Bronchoscopy With N-Acetylcysteine Lavage in Severe Respiratory Failure From Pertussis Infection

abstract

Pertussis is an illness that causes significant morbidity and mortality, especially in infants younger than 3 months old. In the most severe cases, it can cause pneumonia, respiratory failure, acute respiratory distress syndrome, pulmonary hypertension, and death. There are reports of using rescue extracorporeal membrane oxygenation (ECMO) as a rescue therapy. However, the mortality of ECMO with pertussis is higher than with other causes of pediatric respiratory failure. We report here the case of a 2-month-old boy with severe respiratory failure and pulmonary hypertension who satisfied ECMO criteria but was successfully treated with repeated bronchoscopy with instillation of N-acetylcysteine. Our patient’s respiratory failure was refractory to multiple therapies that have shown benefit in pediatric hypoxemic respiratory failure, including open lung strategies, prone positioning, intratracheal surfactant, and inhaled nitric oxide. Although pulmonary hypertension is a key factor in most cases of fatal pertussis, the adverse effects of hyperinflation and air leaks were more important in this patient’s clinical course. Because bronchiolar obstruction from inflammatory, mucous, and airway epithelial debris can be seen in severe pertussis, a regimen of repeated therapeutic bronchoscopy was initiated, and thick, inspissated secretions were retrieved. The patient’s airway obstruction gradually resolved, and he eventually recovered with minimal sequelae. Pediatrics 2013;132:e1418–e1423

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KEY WORDS
pertussis, extracorporeal membrane oxygenation, bronchoscopy, respiratory insufficiency, respiratory distress syndrome

ABBREVIATIONS
ARDS—acute respiratory distress syndrome
ECMO—extracorporeal membrane oxygenation
FiO2—fraction of inspired oxygen
O2I—oxygenation index
WBC—white blood cell

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Pertussis, or whooping cough, is an infection caused by the Gram-negative bacterium *Bordatella pertussis*. Severe pertussis can lead to apnea, pneumonia, pulmonary hypertension, hypoxic respiratory failure, and death. For life-threatening pertussis, extracorporeal membrane oxygenation (ECMO) has been used as a therapy, as it has in other causes of severe pediatric respiratory failure. However, the mortality rate for children who required ECMO for pertussis in the ELSO (Extracorporeal Life Support) registry from 1993 to 2007 was 61%, compared with 43% for all causes of respiratory failure.1 Because of the poor outcome, treatment strategies for severe pertussis other than ECMO should be explored. We report a case of a 2-month-old infant with pertussis, pulmonary hypertension, and severe hypoxic respiratory failure who satisfied indications for requiring ECMO but was successfully treated with repeated bronchoscopy with suctioning and administration of N-acetylcysteine.

**PATIENT PRESENTATION**

A full-term, 2-month-old, 4.7-kg, previously healthy boy was initially diagnosed with bronchiolitis by his primary care pediatrician. He was taken to the emergency department because of increased work of breathing and decreased oral intake. At the time of diagnosis, he had a history of nasal congestion for 10 days and cough for 5 days. He had a low-grade temperature, and there were sick contacts at home. Chest radiograph showed perihilar infiltrates. His initial white blood cell (WBC) count was 48 000/µL with lymphocyte predominance. A nasopharyngeal swab was positive for *Bordatella pertussis*, so he was started on macrolide antibiotics. He was admitted to the PICU for respiratory insufficiency and was intubated. Echocardiography showed elevated right ventricular pressure (approximately one-half to two-thirds of systemic pressure), so he was started on inhaled nitric oxide for pulmonary hypertension. He developed acute respiratory distress syndrome (ARDS) and was given 2 doses of intratracheal surfactant. Because of the severity of his respiratory illness, he was transferred to our facility because of the possibility of requiring ECMO.

