Pertussis: should we improve intensive care management or vaccination strategies?

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Bordetella pertussis, responsible for one of the oldest vaccine-preventable diseases in children, has resurfaced in North America, Europe, Latin America and many countries around the world. Despite new recommended vaccination strategies for adolescents, pregnant women and adults, mortality is still significant in developing and developed countries. For the critical care management of the infant with pertussis, strategies include conventional ventilation, high-frequency oscillatory ventilation, extracorporeal membrane oxygenation, inhaled nitric oxygen, exchange transfusion, plasmapheresis and, more recently, leukodepletion. The paper under evaluation describes the experience of UK investigators in the management of pertussis with rapid leukodepletion for infants with extreme leukocytosis. Using this strategy, a rapid fall in the number of leukocytes was observed in these patients. Their results suggest that rapid leukodepletion should be considered in severely ill infants with pertussis and severe leukocytosis.

Keywords: Bordetella pertussis • deaths • exchange transfusion • intensive care • leukocytosis • mortality • plasmapheresis • pulmonary hypertension • vaccination

Pertussis is the fifth leading cause of vaccine-preventable deaths in children under 5 years of age. The impact of the disease in terms of the number of hospitalizations, complications and deaths is higher in infants younger than 2 months of age who have not yet received their first pertussis immunization. During the last decade, new preventive vaccination strategies have been recommended by the Global Pertussis Initiative and other groups of world leading experts in the field [1–5] aiming to reduce the impact of the disease. Despite this, low awareness of pertussis, low coverage vaccination rates, and the lack of adequate diagnostic laboratory techniques and surveillance networks in many countries, contribute negatively to the spread of the disease.

For the young infant with pertussis that requires hospitalization, the prognosis is worse if the child develops pneumonia, worsening respiratory failure, pulmonary hypertension (PHT) and requires mechanical ventilation. The paper under evaluation by Rowlands and colleagues [6] from the UK discusses the promising results of their experience in the management of infants with severe pertussis, using rapid leukodepletion. Other intensive care aspects of infants with pertussis are discussed.

Methods & results
Subjects & enrollment
This study was a retrospective study of all consecutive infants younger than 3 months of age, with laboratory-confirmed pertussis (positive PCR or culture), who were admitted for critical care management or extracorporeal membrane oxygenation (ECMO) support at the pediatric intensive care unit (PICU) or ECMO service from Great Ormond Street Hospital in London, UK. The study period was January 2001 to August 2009; and a comparison between two periods was made: January 2001–December 2004 and January 2005–August 2009. The latter period was when leukodepletion was adopted as a new policy practice. One of the arguments for this new intervention was their previous experience in the management of pertussis cases with extreme leukocytosis and high mortality rates [7].

Their hypothesis was that critically ill infants younger than 3 months of age with pertussis and
leukocytosis undergoing rapid leukodepletion would have faster total peripheral leukocyte count falls compared with historical control patients.

Intensive care management strategies at their center include low-tidal volume strategy with permissive hypercapnia if no clinical or echocardiographic evidence of PHT is documented, high-frequency oscillatory ventilation if mean airway pressures of 16 cm H₂O or greater are required, inhaled nitric oxide (NO) therapy for the newborn or older infants with right ventricular cardiac failure, and ECMO if conventional management fails.

**Leukodepletion utilization**

Exchange transfusions were performed over 4 h by means of arterial and central venous lines, with replacement fluid (200 cc/kg given as a combination of 4.5% human albumin and packed red blood cells), targeting a final hematocrit of 0.4–0.45 and leukocyte counts below 50,000 cells/mm³. Leukofiltration was performed utilizing a leukocyte filter in the ECMO circuit’s bridge. Once ECMO was initiated, the bridge was opened to the leukocyte filter and the latter was removed from the circuit once white blood cell (WBC) count was less than 15,000 cells/mm³.

**Assignment groups**

All patients in this study were assigned to one of the following four groups:

- Infants younger than 6 weeks’ corrected postpartum age and undergoing ECMO;
- Infants older than 6 weeks’ corrected postpartum age and undergoing ECMO;
- Infants with confirmed pertussis who had leukocyte count at admission above 100,000 cells/mm³;
- Infants with confirmed pertussis who had leukocyte count at admission below 100,000 cells/mm³ and were referred to the PICU but not for ECMO.

