Early blood exchange transfusion in malignant pertussis: A case report

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Objective: **To report early blood exchange transfusion in malignant pertussis and a favorable clinical outcome.**

Setting: **A pediatric intensive care unit in a tertiary hospital in Geneva, Switzerland.**

Design: **A descriptive case report.**

Patient: **An 8-wk-old girl was diagnosed with malignant pertussis (extreme leukocytosis, seizures, pneumonia, and secondary severe hypoxic respiratory failure associated with pulmonary hypertension). After administration of a one-volume blood exchange transfusion, a rapid decrease in white blood cell count (from 119,000/mm^3 to 36,500/mm^3) was observed and followed by clinical improvement and favorable outcome despite the initial presence of all described risk factors associated with a high mortality.**

Conclusion: **The use of exchange blood transfusion early in the course of the disease might help to prevent a fatal outcome of malignant pertussis. (Pediatr Crit Care Med 2011; 12:000–000)**

Key Words: pertussis; white blood cell count; leukocytosis

Bordetella pertussis infection is a serious illness in children of <1 yr old and especially in infants under 6 months of age. Introduction of widespread immunization in the 1930s was followed by a 99% decrease of *B. pertussis* infection. However, since the 1980s, epidemiologic studies are reporting an increasing number of cases in the United States, especially among children of <6 months of age who have not been completely immunized (1–3). Half of the infant cases were infected by parents or siblings whose immunity had waned 5–10 yrs after vaccination (4).

Malignant pertussis is defined by a rapidly evolving combination of pneumonia, respiratory failure, severe leukocytosis, neurologic involvement, and finally, severe pulmonary hypertension leading to death in 75% of cases, despite intensive therapeutic measures. Pertussis has been reported to be the most common cause of death related to infection in children younger than 2 months of age (5–6). We report a case of malignant pertussis with a favorable outcome after aggressive management with early use of a one-volume blood exchange transfusion.

This case report was approved by our institutional ethics committee.

CASE REPORT

A 4.2-kg, 8-wk-old girl was admitted to the hospital after 8 days of low-grade fever, rhinitis with paroxysmal cough, episodes of oxygen desaturation, and fatigue suggesting possible pertussis infection. A white blood cell (WBC) count revealed severe leukocytosis (WBCs 91,300/mm^3, 51% neutrophils and 40% lymphocytes), and the C-reactive protein concentration was elevated (8.3 mg/dL). A chest radiograph revealed upper right lobar infiltrate. On the day of admission, an empirical treatment with intravenous cefuroxime and oral clarithromycin was started, but cefuroxime was stopped 2 days later when pertussis infection was confirmed by a positive polymerase chain reaction on a nasal swab.

On day 7, the patient developed progressive severe respiratory failure, requiring intubation and mechanical ventilation. The chest radiograph showed bilateral upper lobe infiltrates, pleural effusion, and upper right lobe atelectasis. Persistent hypercapnia despite high airway pressures led to high-frequency oscillatory ventilation. A heart ultrasound revealed indirect signs of pulmonary hypertension with an estimated systolic pulmonary arterial pressure of 50 mm Hg from the peak tricuspid regurgitant jet velocity on continuous-wave Doppler. The WBC count peaked at 119,400/mm^3 and was associated with thrombocytosis (579,000/mm^3). Heparin was introduced as prophylaxis for thromboembolic complications (bolus 50 units/kg followed by a continuous infusion of 10–25 units/kg/hr).

A one-volume blood exchange transfusion (2 × 200 mL aliquots over 2 hrs each) with leukocyte-depleted packed red blood cells was performed, which led to a significant decrease in the WBC count to 36,500/mm^3 by the next day (Table 1). Heparin was stopped 72 hrs later once the platelet count normalized. On day 12, the patient was accidentally extubated but remained stable under nasal continuous positive airway pressure with minimal oxygen requirement (F_{IO_2} 33%). On day 13, she suddenly presented with hypoxic spells and seizures, which were treated with midazolam; cerebral magnetic resonance imaging revealed no abnormalities. On day 16, she developed a new episode of fever (38.6°C) with clinical deterioration. C-reactive protein increased from 4.4 mg/dL to 9.1 mg/dL. Broad-spectrum antibiotics were introduced, and the patient was reintubated for progressive respiratory failure with persistent signs of mild pulmonary hypertension. At that time, a trial of inhaled nitric oxide was initiated without significant benefit on pulmonary artery pressure or

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Table 1. ●●●

Day	White Blood Cell Count ($\times 10^3$ Cells/mm^3)	Platelet Count ($\times 10^3$ Cells/mm^3)	Event(s)
−5	19.5	480	First consultation
1			Hospitalization for oxygen- dependent "bronchiolitis"
2	31.8	656	Paroxysmal cough, chest radiograph infiltrate, cefuroxime-clarithromycin treatment
5	104.7	786	Transfer to intensive care unit
7	96.8	321	Intubation for severe respiratory distress
8	119.4	579	High-frequency oscillatory ventilation, pulmonary hypertension (estimated at 50 mm Hg), one-volume blood exchange transfusion
9	36.5	82	
10	51.2	110	
18	27.6	388	Extubation (day 23)

oxygenation. A blood culture was positive for *Haemophilus influenzae*, and the antibiotic treatment was adjusted accordingly. The patient gradually improved from the respiratory standpoint, allowing extubation on day 23 and discharge from the hospital on day 38 with no oxygen requirement despite residual infiltrates on computed tomography scan.

