHE II score > 23 was significantly higher in the surfactant group • All other baseline characteristics similar Surfactant vs. control • 91% received all four doses of surfactant • Significant improvement in PF ratio at 4–24 hr from the first treatment • No difference in PF ratio at 48 hr from the first treatment • No difference in mortality or ventilator-free days Complications with surfactant administration: • Significantly more adverse events in the surfactant group • No significant difference in the number of serious adverse events • Most common events: hypoxemia, hypotension, bradycardia	• Orphan drug status • Synthetic surfactant product • Heterogeneous population of patients with ARDS • Multivariate analysis showed: ◦ Baseline PEEP and PIP associated with increased relative risk of MV – thus, compromised lung function associated with fewer ventilator-free days ◦ Enrollment in the European/South African arm, higher APACHE II, and older patients had increased risk of mortality

Spragg 2011	Multicenter, randomized, controlled, blinded n=419 • Surfactant + standard therapy n=424 • Standard therapy only ARDS • Severe impairment of gas exchange from pneumonia or aspiration • PF ratio ≤ 170 mm Hg • Age 12–85 yr	• Surfactant treatment effect on oxygenation and clinical outcomes • rSP-C 1 mL/kg of LBW in two aliquots intratracheal administration • Up to seven repeat doses at 6, 12, 24, 36, 48, 72, and 96 hr after the first dose • Retreatment criteria: ◦ PF ratio > 60 to ≤ 170 mm Hg AND ◦ PEEP ≥ 5 cm H_2O	• No differences in baseline characteristics Surfactant vs. control • No difference in mortality, gas exchange parameters, need for mechanical ventilation, or the number of non-pulmonary organ failure–free days Complications with surfactant administration: • Significantly more serious adverse events in the surfactant group	• Orphan drug status • Synthetic surfactant product • Fairly homogeneous patient population • Because of alteration in the surfactant suspending process and lack of expected outcome, surfactant activity was performed post hoc ◦ Adding shearing to the surfactant preparation process may have impaired the function of the surfactant, which may explain the deviation from results of previous studies
Willson 2015	Multicenter, randomized, controlled, masked n=151 • Surfactant n=157 • Placebo ARDS • AECC definition because of direct lung injury • Within 48 hr of initiating MV • Age 18–85	• Surfactant treatment effect on oxygenation and clinical outcomes • Calfactant 0.5 mL/cm in two aliquots • Up to two repeat doses Retreatment criteria • 25% improvement in PF ratio (or SF ratio) within 12 hr of the previous dose	• No differences in baseline characteristics Surfactant vs. control: • No significant difference in mortality, ventilator-free days, ICU-free days, or hospital-free days • No significant improvement in measures of oxygenation Complications with surfactant administration: • 116 adverse events possibly related to the treatment intervention • Six events in the surfactant group were graded as severe • Most common adverse events were hypoxia and hypotension	• Combined adult and pediatric trial (table 3 in: Willson 2013) • Study terminated at planned interim analysis for futility • More homogeneous population – direct lung injury only • Calfactant product containing 60 mg/mL of phospholipid • Ventilator algorithm used

APACHE = Acute Physiology and Health Evaluation; LBW = lean body weight; rSP-C = recombinant surfactant protein C.

Information from: Weg JG, Balk, RA, Tharratt RS, et al. Safety and potential efficacy of an aerosolized surfactant in human sepsis-induced adult respiratory distress. JAMA 1994;272:1433-8; Anzueto A, Baughman RP, Guntupalli KK, et al. Aerosolized surfactant in adults with sepsis-induced adult respiratory distress. N Engl J Med 1996;334:1417-21; Gregory TJ, Steinberg KP, Spragg R, et al. Bovine surfactant therapy for patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 1997;155:1309-15.

Spragg RG, Lewis JF, Walmrath HD, et al. Effect of recombinant surfactant protein C-based surfactant on the acute respiratory distress syndrome. N Engl J Med 2004;351:884-92; Spragg RG, Taut FJH, Lewis JF, et al. Recombinant surfactant protein C-based surfactant for patients with severe direct lung injury. Am J Respir Crit Care Med 2011;183:1055-61; Willson WF, Thomas NJ, Tamburro R, et al. Pediatric calfactant in acute respiratory distress syndrome trial. Pediatr Crit Care Med 2013;14:657-65; and Willson DF, Truwit JD, Conaway MR, et al. The adult calfactant in acute respiratory distress syndrome trial. Chest 2015;148:356-64.

Table 1-4. Cost of Beractant, Calfactant, and Poractant Therapy[a]

	Beractant	Calfactant[b]	Poractant Alfa
WAC per vial	8-mL vial = $677.88	6-mL vial = $671.11	3-mL vial = $764.40
Cost of single dose	4 mL/kg × 32 kg = 128 mL Rounded to whole vial = 16 vials Cost per dose = $10,846.08	~0.85 mL/cm × 139 cm = 118 mL Rounded to whole vial = 20 vials × 6 mL Cost per dose = $13,422.20	0.625–2.5 mL/kg = 20–80 mL Rounded to whole vial = 7 – 27 vials × 3 mL Cost per dose = $5350.8–$20,638.80
Cost of studied treatment course	128 mL × 4 doses = 512 mL Rounded to whole vial = 64 vials × 8 mL Cost per treatment course = $43,384.32	118 mL × 3 doses = 354 mL Rounded to whole vial = 60 vials × 6 mL Cost per treatment course = $40,266.60	Cost not calculated secondary to repeat doses varied greatly

[a]Calculated for a 10-yr-old boy with height 55 inches, weight 32 kg.

[b]Equivalent dose based on phospholipid component; calfactant product studied contains 60 mg/mL of phospholipid; Infasurf contains 35 mg/mL of phospholipid.

WAC = wholesale acquisition cost.

Information from: Willson WF, Thomas NJ, Tamburro R, et al. Pediatric calfactant in acute respiratory distress syndrome trial. Pediatr Crit Care Med 2013;14:657-65; and Willson DF, Truwit JD, Conaway MR, et al. The adult calfactant in acute respiratory distress syndrome trial. Chest 2015;148:356-64.

and heterogeneous patient populations. Initial corticosteroid studies focused on prevention and used short courses of high-dose corticosteroids (30 mg/kg of methylprednisolone every 6 hours). These data did not support corticosteroid use in the prevention of ARDS; rather, this treatment strategy may increase the risk of developing ARDS (Deal 2008).

Subsequent investigations have used lower doses for more prolonged courses, generally using methylprednisolone. These investigations have sought to delineate the role of corticosteroids in both the early and late phases of the disease; however, responses in clinical outcomes have been inconsistent (Meduri 2007, 1998; Steinberg 2006). Table 1-5 compares the treatment regimens, phase of ARDS, and outcomes.

Meta-analyses and systematic reviews have also had inconsistent or inconclusive results with respect to treatment effect on mortality or resource use (Ruan 2014; Tang 2009; Peter 2008). Of interest, when evaluating the effect of steroids on mortality in ARDS given the underlying etiology, there is an increased risk of mortality with steroid administration in those with influenza-related ARDS, but mortality is decreased in postoperative patients with ARDS who receive steroids (Ruan 2014).

