

Pertussis Pneumonia, Hypoxemia, Hyperleukocytosis, and Pulmonary Hypertension: Improvement in Oxygenation After a Double Volume Exchange Transfusion

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ABSTRACT. A 3-month-old infant of 33 weeks' gestation was hospitalized with pneumonia caused by *Bordetella pertussis*. Respiratory insufficiency worsened, and on hospital day 3, there was severe pulmonary dysfunction (arterial oxygen pressure/fraction of inspired oxygen ratio: 120), extreme leukocytosis (white blood cell count 104 000/mm³), and severe pulmonary hypertension as assessed by 2-dimensional echocardiogram. A double volume exchange transfusion was performed to reduce the leukocyte mass. Oxygenation began to improve during the exchange and continued to improve over the ensuing 31 hours (arterial oxygen pressure/fraction of inspired oxygen ratio: 280). The white blood cell count fell dramatically after the exchange, and the rate of rise was slower after exchange therapy compared with preexchange. *Pediatrics* 2004;114:e264–e266. URL: <http://www.pediatrics.org/cgi/content/full/114/2/e264>; *Bordetella pertussis*, *pulmonary hypertension*, *hyperleukocytosis*, *extracorporeal life support*, *exchange transfusion*.

ABBREVIATIONS. PHT, pulmonary hypertension; ECLS, extracorporeal life support; WBC, white blood cell; F_{iO_2} , fraction of inspired oxygen; P_{aO_2} , arterial oxygen pressure; NO, nitric oxide.

The constellation of bronchopneumonia, extreme leukocytosis, refractory hypoxemia, and pulmonary hypertension (PHT) is well described in severe *Bordetella pertussis* infection in infants.^{1,2} The onset of refractory hypoxemia typically is rapid^{3,4} and responds poorly to advanced ventilation maneuvers, including high-frequency oscillatory ventilation, inhaled nitric oxide, and extracorporeal life support (ECLS).^{5,6} The mechanism of hypoxemia and pulmonary hypertension in this setting is undetermined; however, several lines of evidence support leukocyte thrombi as the cause. White blood cell (WBC) counts >100 000 in the setting of *B pertussis* pneumonia are associated with increased mortality.^{7,8} A leukocyte thrombus in a pulmonary venule has been reported in a fatal case of *B pertussis* pneumonia.³ Finally, respiratory distress has been described in adults and children with hyperleukocytosis secondary to leukemia.^{9,10} In the last setting,

respiratory distress has resolved after the application of techniques to reduce the leukocyte mass, including leukopheresis and exchange transfusion. We postulated that the application of a similar strategy to reduce leukocyte mass in the setting of *B pertussis* pneumonia, hypoxemia, and PHT may prevent additional thrombi formation and allow resolution of preexisting thrombi. We report the first use of a double volume exchange transfusion as a therapy for *B pertussis* pneumonia with PHT and hypoxemia and describe the improvements in oxygenation temporally associated with that therapy.

CASE REPORTS

A 3-month-old, 5-kg, white girl had been seen 3 times in the 16 days before admission for cough and rhinitis. She was prescribed albuterol and a 2-day course of prednisone when she first became ill, and nebulized albuterol was prescribed at 2 subsequent visits, all with minimal improvement. The patient was seen by her primary care physician and admitted to a local hospital with mild respiratory distress. Her physical examination was remarkable for temperature 101.1° F, heart rate 176 beats/min, respiratory rate 60 breaths/min, and oxygen saturation 96% with the fraction of inspired oxygen (F_{iO_2}) 0.27. Lung examination was significant for rales in all fields with a congested, "hacking" cough. The remainder of the examination was unremarkable. She had a WBC count of 41 800/mm³, with 68% lymphocytes and 26% neutrophils. Arterial blood gas showed a pH of 7.36, P_{CO_2} of 57 torr, and P_{O_2} of 53 torr. A chest radiograph showed an opacification of the right upper lobe. The patient was treated with ceftriaxone and azithromycin.

Her medical history includes preterm birth at 33 weeks via cesarean section as a result of placental abruption. She required mechanical ventilation for 1 week. Her total neonatal intensive care unit stay was 3 weeks. The patient had no surgical history and was not taking any medications. Immunizations given were the first dose of hepatitis B. Family history was significant for multiple family members with coughs of 10 to 20 days' duration.

The patient's condition rapidly worsened, necessitating endotracheal intubation. The postintubation arterial blood gas had a pH of 7.18, P_{CO_2} of 95 torr, and P_{O_2} of 85 torr on F_{iO_2} of 1.0.