One year later, the chest radiograph was still abnormal, showing diffuse bilateral infiltrates and signs of mild overdistention. However the patient was asymptomatic with no clinical signs of respiratory distress other than several wheezing episodes associated with viral infections.

DISCUSSION

Malignant pertussis is defined by the combination of pneumonia, respiratory failure, severe leukocytosis, neurologic involvement, and pulmonary hypertension. The predictors of death include young age, lack of and/or incomplete vaccination, pneumonia, seizures (7–10), and severe leukocytosis (WBCs >100,000/mm^3); the latter has been previously described to be an independent predictor of death (11).

Leukocytosis and T-lymphocyte activation after pertussis infection have been well documented (12). In mice, exposure to pertussis toxin results in a dose-dependent increase of cyclic adenosine monophosphate with extreme leukocytosis and destruction of pulmonary-ciliated epithelial cells (13). The association between leukocytosis and increased mortality (11) or leukocytosis and respiratory distress has also been described in leukemic patients (14). Mechanisms leading to pulmonary hypertension are still not well defined, but microvascular thrombi and cytokine-mediated inflammatory procoagulants might be involved (12, 15). Histopathologic examination of fatal cases revealed the presence of microthrombi in pulmonary veins, which could be the result of toxin-mediated vascular injury, leukocytosis, and/or hyperviscosity (12, 15–17). The combination of vascular and bronchial obstruction by mucus plugs could be responsible for hypoxemic respiratory failure, acidosis, and pulmonary hypertension; the latter may lead in severe cases to right ventricular failure and fatal outcome.

Malignant pertussis characterized mainly by marked leukocytosis, acute respiratory failure, and severe pulmonary hypertension is difficult to treat. To date, antibiotics, immunoglobulins, vasodilators such as nitric oxide or sildenafil, high-frequency oscillatory ventilation, and extracorporeal membrane oxygenation have showed disappointing results in preventing pertussis-related deaths in infants (15, 18–23).

Our patient exhibited all the described risk factors for death (young age, lack of vaccination, pneumonia, seizures, and extreme leukocytosis). After only one one-volume blood exchange transfusion (Table 1), we observed a dramatic and persistent fall of WBCs, and this was followed by rapid clinical improvement. Similarly, the use of a double-volume blood exchange transfusion (24–25) or leukopheresis (26) has allowed successful treatment of malignant pertussis in infants by reducing leukocyte mass and platelets, and probably other potential deleterious factors (e.g., circulating inflammatory mediators) as well. These observations are very similar to what has been reported from patients with hyperleukocytic leukemia in whom exchange transfusion led to a spectacular regression of respiratory symptoms (14).

The observed positive response to such treatment could be explained at least partially by the decrease in blood viscosity, which may reduce the tendency for microthrombus formation and for the adhesion of activated leukocytes to the vascular endothelium with subsequent vascular obstruction. Given that *B. pertussis* can enter and survive in macrophages for >40 days (16) and that exchange transfusion on its own can hardly achieve complete washout of pertussis toxin, the rapid clinical response observed seems likely to be the result of leukocyte mass reduction.

This case outlines that blood exchange transfusion should be considered early in the course of disease, before severe pulmonary hypertension and multiorgan failure develop. Indeed, Berthomieu et al (27) recently reported failure of this treatment in a 1-month-old infant with measured suprasytemic pulmonary pressure when treatment was initiated late in the course of the disease. Therefore, we suggest that infants with suspicion of malignant pertussis should be transferred as soon as possible into a tertiary care hospital where such treatments are available.

When exposed to *B. pertussis*, infants of <6 months of age are particularly susceptible because of insufficient protection by maternal antibodies (28) and limited protection by their own antibodies until they receive full pertussis vaccination. Because most infants are infected by surrounding adults (29), an increasing number of countries propose to treat prophylactically all family members exposed to pertussis with macrolids and to add a tetanus, diphtheria, acellular pertussis booster to adolescents, adults, new parents, and health workers in contact with neonates (29–32). However, although such immunization could prevent the wide spread of pertussis, it does not change the severity of the disease, and its treatment remains challenging.

CONCLUSIONS

The favorable outcome of our patient despite the presence of all known risk factors for death strongly suggests that the early use of blood exchange transfusions in malignant pertussis with extreme leukocytosis is beneficial, probably more so if the treatment is initiated before severe pulmonary hypertension develops. This ag-

gressive medical management might prevent or at least limit the development of microthrombi and secondary pulmonary hypertension in patients suffering from malignant pertussis and thus potentially improve the outcome. Validation of this proposed early approach will require further investigations.

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