Data for pediatric patients are lacking. Published reports of corticosteroid use in pediatric ARDS are limited to three case reports and one case series of six patients. Similar to the data available in adult patients, dosing regimens, time since onset of the syndrome to initiation of corticosteroids, and underlying cause of ARDS vary greatly. The combination of the lack of data and variability prevents the ability to form conclusions on the use of corticosteroids in pediatric patients with ARDS using pediatric data (Guglani 2006; Haselton 2000; Goh 1999; Martinot 1997).

Because of an overwhelming lack of evidence in pediatric patients and inconsistent evidence in adult ARDS studies, similar to surfactant therapy, the pulmonary-specific therapy subgroup of the PALICC strongly agreed that corticosteroids cannot be recommended as part of routine care in PARDS (Tamburro 2015). According to adult data, if corticosteroids are used in PARDS, moderate- to low-dose prolonged therapy courses should be used. In addition, initiating this therapy is likely most useful in the late phase, but initiation should occur on or before day 13 of onset of the syndrome. Pending additional data, corticosteroids for ARDS should be avoided in patients with influenza-related ARDS.

Consequences of Corticosteroid Use in the Critically Ill Patient

Concerns with corticosteroid use in critically ill patients with ARDS include risk of infection, hyperglycemia, and neuromuscular weakness. In randomized controlled trials, the risk of infection has not been identified more commonly in the corticosteroid treatment group than in the control groups (Meduri 2007; Steinberg 2006; Meduri 1998). Both hyperglycemia and neuromyopathy have been identified as occurring more commonly in methylprednisolone-treated patients (Steinberg 2006).

VENTILATOR-ASSOCIATED EVENTS

Enhancing the quality of medical care through preventing health care–associated infections is imperative in

Table 1-5. Randomized Controlled Trials of Methylprednisolone in Adult ARDS

	Meduri 1998	Steinberg 2006	Meduri 2007
Number of subjects	24 Methylprednisolone (n=16)	180 Methylprednisolone (n=89)	91 Methylprednisolone (n=63)
Phase of ARDS	Late	Late	Early
Time since onset of ARDS	7 days	7–28 days	Within 72 hr
Dosing regimen (mg/kg PER dose)	Day 1: 2 mg/kg loading dose × 1 Days 1–14: 0.5 mg/kg q6hr Days 15–21: 0.25 mg/kg q6hr Days 22–28: 0.125 mg/kg q6hr Days 29–30: 0.063 mg/kg q6hr Days 31–32: 0.031 mg/kg q6hr Note: Patients extubated before day 14 were advanced to day 15 and weaned	Day 1: 2 mg/kg loading dose × 1 Days 1–14: 0.5 mg/kg q6hr Days 15–21: 0.5 mg/kg q12hr Note: Those still intubated at day 21 were tapered over 4 days. If extubated by day 21, or developed infection weaned over 2 days	Day 1: 1 mg/kg loading dose x 1 Days 1–14: 1 mg/kg Days 15–21: 0.5 mg/kg Days 22–25: 0.25 mg/kg Days 26–28: 0.125 mg/kg Note: Patients extubated before day 14 were advanced to day 15 and weaned Administered as continuous infusion, transitioned to daily oral dose, once possible
Oxygenation	Significant improvement in PF ratio by day 5	Significant improvement in PF ratio at days 3 and 14	NR
LIS	Significant improvement by day 5	NR	Significantly more likely to have improvement at day 7
Mortality	Significantly higher in the placebo group	No difference Higher risk of mortality in methylprednisolone group for those enrolled at > 14 days after ARDS onset	No difference
ICU length of stay	NR	Significantly shorter	Significantly shorter
MV	Significantly shorter duration	Significantly shorter duration	Significantly more likely to be extubated by day 7

LIS = lung injury score; NR = not reported; q = every.

Information from: Meduri GU, Golden A, Freire AX, et al. Methylprednisolone infusion in early severe ARDS: results of a randomized controlled trial. Chest 2007;131:954-63; Steinberg KP, Hudson LD, Goodman RB, et al. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. N Engl J Med 2006;354:1671-84; and Meduri GU, Headley AS, Golden E, et al. Effect of prolonged methylprednisolone therapy in unresolving acute respiratory distress syndrome: a randomized controlled trial. JAMA 1998;280:159-65.

optimizing care for patients and minimizing resource use. Ventilator-associated pneumonia is one such health care–associated infection that must be considered for surveillance and prevention. At this time in PICUs, VAP is the only ventilator-associated event (VAE) that is considered for surveillance. However, this current state of quality surveillance is being evaluated to ensure that an objective and outcomes-focused definition is used.

Defining VAP in Pediatric Patients

Ventilator-associated pneumonia is a device-related, reportable, health care–associated infection. Definitions of VAP vary depending on the patient's age. Figure 1-2 delineates the current pediatric surveillance definition for the pneumonia-reporting module (CDC 2016a). Applying this definition is contingent on meeting the criteria for a health care–associated infection, which states that the date of occurrence must be on or after the third calendar day of an inpatient admission. In patients receiving mechanical ventilation on the date of the occurrence, the event must occur more than 2 calendar days from the date of tracheal intubation to be considered ventilator associated. In addition to these criteria, further laboratory assessments primarily concerning lower respiratory tract specimens can be used in determining VAP. Concerns