The patient was referred to our intensive care unit with a presumptive diagnosis of *B pertussis* pneumonia and respiratory failure. On arrival, she was placed on pressure-control ventilation set at 24 cm of water, end expiratory pressure of 4 cm of water, with a rate of 30 breath/min and F_{iO_2} 1.0. Her temperature was 102° F, pulse was 189 beats/min, and blood pressure was 80/50 mm Hg. Lung examination demonstrated diffuse rales and wheezes throughout. Mottling and poor perfusion in her distal extremities responded to a 10-mL/kg bolus of 0.9% saline. Antibiotics were changed to piperacillin/tazobactam and azithromycin. Admission laboratory studies revealed a WBC count of 49 400/mm³ and a venous blood gas of pH 7.25, P_{CO_2} 70.3 torr, and P_{O_2} 38 torr. The F_{iO_2} was decreased to 0.50 within 4 hours of admission based on pulse oximetry. Initial tracheal aspirate showed very rare WBCs, rare Gram-positive cocci in pairs, and many Gram-negative rods. The tracheal culture grew mixed Gram-negative rods, predominately *Pseudomonas aeruginosa*, for

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which gentamicin was added on hospital day 4. Viral cultures of a tracheal aspirate using a shell amplification technique with milk lung mixed cells and human lung carcinoma cells were negative for respiratory syncytial virus; adenovirus; influenza A and B; and parainfluenza 1, 2, and 3. Culture of tracheal secretions on Bordet-Gengou media yielded no growth. Polymerase chain reaction analysis of tracheal secretions demonstrated DNA of *B pertussis*.

The patient's chest radiograph worsened over the next 3 days, with an increase in the right apical opacity and consolidation in the left apex. The patient had increasing ventilatory requirements necessitating a change to pressure-regulated volume control. Frequent coughing and desaturation episodes were managed with increasing doses of sedatives. Ultimately, she required continuous infusions of fentanyl, midazolam, and vecuronium to maintain adequate oxygenation and ventilation. The patient's Fio_2 requirement increased to 0.70 late on hospital day 2 in response to worsening oxygen saturations.

On hospital day 3 the patient's WBC count peaked at 104 000/ mm^3 . An echocardiogram demonstrated dilation of the right ventricle with tricuspid regurgitation, flattened ventricular septum, leftward bowing of the atrial septum, and suprasystemic right ventricular pressure. An arterial catheter was placed. Arterial blood gas analysis demonstrated significantly impaired oxygenation with a arterial oxygen pressure (PaO_2)/ Fio_2 ratio of 120. A repeat arterial blood gas ~3 hours later was essentially unchanged. Faced with the rapid progression of pulmonary dysfunction with severe pulmonary hypertension and the historically poor responses to aggressive support once hypotension and shock have occurred, we proposed a strategy to reduce the leukocyte mass. A double volume exchange transfusion was used, rather than leukopheresis, based on rapid availability within our institution. Parental consent was obtained.

The patient underwent an 800-mL double volume exchange transfusion, in 20-mL aliquots, using cytomegalovirus-negative, leukophor-filtered, irradiated packed red blood cells reconstituted to an estimated hematocrit of 45%. The procedure was performed in ~2 hours and was well tolerated. Hypocalcemia was treated with a total of 180 mg/kg calcium chloride during the exchange. The postexchange WBC count fell to 15 200/ mm^3 . The WBC count rose postexchange, peaking on post exchange day 3 at 76 500/ mm^3 ; however, the rate of rise was significantly slower than preexchange transfusion (data not shown).

The changes in oxygenation are presented in Fig 1. $\text{PaO}_2/\text{Fio}_2$ ratios during the 3 hours before exchange were stable and consistent with severe respiratory dysfunction (120 and 122). Midway through the exchange, the $\text{PaO}_2/\text{Fio}_2$ ratio had begun to improve (168). With the exception of 1 measurement obtained during a cyanotic spell at 7 hours postexchange, oxygenation continued to improve over the next 31 hours. Mean airway pressure remained 13 to 14 cm water throughout this period. An echocardiogram performed 24 hours after the exchange transfusion demonstrated qualitatively less flattening of the interventricular septum. The estimated right ventricular pressure remained essentially unchanged at 55% of the systemic pressure.

The patient had a prolonged ventilator course characterized by episodes of atelectasis, recurrent coughing, and cyanotic spells

when sedation and paralysis were weaned. Her course was complicated by a *Candida albicans* urinary tract infection. She was extubated successfully on hospital day 22 and discharged on hospital day 35, without any apparent neurologic deficit. An echocardiogram on hospital day 17 demonstrated normal function with total resolution of pulmonary hypertension.