Upon arrival to our facility, his oxygenation was adequate. His PaO2 was >300 mm Hg with a mean airway pressure of 14 and a fraction of inspired oxygen (FiO2) of 0.4 on conventional ventilation, which corresponded to an oxygenation index (OI = 100 × FiO2 × mean airway pressure/PaO2) of ∼2. However, his WBC count continued to increase, to as high as 70 000 cells per µL. Several days into his course, his oxygenation and ventilation worsened. His PaO2 was 55 mm Hg with a mean airway pressure of 15 and an FiO2 of 1.0 on conventional ventilation, which corresponded to an OI of ∼30. He also had evidence of secondary pulmonary infection with *Enterobacter aerogenes* and *Pseudomonas fluorescens*. He was treated with broad-spectrum antibiotics in addition to a macrolide for pertussis. In subsequent days his oxygenation continued to worsen, and he was placed on high-frequency oscillatory ventilation. His PaO2 was 60 mm Hg with a mean airway pressure of 24 and an FiO2 of 1.0, which corresponded to an OI of 40. Chest radiograph showed diffuse bilateral air space disease with hyperinflation. Mucolytic therapy was started with nebulized N-acetylcysteine because the patient had thick, copious secretions. Other therapies he received included systemic steroids for ARDS, double-volume whole-blood exchange transfusion for severe pertussis, and 2 subsequent doses of intratracheal surfactant. He also received neuromuscular blockade and was kept heavily sedated. He did not develop acute kidney injury, shock, coagulopathy, encephalopathy, or any other significant derangement of nonpulmonary organ systems. He developed worsening hyperinflation, pneumothorax, and pneumomediastinum and his oxygen saturations decreased to <80%. Chest tubes and a mediastinal tube were placed, but his OI remained >50 (Fig 1). At that point, ECMO was considered. However, consistent with the practice in our institution, he was not considered an ECMO candidate at the discretion of the consulting surgeons because of his relatively long duration of illness and secondary bacterial infections. Considering the failure of high-frequency oscillatory ventilation, the patient was placed back on conventional ventilation.

Despite lower mean airway pressures, the patient’s hyperinflation persisted, although there was a modest improvement in his grave status. Administration of mucolytic therapy given at the tracheal level was not successful in clearing his lower airway secretions. Therapeutic bronchoscopy was then performed by using a technique previously described.2 The bronchoscope was wedged in a subsegmental bronchus, and lavage fluid containing equal parts of N-acetylcysteine and 0.9% NaCl was instilled and suctioned. Each lobar bronchus was entered and lavaged as tolerated by the patient’s oxygenation. After the lavage, more secretions were retrieved during routine suctioning, and the chest radiograph after the procedure revealed modestly improved hyperinflation (Fig 2 A and B). Over the next 2 weeks, therapeutic bronchoscopy was routinely performed with a similar procedure of lavage every 2 to 3 days. During that time, his hyperinflation, oxygenation, and lung compliance continued to improve, and he was weaned from the ventilator. One week after the final bronchoscopy, he was successfully extubated. He was transferred to the hospital floor a total of 5 weeks after his
PICU admission and eventually discharged from the hospital with a completely normal neurologic examination, taking all of his feedings by mouth, and requiring 0.5 L of oxygen by nasal cannula.

DISCUSSION

Before 1940, pertussis was one of the major causes of childhood mortality. Pertussis vaccination has been one of the greatest triumphs of public health history, because morbidity and mortality of pertussis decreased instantaneously and dramatically.3,4 Because pertussis and other vaccine-preventable childhood illnesses have become rare, the focus of parental concern has shifted from preventing diseases toward vaccine safety. Consequently, children who have not received vaccines because they are too young or because of parental refusal are susceptible to morbidity and mortality associated with pertussis.5 The former group has proven to be particularly vulnerable, in children hospitalized in the United States with pertussis between 1993 and 2004, 95% of infants requiring mechanical ventilation and all of the infants who died were <3 months old.6

Pneumonia, apnea, and episodic cyanosis are the most common complications of pertussis.7 However, the most severe cases can involve respiratory failure, ARDS, pulmonary hypertension, and death. Severe leukocytosis may be a predictor of pulmonary hypertension and mortality in pertussis infection.8 Our patient suffered from pulmonary hypertension and ARDS, which is defined as a Paco2:Fio2 ratio of <200, bilateral infiltrates on chest radiograph, and noncardiogenic pulmonary edema.9 The “open lung strategy” is the mainstay of evidence-based ventilator management of pediatric ARDS and generally involves applying adequate mean airway pressure to maintain functional residual capacity, permissive hypercapnia, and limitation of peak inspiratory pressure, Fio2 and tidal volume.10 Other strategies that have shown benefit in ARDS and hypoxemic respiratory failure include prone positioning, intratracheal surfactant, inhaled nitric oxide, and high-frequency ventilation.11 Despite receiving all of these strategies, our patient continued to deteriorate. We considered placing him on ECMO, which has been used as a rescue strategy for severe neonatal and pediatric respiratory failure.1,12 Selection criteria for ECMO for pediatric respiratory failure have been proposed, including an Fio2 >0.6, mean airway pressure >20 cm H2O, presence of air leak or barotrauma, a markedly and/or persistently elevated OI, and evidence of reversibility of disease.13 These criteria were developed on the basis of predictors of mortality of pediatric respiratory failure.14,15 Our patient fulfilled all of these criteria. In addition to other causes of respiratory failure, ECMO has been successfully used in pertussis, including with severe leukocytosis and pulmonary hypertension.16,17 However, queries of the ELSO registry have shown much higher mortality rates and duration of ECMO for pertussis compared with all respiratory causes.1

The reason for this disparity is unclear but could be due to the relatively unique combination of respiratory failure and pulmonary hypertension outside of the newborn age group.