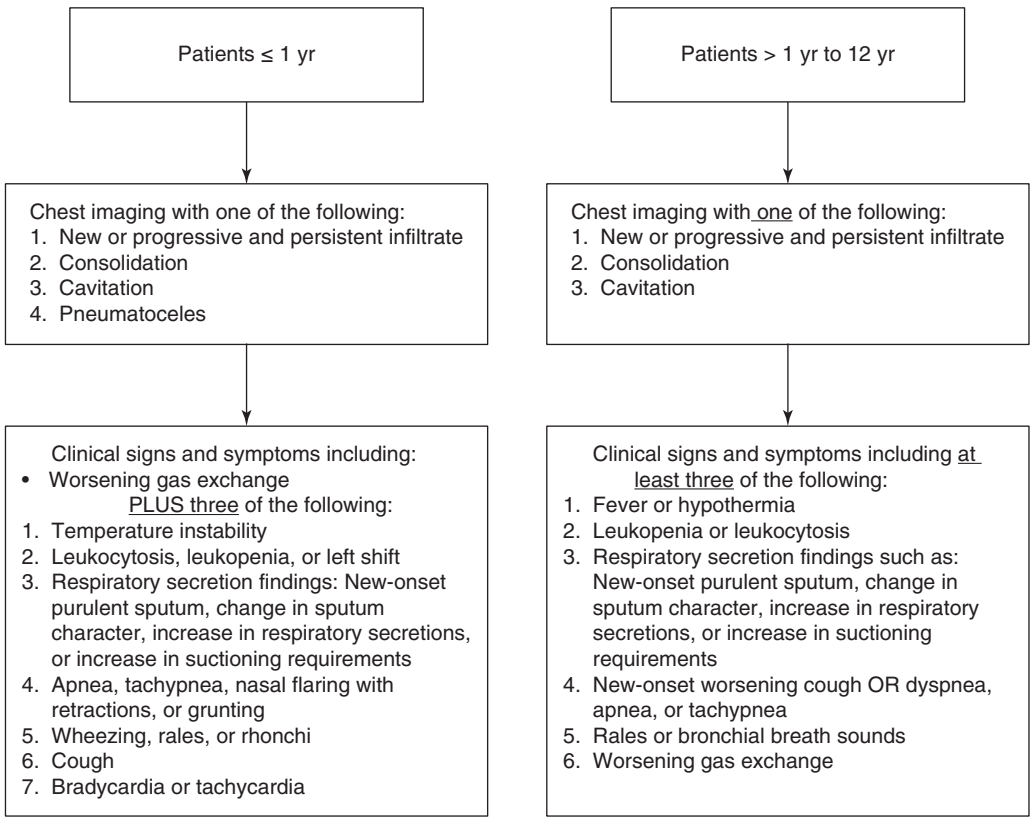

Figure 1-2. Hospital-acquired/ventilator-associated pneumonia clinical criteria for infants and children.

Information from: CDC. CDC/NHSN Surveillance Device-Associated Module: Pneumonia (ventilator-associated and non-ventilator-associate pneumonia) Event. 2016.

with the complexity and subjectivity of this definition are discussed later in this section.

Prevalence, Outcomes, and Associated Cost of VAP in Pediatric Patients

Reported rates of VAP vary depending on the reference, likely because of inter-reporter variability in data collection and interpretation (Phongjitsiri 2015). Regardless, VAP is a common cause of health care–associated infections in pediatric patients requiring mechanical ventilation. The most current report of the device-associated module, which includes VAP, from the National Healthcare Safety Network summarizes surveillance data from January to December 2013. This report provides VAP data from 134 pediatric locations including 14 cardiothoracic critical care units (CCUs), 10 medical CCUs, and 110-combined medical-surgical CCUs. The overall ventilator use ratio, defined as the total number of ventilator-days to total patient-days, was 0.37, with a VAP rate of 0.67 cases per 1000 ventilator-days (Dudeck 2015). This rate is less than the rates reported in the literature. A recent multicenter, prospective evaluation, which used the CDC surveillance definition current at the time of data collection, identified a VAP prevalence in the PICU of 7.1 cases per 1000 ventilator-days (Gupta 2015).

Health care–acquired infections, including VAP, can be associated with worse outcomes and increased health care costs. Ventilator-associated pneumonia in pediatric patients has been associated with a significant increase in PICU length of stay, duration of mechanical ventilation, and mortality (Gupta 2015; Bigham 2009). Even when controlling for severity of illness, PICU patients who develop VAP are 3 times more likely to die than are those who did not develop the infection (Gupta 2015). In addition to these worse outcomes, increased health care use results in increased health care cost. The VAP-attributable cost in pediatric patients has been reported at about $50,000 per incident (Brilli 2008).

CURRENT QUALITY OF CARE SURVEILLANCE

Because of concerns with the complexity and subjectivity of the surveillance definitions for VAP, surveillance in adult institutions was redirected in 2013. The goal was to develop a more

objective and reliable approach, resulting in a refocus on VAEs when the surveillance is prompted by worsening oxygenation as opposed to chest radiograph changes (CDC VAE 2016).

Currently, pediatric units continue to report device-associated events according to the VAP definition (see Figure 1-2), whereas adult units report VAEs. Pediatric reporting is only for PICU areas. Neonatal ICUs can track VAP internally, but VAP is no longer part of the surveillance plan option to be analyzed by the National Healthcare Safety Network. The surveillance definition used for reporting is determined by the location, not the age, of the patient undergoing surveillance. Thus, a patient 18 years or younger in an adult unit would report by the VAE module, and a patient 18 years or older in a pediatric unit would report by the pneumonia module (CDC 2016a, 2016b).

Differences in Adult vs. Pediatric Surveillance

The pediatric pneumonia surveillance definition is a single-tier approach, initiated by changes in chest radiography. The adult VAE surveillance definition is a three-tier approach that is initiated secondary to indicators of worsening oxygenation after at least 2 calendar days of respiratory improvement or stability. Thus, the adult approach focuses on a change in respiratory clinical status as opposed to less objective changes in chest radiography. Streamlining and enhancing the objectivity of the surveillance definition in pediatric patients will hopefully allow for automation of surveillance in the future. In comparison, the pediatric VAP definition is far less objective. Table 1-6 compares the current pediatric and adult unit surveillance modules. For completeness, the table includes criteria that were used to assess ventilator-associated tracheobronchitis (VAT) in studies discussed later in the chapter.

Classification of VAEs

Ventilator-associated events are further delineated into ventilator-associated conditions (VACs), infection-related ventilator-associated conditions (IVACs), and possible ventilator-associated pneumonia (PVAP). After initiating mechanical ventilation, calendar day 3 is the earliest an event may occur that can meet the criteria of a VAE on day 4 of mechanical ventilation.

Table 1-6. Comparison of Ventilator-Associated Event Criteria

	PedVAP	VAT	VAC	IVAC[a]	PVAP
Worsening after stability or improvement	Not considered	Not considered	Required	Required	Required
Chest imaging	Change in chest imaging required	No change in chest imaging	Not considered	Not considered	Not considered
Change in Fio_2	No specific criteria but "worsening gas exchange" ≤ 1 yr: required 1–12 yr: optional	Not considered	Specific for worsening oxygenation	Specific for worsening oxygenation	Specific for worsening oxygenation
Change in PEEP	No specific criteria but "worsening gas exchange" ≤ 1 yr: required 1–12 yr: optional	Not considered	Specific for worsening oxygenation	Specific for worsening oxygenation	Specific for worsening oxygenation
WBC	Leukocytosis, leukopenia, or left-shift (≤ 1 yr)	≤ 12 yr: ≥ 15 × 10^3 cells/mm^3 OR < 4 × 10^3 cells/mm^3 > 12 yr: ≥ 12 × 10^3 cells/mm^3 OR < 4 × 10^3 cells/mm^3		≥ 12 × 10^3 cells/mm^3 OR < 4 × 10^3 cells/mm^3	≥ 12 × 10^3 cells/mm^3 OR < 4 × 10^3 cells/mm^3
Temperature	≤ 1 yr: instability 1–12 yr: fever or hypothermia	> 38°C OR < 36°C		> 38°C OR < 36°C	> 38°C OR < 36°C

(*continued*)

Table 1-6. Comparison of Ventilator-Associated Event Criteria (*continued*)