DISCUSSION

The incidence of *B pertussis* in the United States has increased by 50% from the 1980s to the 1990s, primarily among those aged 4 months and younger.¹¹ Worldwide, pertussis is a significant cause of infectious mortality, with 20 to 40 million cases and 200 000 to 400 000 deaths per year. Most of these cases and deaths occur in infancy.¹² The phenomena of severe hypoxemia and PHT in *B pertussis* pneumonia is being recognized with increasing frequency in the pediatric critical care community and seems to be a relatively common finding in life-threatening cases. Vitek et al² found evidence of PHT in 38 (84%) of 45 cases of fatal *B pertussis* pneumonia in which records and/or echocardiograms were available for analysis. Pooboni et al⁵ found PHT in 9 (75%) of 12 patients who were placed on ECLS for severe pertussis. The onset of severe PHT with myocardial failure and shock is frequently rapid and relentless. Our patient had a number of risk factors associated with severe disease and mortality, including prematurity,² young age,^{2,8} and a high WBC count.^{7,8}

Once PHT and severe hypoxemia are established, the options for the treatment are limited. The use of nitric oxide (NO) has been described^{3,5}; however, there are no published reports of the hemodynamic or oxygenation response to NO in this setting. Clinical infection with *B pertussis* is characterized by destruction of ciliated epithelial cells. Heiss et al¹³ and others have demonstrated that in the presence of tracheal cytotoxin produced by *B pertussis*, NO synthase is induced and NO is necessary to manifest the ciliated epithelial cell injury seen in the disease. We suggest that NO therefore must be used with caution in this setting. Furthermore, as a vasodilator, NO would be expected to have little effect if the causative basis of the hypoxemia and PHT is leukocyte thrombi in pulmonary capillaries and venules.

The use of ECLS has been described in several series of patients with *B pertussis* pneumonia, hypox-

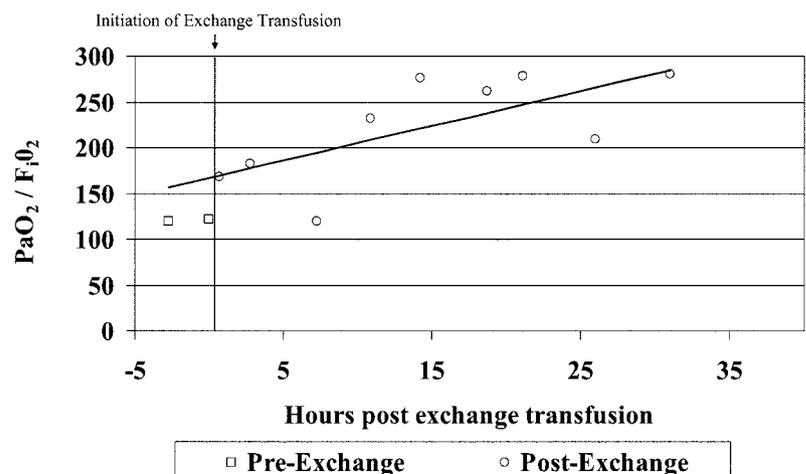


Fig 1. $\text{PaO}_2/\text{Fio}_2$ ratios before and after double volume exchange transfusion. First postexchange value obtained approximately halfway through procedure.

emia, and PHT. Pooboni et al⁵ reported a 58% mortality rate in 12 infants who had pertussis and received ECLS in a single British center. Halasa et al⁶ recently summarized Extracorporeal Life Support Organization's database for patients with a diagnosis of pertussis. Since 1990, 61 children with pertussis have been treated with ECLS, with an overall mortality rate of 70.5%. These reports likely represent the most salvageable cases, with many patients dying before being able to arrive at an ECLS center.

Respiratory distress associated with hyperleukocytosis is well described in the oncology literature. Vernant et al⁹ described 25 adults with leukemia, respiratory distress, and hyperleukocytosis. He noted that the appearance of respiratory symptoms paralleled the rise in leukocyte count. Thirteen patients died either before receiving therapies to acutely lower the WBC count or before the WBC count decreased. The remaining 12 patients received rapidly acting chemotherapy, and 6 of these patients, those with severe respiratory distress, received leukopheresis. In this series, the resolution of respiratory symptoms paralleled the fall in WBC count, and leukopheresis resulted in "spectacular" improvement in clinical symptoms of respiratory distress and hypoxemia.

Bunin et al¹⁰ described a series of children who had leukemia and hyperleukocytosis and were treated with exchange transfusion or leukopheresis. Three of 35 patients presented with respiratory distress, and all experienced improvement in their symptoms after cyto-reduction therapy.

CONCLUSION

We report the first use of a double volume exchange transfusion in the treatment of severe pertussis pneumonia with PHT. Before this intervention, the patient's condition was worsening, as demonstrated by increasing oxygen requirements and very low Pao₂/Fio₂ ratios. Echocardiography demonstrated severe PHT. There was a clear temporal relationship between the initiation of the exchange transfusion and improvement in oxygenation. The

improvement in oxygenation seen in our patient is inconsistent with the natural course of this disease and suggests a salutary effect of the exchange transfusion. Given the poor outcomes of patients who receive ECLS for this disease, particularly once hypotension and shock have ensued, we suggest early consideration of exchange transfusion in the setting of severe PHT and hypoxemia before the onset of cardiovascular collapse. The need for a low-cost, low-technology intervention is most important for developing countries that bear the brunt of infantile pertussis cases and deaths. Exchange transfusion in the setting of pertussis pneumonia with hyperleukocytosis may be such a development.

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