In addition to a severe oxygenation defect associated with ARDS, our patient exhibited hyperinflation, pneumothorax, pneumomediastinum, and impaired ventilation. These conditions could have been due to barotrauma caused by the high ventilator settings required to maintain oxygenation and ventilation. Another contributing factor to hyperinflation and air leaks could have been bronchiolar obstruction. In a recent study by Paddock et al,18 histopathologic examination of 14 infants with fatal pertussis revealed necrotizing bronchiolitis with luminal occlusion.
of bronchioles from necrotic debris, inflammatory cells, and denuded epithelium. N-acetylcysteine, which reduces the viscosity of mucus by splitting the disulfide bonds that link the mucoproteins, has been used as a mucolytic agent in adults and children with respiratory conditions associated with thick mucus such as cystic fibrosis, bronchitis, and bronchiectasis. Recombinant human DNase has also been used in acute and chronic respiratory conditions to reduce the viscosity of secretions, and mucolysis using bronchoscopically applied DNase in a patient with severe respiratory failure from pertussis similar to ours has been reported. We selected N-acetylcysteine as the mucolytic agent in our patient for several reasons. To our knowledge, there are no studies comparing the efficacy of N-acetylcysteine to DNase or saline. Because few WBCs were seen in our patient's bronchoalveolar lavage fluid, and because his WBC count had decreased to normal, the mechanism of DNA inhibiting mucin proteolysis may not have been predominant. Furthermore, DNase was subject to restriction due to a drug shortage at the time.

During each bronchoscopy procedure, thick secretions were visualized, and more debris was retrieved after the instillation of N-acetylcysteine both during the procedure and during routine suctioning after the procedure. We observed improvement in oxygenation, ventilation, and hyperinflation after each bronchoscopy procedure. Although we attempted several other strategies, the patient did not have sustained improvement in the trajectory of his oxygenation and ventilation until we started to perform repeated bronchoscopy (Fig 3).

There are some important drawbacks to this case report. Although the patient's improvement was temporally related to the initiation of repeated bronchoscopy, there were several other factors that could have contributed to his good outcome. For example, the exchange transfusion and resulting leukoreduction may have attenuated the effects of pulmonary hypertension and hypoxemia, although the efficacy of this therapy in the literature is not conclusive. Our patient had several
different respiratory pathophysiologic processes, including mucous bronchiolar obstruction, ARDS, and air leaks. The degree to which each process affected oxygenation and ventilation is unclear, as is the efficacy of the different therapeutic strategies. For example, whereas early intratracheal surfactant may have attenuated the ARDS process, uneven surfactant distribution from inhomogeneous ventilation may have contributed to air leaks. Resolution of this process could have contributed to the recovery. Also, the time course and efficacy of the different ventilator strategies used in this patient are unclear. Although we used high-frequency oscillatory ventilation for lung recruitment in ARDS, and it can limit barotrauma and air leaks, it could have caused frequency-dependent worsening of dynamic hyperinflation, which can occur in patients with airway obstruction.27 The possibility that reverting to conventional ventilation contributed to his improvement cannot be ruled out, because there was a modest improvement in gas exchange even before bronchoscopy was initiated. However, it should be noted that the patient had previously failed that therapy.

In conclusion, our patient with severe respiratory failure from pertussis had failed most conventional strategies of ARDS management, including “open lung” strategies, high-frequency ventilation, intratracheal surfactant, and heavy sedation and neuromuscular blockade. He also received specific therapies for pertussis including antibiotics and whole-blood exchange and inhaled nitric oxide for pulmonary hypertension. Despite these therapies, he continued to worsen and faced either death or ECMO, which carries a particularly high mortality rate in pertussis. Therapeutic bronchoscopy with instillation of N-acetylcysteine may have contributed to his remarkable recovery and should be considered in patients with mucosal airway obstruction in pertussis.

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