	PedVAP	VAT	VAC	IVAC[a]	PVAP
New antimicrobial	Not considered	Not considered		Started and continued for ≥ 4 days	Started and continued for ≥ 4 days
Sputum change	New, changed, or increased	Not considered			Not considered
Respiratory culture quantitation[b]	BAL: ≥ 100,000 CFU Lung tissue: ≥ 100,000 CFU PBS: ≥ 10,000 CFU	≥ 10,000 CFU			EA: ≥ 1,000,000 CFU BAL: ≥ 100,000 CFU Lung tissue: ≥ 100,000 CFU PBS: ≥ 10,000 CFU
Sputum WBC[c]	Not considered	At least moderate			≥ 25 neutrophils AND ≤ 10 epithelial cells per low-power field
Other positive infectious testing[d]	Organism from pleural fluid Lung histopathology showing: abscess formation OR fungal infiltration Positive *Legionella* Positive respiratory virus	N/A			Organism from pleural fluid Lung histopathology showing: abscess formation OR fungal infiltration Positive *Legionella* Positive respiratory virus
Clinical symptoms of respiratory distress	Required	N/A			Not considered

[a]Require only that either WBC or temperature criteria be met.

[b]Considered in criteria 1 and 2 for PVAP.

[c]Considered in criterion 2 for PVAP.

[d]Considered in criterion 3 for PVAP.

BAL = bronchoalveolar lavage; EA = endotracheal aspirate; IVAC = infection-related ventilator-associated condition; N/A = not applicable; PBS = protected brush specimen; PedVAP = pneumonia criteria for pediatrics; PVAP = possible VAP; VAC = ventilator-associated condition; VAT = ventilator-associated tracheobronchitis.

Information from: Beardsley AL, Nitu ME, Cox EG, et al. An evaluation of various ventilator-associated infection criteria in a PICU. Pediatr Crit Care Med 2016;17:73-80; CDC. CDC/NHSN Surveillance Device-Associated Module: Pneumonia (ventilator-associated and non-ventilator-associate pneumonia) Event; and CDC. CDC/NHSN Surveillance Device-Associated Module: Ventilator-Associated Events. 2016.

Ventilator-Associated Conditions

After a period of stability or improvement on the ventilator, an increase in the daily minimum Fio_2 of at least 0.2 or an increase in the daily minimum PEEP of at least 3 mm Hg is defined as a VAC. These changes must be sustained for 2 or more calendar days.

IVAC Complications

Patients presenting within 2 days before or after the onset of the VAC are considered to have IVACs if they have either temperature or WBC count abnormalities plus initiation of a new antimicrobial agent that is continued for at least 4 days.

Possible Ventilator-Associated Pneumonia

Categorization as PVAP occurs if one of three criteria is met within 2 days before or after the onset of the VAC. The criteria for PVAP incorporate information that may suggest an infectious pathology. Concerning microbiologic data, one of three criteria may be used to meet the definition of PVAP. Criterion 1 is a report of quantitative or semiquantitative growth from

endotracheal aspirates, bronchoalveolar lavage (BAL), lung tissue, or protected brush specimen. Criterion 2 is purulent respiratory secretions evaluated in combination with quantitative or semiquantitative respiratory culture results that do not meet specified quantitation thresholds. Criterion 3 are identification of pathologic organisms from positive pleural fluid culture, lung histology consistent with abscess or parenchymal invasion by fungi, *Legionella*, or viral testing positive for respiratory viruses.

Utility of Surveillance Definitions

The paradigm shift in the need for a new surveillance method in adult patients arose secondary to the fact that the current definition used for surveillance of pneumonia is neither sensitive nor specific. In a recent retrospective analysis, the current pediatric VAP, IVAC, VAT, and lower respiratory tract definitions were compared in 300 episodes of mechanical ventilation in which there were 30 ventilator-associated infections. Of the 30 infections, 9 met more than one of the ventilator-associated infection criteria. Despite only moderate overlap in the definitions with respect to diagnosis, the risk factors for developing a ventilator-associated infection and outcomes were similar, suggesting that each definition has some validity (Beardsley 2016).

In adults, significant concern surrounded the use of a definition in which surveillance was prompted by radiographic findings, which may not accurately identify VAP. In addition, the clinical signs and symptoms, although potentially useful in diagnosis, may not consistently be documented, making them poor surveillance features for quality improvement endeavors. Optimizing surveillance definitions is important in facilitating the development of optimal prevention strategies (CDC 2016b).

Potential Transition of Pediatric Surveillance

Understanding that a new approach to surveillance would be required for pediatric patients, a workgroup was convened to explore the possibility of a new surveillance definition. This workgroup agreed that the current surveillance definition had room for optimization, but it was cautious about adopting the adult definitions for VAE without further data.

A single-center, retrospective study applied the current adult VAE definitions to a pediatric cohort. Rates of VACs and IVACs per 1000 ventilator-days were 20.9 and 12.9 cases, respectively. Most of the patients classified as having an IVAC were then further classified as having either possible or probable pneumonia. Compared with those without a VAC, patients with a VAC had a significantly longer duration of mechanical ventilation and duration of both hospitalization and ICU length of stay, as well as a higher risk of mortality. Immunocompromised status, tracheostomy dependence, and chronic respiratory failure were identified as independent risk factors for developing a VAC (Phongjitsiri 2015).

A multicenter, retrospective, matched cohort study of PICU, cardiac ICU, and neonatal ICU was conducted to find a pediatric VAC definition that would identify patients at risk of worse outcomes. Worsening of oxygenation for at least 2 days after 2 days of stability or improvement was defined by Fio_2 daily increases of 0.2, 0.25, and 0.3 and mean airway pressure (MAP) daily increases of 4, 5, 6, and 7 cm H_2O. Patients with a VAC were matched with patients without a VAC. Mean airway pressure was used for this investigation because it better reflects changes in lung compliance and allows for an assessment of patients receiving high-frequency oscillatory ventilation. The rate of VACs, according to these definitions, including MAP in a multicenter approach, resulted in a significantly lower rate of VACs of 2.9–3.2 cases per 1000 ventilator-days than in the 2015 single-center cohort study. Each assessed increase in Fio_2 and MAP was associated with a greater risk of death and, among survivors, prolonged hospitalization, time in the ICU, and duration of mechanical ventilation. Outcomes assessment was consistent with the earlier single-center cohort study (Cocoros 2016). Given these results, the advisory committee recommended the use of a daily minimum increase in Fio_2 of 0.25 or a daily minimum increase in MAP of 4 cm H_2O for a pediatric VAC. This definition should be used in further studies to assess risk factors and preventive measures.

Given these data and the overwhelming concern with the current surveillance definition, it seems probable that there will soon be a shift in the surveillance of pediatric VAP to something consistent with the VAE surveillance now used by adult institutions. The utility of a more objective surveillance definition that identifies more than just VAP may help enhance prevention strategies and better anticipate outcomes in these patients.

ANTIBIOTIC STEWARDSHIP FOR IVAC COMPLICATIONS AND VAP

While optimizing the surveillance and diagnostic criteria for IVAC and VAP, pharmacists can focus on antimicrobial stewardship for these health care–associated infections. The primary goal is to enhance clinical outcomes while minimizing any undue consequences (Dellit 2007). Antimicrobial stewardship in IVAC and VAP can be achieved through several of the standard strategies, including implementing institutional guidelines or clinical pathways, minimizing combination therapy when appropriate, de-escalating therapy, and optimizing therapy duration, depending on the diagnosis and culture data. Institutional guidelines and clinical pathways considering the diagnostic criteria for IVAC and VAP, and an understanding of institution and local bacterial resistance patterns, can help facilitate the use of appropriate but not overly broad empiric antimicrobial therapy, pending culture results.

Use of combination therapy for either empiric or targeted therapy is a management strategy with more questions

than answers. Use of combination therapy has long been recommended as a method to prevent the emergence of resistance, but evidence to support the routine use of this strategy is lacking (Dellit 2007). However, use of combination therapy for empiric coverage may be appropriate in certain instances.

At the time of publication, current guidelines for adults with VAP recommend empiric combination therapy for patients at risk of multidrug-resistant bacterial pathogens; however, this set of guidelines is now more than 10 years old (ATS 2005). Recently, two studies evaluated the outcomes for pediatric patients with gram-negative bacteremia treated with combination antibiotics versus monotherapy. Neither study found improved time to bacteremia resolution or mortality with empiric combination therapy compared with monotherapy (Berkowitz 2015; Sick 2014).

Survival benefit was identified in one study of patients with multidrug-resistant gram-negative organisms (MDRGN), leading the authors to conclude that in patients with risk factors for MDRGN, empiric combination therapy may be beneficial. Risk factors for MDRGN were a history of colonization or infection with MDRGN, exposure to broad-spectrum antibiotic therapy in the past 30 days, prolonged current hospitalization, or a high prevalence of MDRGN in the community (Sick 2014). This list is much less extensive than that provided in the adult VAP guidelines.

An assessment of antibiotic duration in VAT in pediatric patients identified an increased risk of subsequent development of colonization or infection with a multidrug-resistant organism in patients receiving combination therapy (Tamma 2011). Given these data, as well as the lack of pediatric VAP guidelines, the outdated nature of the adult VAP guidelines, and the risk of common combination agents (particularly aminoglycosides), it seems prudent for pharmacists and other health care providers to judiciously consider which patients should receive empiric combination therapy. Furthermore, therapy de-escalation to the narrowest-spectrum agent(s) should occur once culture and sensitivity data are available. Therapy de-escalation is often hindered by the rate-limiting step of culture speciation and susceptibility data. Progress in developing rapid diagnostic testing that will provide both organism and susceptibility for respiratory specimens will facilitate earlier optimization of therapy.

Clarifying the IVAC being treated, especially when considering therapy for VAT versus VAP, can optimize the therapy duration provided. A retrospective, cohort study of pediatric patients with clinically diagnosed VAT compared the outcome of progression with hospital-acquired pneumonia (HAP) or VAP for prolonged (≥ 7 days) versus short (< 7 days) courses of antibiotic therapy. Prolonged courses of antibiotics did not provide a protective effect for progression to HAP or VAP. Patients who received prolonged courses of antibiotics were more likely to develop an infection or colonization with a multidrug-resistant organism (Tamma 2011). These data support that courses of therapy less than 7 days may be appropriate in patients with signs and symptoms consistent with VAT.

Pharmacists can intervene to optimize duration of therapy in patients with VAP. No pediatric data comparing durations of antibiotics for VAP are available; however, one randomized, prospective, double-blind study compared treatment durations for VAP in adult patients. Patients were randomized to receive 8 or 15 days of an antibiotic regimen chosen by the treating physician. No difference was found in mortality, recurrent infections, ventilator-free days, organ failure–free days, or length of ICU stay between the two treatment groups. However, the 8-day group had significantly more antibiotic-free days, as would be expected. In patients with nonfermenting gram-negative organisms (e.g., *Pseudomonas, Acinetobacter*), the risk of pulmonary infection recurrence was higher in the 8-day group; thus, for this group, the noninferiority of 8 days could not be confirmed (Chastre 2003).

Despite these data, it is reasonable to reassess patients with nonfermenting gram-negative organisms at 8 days of therapy to determine whether, given the patient's clinical improvement and status, the treatment duration is appropriate. For all other patients with VAP having clinical improvement, 8 days is a reasonable therapy duration.

STRATEGIES FOR PREVENTION OF VAES

As with all health care–associated conditions, prevention is key. To this point, prevention strategies for VAE are focused on preventing infectious-related complications. As surveillance shifts to include noninfectious VAE, expanded surveillance will allow for the implementation of prevention strategies for VAC. Improved surveillance may also help with determining methods to prevent progression to IVAC and VAP/PVAP. Prevention includes a combination of reducing modifiable risk factors (Box 1-2), when possible, and implementing prevention bundles (Liu 2013; Foglia 2007).

Of the potentially modifiable risk factors that have been identified, only the need for reintubation or self-extubation, steroid administration, bloodstream infection, prior antibiotic therapy, bronchoscopy, and presence of a genetic syndrome were risk factors in a meta-analysis of VAP in the PICU (Lui 2013). Increased risk with the administration of acid-suppressive therapy has been somewhat controversial. Although there is a known increased risk of community-acquired pneumonia with proton pump inhibitor therapy, data for increased risk of VAP in adult patients have been inconsistent (Plummer 2014). It is theorized that when the potentially immune protective effects of gastric acid are neutralized with acid-suppressive therapy, patients are at an increased risk of bacterial growth in their gastric contents, which may heighten the risk of pneumonia during periods of aspiration.

Patient Care Scenario

A 13-month-old boy born at 28 weeks' gestation has a medical history that includes chronic lung disease of prematurity and pulmonary hypertension. He presents to the PICU with respiratory failure secondary to respiratory syncytial virus requiring mechanical ventilation. He was discharged from the neonatal ICU at 3 months of age and has not been readmitted; he has no recent antibiotic exposure. During the first 48 hours of admission, he develops worsening respiratory status, and he is given a diagnosis of severe ARDS. On day 6 of mechanical ventilation, his temperature is 101.7°F (38.7°C), and chest radiography reveals a new infiltrate. Because of concern for developing VAP, a mini-BAL is obtained. Considering the risk of potential drug-resistant organisms and the tenets of antimicrobial stewardship, what is the best empiric antibiotic coverage to initiate?

ANSWER

The best empiric antibiotic coverage in this patient would be an antipseudomonal β-lactam such as cefepime or piperacillin/tazobactam plus vancomycin. Given the duration of hospitalization, the patient would potentially be at risk of resistant organisms. Although duration of hospitalization may place the patient at risk of resistant organisms, data do not support the routine use of combination empiric therapy for gram-negative organisms, most commonly the addition of an aminoglycoside. Outcomes data in pediatric bacteremia support consideration of combination therapy in patients with a history of colonization or infection with MDRGN, exposure to broad-spectrum antibiotic therapy in the past 30 days, prolonged current hospitalization, or a high prevalence of MDRGN in the community. This patient does not have these risk factors. As well, data do not support that combination therapy is a strategy that prevents the development of resistance.

1. **Berkowitz NM, Spaeder MC, DeBiasi RL, et al. Empiric monotherapy versus combination therapy for Enterobacteriaceae bacteremia in children. Pediatr Infect Dis J 2015;34:1203-6.**
2. **Sick AC, Tschudin-Sutter S, Turnbull AE, et al. Empiric combination therapy for gram-negative bacteremia. Pediatrics 2014;133:1-8.**
3. **Dellit TH, Owens RC, McGowan JE, et al. Infectious Diseases Society of America and the Society of Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. CID 2007;44:159-77.**

Box 1-2. Potentially Modifiable Factors That Increase VAP Risk[a]

- Acid-suppressive therapy
- Bloodstream infection[b]
- Bronchoscopy[b]
- Continuous enteral nutrition
- Mechanical ventilation and duration > 3 days
- Need for reintubation or self-extubation[b]
- Neuromuscular blockade
- Prior antibiotic therapy[b]
- Steroid administration[b]
- Supine positioning
- Transfusion
- Transport out of PICU
- Trauma
- Uncuffed endotracheal tube

[a]As identified in both adult and pediatric studies.

[b]Identified as a risk factor in a meta-analysis of pediatric VAP studies.

Box 1-3. Example of a Pediatric VAP Prevention Bundle

Prevent colonization of the oropharynx, stomach, and sinuses

- Change ventilator circuit and in-line suction only when visibly soiled
- Drain condensation from the ventilator circuit every 2–4 hr
- Rinse oral suction device after use; then store in a nonsealed plastic bag
- Use hand hygiene before and after ventilator circuit contact
- Wear gown when caring for patient if soiling from respiratory secretions is expected
- Provide mouth care every 2–4 hr

Prevent aspiration of contaminated secretions

- Elevate head of bed 30–45 degrees
- Drain ventilator circuit before repositioning
- In patients > 12 yr, use endotracheal tube with dorsal lumen, when possible

Adapted from: Bigham MT, Amato R, Bondurrant P, et al. Ventilator-associated pneumonia in the pediatric ICU: characterizing the problem and implementing a sustainable solution. J Pediatr 2009;154:582-7.

Administration of histamine-2 receptor antagonists or proton pump inhibitors was not associated with an increased risk of VAP in the aforementioned meta-analysis (Lui 2013).

The Institute for Healthcare Improvement (IHI) offers ventilator bundle recommendations, including semirecumbent positioning (elevating head of bed 30–45 degrees), daily sedation holidays and assessment of extubation readiness, prophylaxis against SRMD, VTE prophylaxis, and oral hygiene with chlorhexidine. Despite the potential increased risk of VAP with acid-suppressive therapy, the IHI ventilator bundle recommends that prophylaxis against SRMD be used in mechanically ventilated patients when the benefits outweigh the risks (IHI 2012). Ventilator-associated pneumonia bundles decrease the risk of VAP in pediatric patients, and one such

bundle reduced hospital cost by about $2.5 million over 2 fiscal years (Brilli 2008). One evaluated bundle (Box 1-3) reduced the rate of VAP from 5.6 cases to 0.3 cases per 1000 ventilator-days (Bigham 2009).

As with all prevention strategies, sustaining the use of the prevention bundle is of utmost importance. Compliance with the various components of the bundle described in the text that follows waned to 78%–100% 2 years after implementation, thus delineating the need for continued follow-up and assessment of compliance to ensure persistence with prevention strategies.

CONCLUSION

Pulmonary morbidities in pediatric patients are significant and can lead to poor outcomes and death. Unfortunately, in ARDS, pulmonary-specific pharmacotherapies have proven less than successful at altering clinical outcomes. For corticosteroids, pediatric data are lacking, and the pediatric pharmacist must have a working knowledge of adult data to help discern corticosteroid use. Similarly, with VAE and the shift in the surveillance process, which is likely to affect pediatric patients in the near future, pharmacists must understand the reasons for this shift as well as the new conditions to be considered. Pharmacists should be actively involved in VAP prevention strategies and in optimizing treatment in patients who develop IVAC or VAP.

Practice Points

When designing evidence-based pharmacotherapy regimens for ARDS, pharmacy practitioners should consider the following:

- **Intensive assessment of exogenous surfactant products has not resulted in significant improvements in patient outcomes.**
- **An ongoing study is assessing the effect of exogenous surfactant on outcomes in the leukemia and stem cell transplant populations. Previous studies have alluded to the potential benefit in this population; thus, cautious consideration and risk-benefit analysis may be considered.**
- **In the absence of pediatric data, cautious consideration of glucocorticoid use in both early and late phases of ARDS may be evaluated on a patient-by-patient basis.**
- **Pending further data, glucocorticoids should be avoided for ARDS secondary to influenza or in those whose onset of disease was more than 13 days before initiation of therapy.**

The pharmacist's role in the care of PICU patients results in the need to:

- **Have an understanding of health care–associated infection surveillance, including the concerns surrounding the current VAP surveillance module**
- **Use understanding of antibiotic pharmacotherapy, geographic resistance patterns, and tenets of antimicrobial stewardship to apply the principles of judicious empiric and targeted antibiotic use for VAP and VAT in this population**
- **Participate in developing prevention strategies and programs for health care–associated conditions, including VAP**

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Self-Assessment Questions

Questions 1–7 pertain to the following case.

E.S. is a 5-year-old boy (height 42 inches, weight 31 kg) who received a stem cell transplant for hemophagocytic lymphohistiocytosis. However, despite initial engraftment, E.S. experienced graft rejection. He. is admitted to the PICU with signs and symptoms consistent with septic shock. His blood cultures are positive for gram-negative rods, and he is initiated on meropenem and amikacin. On PICU day 1, despite bilevel positive airway pressure (BiPAP), his respiratory status continues to deteriorate. E.S. is intubated for impending respiratory failure. He is initiated on continuous infusion fentanyl and midazolam for pain and sedation management during mechanical ventilation. He is maintained NPO (nothing by mouth) and is initiated on intravenous pantoprazole for stress-related mucosal disease (SRMD) prophylaxis. Over the first 24 hours in the PICU, his oxygenation continues to worsen. Morning chest radiography is consistent with new bilateral infiltrates. His ventilator settings and arterial blood gas are as follows:

Ventilator settings	Arterial blood gas
SIMV-VC Rate = 18 Fio_2 = 0.55 Ti = 0.8 Positive inspiratory pressure (PIP) = 41 cm H_2O Set Vt = 200 mL Positive end-expiratory pressure (PEEP) = 10 cm H_2O PS = 10 cm H_2O Paw = 18 cm H_2O	pH = 7.26 Pco_2 = 61 Pao_2 = 99 Bicarbonate (calculated) = 27 Sao_2 = 97

Blood culture data: Three of three sets of cultures are positive for *Klebsiella pneumonia* – susceptibility data as follows:

Susceptible	Intermediate	Resistant
Amikacin ([MIC] = 16)	Imipenem (MIC = 2) Tigecycline (MIC = 4)	Cefepime (MIC ≥ 64) Gentamicin (MIC ≥ 16) Levofloxacin (MIC ≥ 8) Meropenem (MIC = 8) Piperacillin/tazobactam (MIC ≥ 128) Tobramycin (MIC ≥ 16)

1. Given his clinical signs and symptoms and his clinical and laboratory data, which one of the following best describes E.S.'s diagnosis?
   A. Oxygenation index (OI) = 10, moderate pediatric acute respiratory distress syndrome (PARDS)
   B. OI = 10, severe PARDS
   C. PF ratio less than 200 and PEEP of 5 cm H_2O or greater, moderate PARDS
   D. PF ratio less than 200 and PEEP of 5 cm H_2O or greater, severe PARDS

2. On day 2 of intubation and mechanical ventilation, E.S.'s oxygenation continues to worsen; his OI is now 18, and the team is considering a transition to high-frequency oscillatory ventilation (HFOV). Because of the patient's worsening clinical status, the PICU attending would like to discuss administering calfactant. Which one of the following best justifies administering a single dose of calfactant by endotracheal tube for E.S.?
   A. His oxygenation status is worsening, and surfactant has consistently shown sustained improvements in oxygenation.
   B. With an immunocompromised host, surfactant has shown a potential improvement in clinical outcomes.
   C. Because he developed acute respiratory distress syndrome (ARDS) from an indirect lung injury, surfactant is most likely to be beneficial.
   D. With the impending need for HFOV, surfactant may be used as a strategy to prevent the need to escalate mechanical ventilation support.

3. On day 8 of mechanical ventilation, E.S.'s oxygenation has not improved clinically, and his PARDS is still categorized as severe. Which one of the following drugs is best to recommend for E.S.?
   A. Calfactant 80 mL/m^2 by endotracheal tube once
   B. Methylprednisolone 60 mg intravenously every 12 hours
   C. Inhaled nitric oxide 20 ppm continuous
   D. Albuterol 2.5 mg nebulized every 4 hours

4. Which one of the following strategies would best prevent ventilator-associated pneumonia (VAP) in E.S.?
   A. Discontinue pantoprazole, assess safety of daily sedation awakening, elevate head of the bed to 30 degrees, change ventilator circuit every 24 hours, and provide routine oral care with chlorhexidine.
   B. Continue pantoprazole, assess safety of daily sedation awakening, elevate head of the bed to 15 degrees, change ventilator circuit every 24 hours, and provide routine oral care with chlorhexidine.
   C. Continue pantoprazole, assess safety of daily sedation awakening, elevate head of the bed to 30 degrees, change ventilator circuit when visibly soiled, and provide routine oral care with chlorhexidine.
   D. Discontinue pantoprazole, assess safety of daily sedation awakening, elevate head of the bed to 15 degrees, change ventilator circuit when visibly soiled, and provide routine oral care with chlorhexidine.

5. On day 14 of mechanical ventilation, E.S. develops a new consolidation on chest radiography. Despite previous improvements in oxygenation, his Fio_2 requirement is increasing this morning, and he is febrile (temperature 102.2°F [39°C]). His WBC is 1.57 x 10^3 cells/mm^3. A mini-BAL is obtained, and Gram stain shows few WBCs and rare gram-negative rods. Which one of the following best describes E.S.'s clinical criteria for a diagnosis of VAP?

   A. New consolidation on chest radiography, worsening gas exchange, febrile
   B. Worsening gas exchange, febrile, leukopenia
   C. New consolidation on chest radiograph, worsening gas exchange, mini-BAL Gram stain positive for gram-negative rods
   D. Worsening gas exchange, febrile, mini-BAL Gram stain positive for gram-negative rods

6. Given his historical data and the new information, which one of the following regimens is most appropriate to recommend for E.S.?

   A. Cefepime and amikacin
   B. Imipenem/cilastatin and amikacin
   C. Cefepime and tobramycin
   D. Imipenem/cilastatin and tobramycin

7. On hospitalization day 16 for E.S., the culture results from the mini-BAL done 2 days earlier return:

   Mini-BAL: Many WBCs, no epithelial cells > 100,000 CFU/mL *Klebsiella pneumoniae* Susceptibilities:
   Susceptible: Amikacin (MIC = 2), cefepime (MIC = 1), ciprofloxacin (MIC = 1), levofloxacin (MIC = 1), meropenem (MIC ≤ 0.25), piperacillin/tazobactam (MIC = 16)
   Resistant: Ceftriaxone, gentamicin (MIC ≥ 16), tobramycin (MIC ≥ 16)
   During this period, E.S.'s oxygenation has improved clinically. Given his clinical status and culture data, which one of the following is best to recommend for E.S.?

   A. Ciprofloxacin, complete a total antibiotic course of 8 days
   B. Ciprofloxacin, complete a total antibiotic course of 15 days
   C. Cefepime, complete a total antibiotic course of 8 days
   D. Cefepime, complete a total antibiotic course of 15 days

Questions 8–10 pertain to the following case.

K.M. is a 2-year-old girl (weight 15 kg) with a medical history positive for trisomy 21, complete atrioventricular canal after repair at 6 months, and mild pulmonary hypertension. She presents to the PICU with respiratory distress requiring full face mask BiPAP, for which she is receiving dexmedetomidine infusion to enhance tolerance of therapy. Her BiPAP settings are 10 cm H_2O/6 cm H_2O with an Fio_2 of 60%, and her current Sao_2 is 85%. K.M.'s respiratory viral diagnostics are positive for influenza A.

8. Which one of the following best describes K.M.'s oxygenation impairment?

   A. PF ratio = 140
   B. SF ratio = 140
   C. PF ratio = 7
   D. SF ratio = 7

9. K.M.'s condition continues to worsen on BiPAP, and she requires intubation for mechanical ventilation. Given her OI, she is classified as having severe PARDS. The attending physician requests beractant administration for PARDS secondary to pneumonia. Which one of the following responses to this request would be best for K.M.?

   A. Beractant is not FDA labeled for this indication; the medical team should submit an emergency Investigational New Drug application before use.
   B. Exogenous surfactant does not improve clinical outcomes and is not recommended for use in PARDS.
   C. Calfactant is a better choice of surfactant product than beractant to treat ARDS.
   D. Exogenous surfactant cannot be used beyond the neonatal period because of the excessive instillation volume.

10. On intubation day 14, K.M. continues to require significant ventilator support, and the team would like to initiate methylprednisolone by "the Meduri" protocol. Which one of the following is best to recommend for K.M.?

    A. Do not use corticosteroids in this patient with ARDS.
    B. Use an alternative dosing protocol that has been reported in pediatric patients.
    C. Use hydrocortisone at doses equivalent to the methylprednisolone dosing protocol.
    D. Provide frequent blood glucose monitoring.

11. Which one of the following statements best describes the risk and benefits of using corticosteroids in adult patients with ARDS?

    A. High-dose methylprednisolone may be beneficial in the prevention of ARDS, but patients should be closely monitored for the development of new infections.

B. Low- to moderate-dose methylprednisolone is associated with a higher risk of death when used in the late phase of ARDS and places patients at an increased risk of infections.
C. High-dose methylprednisolone may be beneficial in the prevention of ARDS, but patients should be closely monitored for neuromuscular weakness.
D. Low- to moderate-dose methylprednisolone may beneficial in the late phase of ARDS when initiated before day 14 of illness, but patients should be monitored closely for neuromuscular weakness.

12. A 15-year-old girl is admitted to an adult ICU after a coiling arteriovenous malformation; she remains intubated. Which one of the following is the best quality reporting approach for this patient?

A. Given her age, reporting should occur by the device-related pneumonia module. Surveillance reporting begins on day 1 of mechanical ventilation.
B. Given her age, reporting should occur by the device-related pneumonia module. Surveillance reporting begins on day 3 of mechanical ventilation.
C. Given her location, reporting should occur by the device-related ventilator-associated event (VAE) module. Surveillance reporting begins on day 1 of mechanical ventilation.
D. Given her location, reporting should occur by the device-related VAE module. Surveillance reporting begins on day 3 of mechanical ventilation.

13. Which one of the following statements best supports reevaluating the current reporting structure for the device-related pneumonia module used in pediatric units?

A. Clinical criteria used for surveillance reporting are consistently documented in the medical record.
B. Change in oxygenation after a period of stability is an objective measure of clinical deterioration.
C. Chest radiography is likely to accurately identify VAP.
D. Clinical criteria used for surveillance reporting are objective.

Questions 14–16 pertain to the following case.

K.N. is a 19-month-old boy (weight 8.3 kg) with a medical history of very long-chain acyl-coenzyme A dehydrogenase deficiency. He was admitted to the PICU for respiratory failure secondary to respiratory syncytial virus (RSV) bronchiolitis. He was subsequently intubated and placed on continuous infusions of fentanyl and midazolam for pain and sedation management. Before this hospitalization, K.N. had been relatively healthy. His home acid suppression of ranitidine was continued. He remained intubated for a prolonged course because of weakness, and the care team planned to place a tracheostomy. Now, on day 16 of mechanical ventilation, 2 days before his scheduled tracheostomy, K.N. is febrile (temperature 101.3°F [38.5°C]). The volume and thickness of his secretions have not changed. A mini-BAL is sent. His chest radiography is stable with no signs of new infiltrate. K.N.'s WBC is 10.5×10^3 cells/mm^3. His ventilator parameters remain stable, and K.N. continues to oxygenate well.

14. Given his clinical signs and symptoms, which one of the following diagnoses is K.N. most likely to receive?

A. Ventilator-associated tracheobronchitis
B. Ventilator-associated condition (VAC)
C. VAP
D. Infection-related VAC (IVAC)

15. The Gram stain from K.N.'s mini-BAL specimen shows moderate WBC and gram-negative rods. The team wishes to initiate antibiotic therapy, pending culture results. K.N. has not received any antimicrobial therapy during this hospitalization. Which one of the following is the most appropriate empiric antibiotic regimen for K.N?

A. Ceftriaxone plus gentamicin
B. Ceftriaxone
C. Cefepime plus gentamicin
D. Cefepime

16. On day 2 of K.N.'s antimicrobial therapy, the following culture data become available:

Mini-BAL: Moderate WBCs, no epithelial cells
> 10,000 CFU/mL *Pseudomonas aeruginosa*
Pan-susceptible
K.N.'s chest radiography continues to be without signs of a pneumonia, and his oxygenation has not worsened. Which one of the following therapy durations (in days) is best to recommend for K.N.?

A. 5
B. 10
C. 15
D. 21

17. Empiric combination therapy for gram-negative organisms may not be needed in all patients initiated on antibiotic therapy for IVACs or VAP. Assuming a low risk of MDRGN (multidrug-resistant gram-negative organisms) from the community, in which one of the following patients would combination empiric coverage best be initiated?

A. A previously healthy 7-month-old boy, mechanically ventilated 3 days for respiratory failure secondary to RSV bronchiolitis
B. A previously healthy 14-year-old boy, mechanically ventilated for 6 days secondary to a traumatic brain injury

C. A 6-year-old girl receiving induction chemotherapy for acute lymphocytic leukemia, mechanically ventilated for 8 days secondary to septic shock
D. A 12-year-old girl with asthma, mechanically ventilated for 2 days secondary to an acute asthma exacerbation

18. The new model of device-related event reporting for ventilated adult patients is a multi-tier approach for which surveillance is initiated on the basis of changes in oxygenation versus change in chest radiography. A similar set of surveillance definitions will likely be developed for pediatric patients, with the recommendation to use mean airway pressures (MAPs) instead of PEEP. Which one of the following best justifies this change?

A. MAP allows the surveillance definition to be used in the evaluation of patients receiving HFOV.
B. PEEP is a better marker of lung compliance.
C. MAP is more affected by worsening gas exchange in pediatric patients.
D. PEEP use is inconsistent among pediatric intensivists.

Questions 19 and 20 pertain to the following case.

Homefield Children's Hospital is part of a large health system. As the PICU pharmacist, you serve on a quality committee responsible for developing a VAP prevention bundle. The working group's plan is to incorporate bundle recommendations from both IHI and the literature. You have been tasked with two areas of the bundle. First, as a means of mitigating modifiable risk factors, you are asked to identify patients in whom discontinuing SRMD prophylaxis is acceptable. Second, you are asked to develop a plan to identify which pediatric patients should receive venous thromboembolism (VTE) prophylaxis.

19. In which one of the following Homefield patients would it be most appropriate to discontinue SRMD prophylaxis while the patient is receiving mechanical ventilation?

A. A patient who sustained multiple traumatic injuries, including a severe traumatic brain injury, who is receiving continuous jejunal feeding
B. A patient with chronic respiratory failure, receiving gastric feeding, who has not received acid-suppressive therapy chronically
C. A patient with Guillain-Barré syndrome receiving pulse dose steroids (methylprednisolone 1000 mg x 3 doses) and gastric feeding
D. A patient with acute-on-chronic hepatic failure who has now developed acute kidney injury, receiving jejunal feeding

20. Which one of the following responses is best to give the Homefield Hospital working group regarding the request to identify patients who should receive VTE prophylaxis?

A. No patients; pediatric patients are not at an increased risk of VTE.
B. No patients; although some might be at an increased risk of VTE, no data support that prophylaxis mitigates this risk in pediatric patients.
C. Adolescent patients with known risk factors for developing VTE and no contraindications: should receive at least mechanical prophylaxis.
D. All immobilized pediatric patients as long as they have a normal platelet count.