**Results**

At this large referral center, 19 infants younger than 90 days old with laboratory-confirmed pertussis required critical care management from January 2001 to August 2009. Of these, 12 patients (63%) were girls. From 2001 to 2004, nine patients required intensive care management, six of whom underwent ECMO and three required PICU only. During the second part of the study period, January 2005–August 2009, ten infants with pertussis were managed, five requiring ECMO and five requiring PICU admission and treatment alone. When the two study periods were compared in terms of the number of days of ventilation in the referring ICUs for patients that were transferred for ECMO, during 2001–2004 patients underwent a median of 5.5 days of ventilation, compared with a median of 1 day during the period 2005–2009.

**Leukocyte count reduction**

In the 2001–2004 study period, mean leukocyte count on admission to the PICU was 52,000/mm³ (range: 36,000–68,000) compared with 75,000 cells/mm³ (range: 40,000–119,000) during 2005–2009. In all patients, the observed leukocytosis was due to a combination of lymphocytosis and neutrophilia.

Leukocyte counts were compared following admission in patients who underwent ECMO, ECMO with leukofiltration and patients undergoing double-volume exchange transfusion. During 2001–2004, infants who underwent ECMO alone without leukodepletion had a rapid fall in admission WBC count, with a 55% reduction of these cells by 10 h compared with those without ECMO. After the leukofiltration strategy was implemented in 2005–2009, patients receiving ECMO and leukofiltration had a 83% decrease of WBC at 10 h, which represented a significantly higher drop in total WBC count (p = 0.017). Similarly, three patients that underwent double-volume exchange transfusion without ECMO had a 67–74% fall in leukocytes by 10 h.

**Comparison of mortality rates**

During the first part of the study period, 2001–2004, the observed mortality rate was 45% (four patients). During the second half of the study period, 2005–2009, the mortality rate dropped to 10% (one patient). However, these differences were not statistically significant.

Case-mix adjustments were made according to age, WBC count and ECMO referral. During the 2001–2004 period, the predicted survival rate (4.4 of 9.0 [49%]) was similar to the observed mortality (4.0 of 9.0 [44%]). During the period 2005–2009, the observed mortality (1.0 of 10.0 [10%]) was significantly improved compared with the predicted mortality (4.7 of 10.0 [47%]).

**Complications**

Of the ten patients from the 2005–2009 period, five underwent leukofiltration on ECMO, of whom four (80%) survived. None of these five patients had associated complications due to the procedure.

**Proposed algorithm for management**

Based on their experience and results, these UK investigators propose a management algorithm for clinicians treating life-threatening suspected or confirmed pertussis in infants less than 3 months of age.

If the patient has severe cardiorespiratory failure nonresponsive to medical therapy, the patient should be referred for ECMO support if available. Admission WBC values should guide the clinician on the other decisions. If the child has a WBC count less than 30,000/mm³, standard respiratory care, ECMO and WBC should be considered. If the patient has a WBC count above 30,000/mm³, ECMO and leukofiltration should be considered if leukocytes do not decrease rapidly. If WBC count is above 50,000/mm³, ECMO and leukofiltration are recommended until these cells drop below 15,000/mm³.

Urgent double-volume exchange transfusion is suggested in the following situations:

- If the patient has no severe cardiorespiratory failure nonresponsive to medical therapy but WBC count is above 100,000/mm³;
Discussion, expert commentary & five-year view

Among the classic and severe complications of pertussis, the most commonly described are pneumonia, seizures, encephalopathy, respiratory failure, and cardiac failure and shock occurring as the result of adult respiratory distress syndrome and PHT [8,9]. The pathogenesis of PHT in pertussis is not completely understood [8,10]. Unfortunately, the refractory hypoxemia in pertussis has a rapid onset and responds poorly to conventional mechanical ventilation, high-frequency oscillatory ventilation, inhaled NO and ECMO. One of the most important and striking features in PHT is leukocytosis, especially extreme leukocytosis (i.e., WBC count >100,000/mm³), and in this case the outcome is poor [7]. Accumulation of leukocyte thrombi and hyperviscosity in the pulmonary vascular bed has been mentioned to be one of the most important key factors in the development of PHT. Inhaled NO has little or no effect as a vasodilator if leukocyte thrombi in pulmonary venules and capillaries are responsible for hypoxemia and PHT [11]. Pertussis toxin stimulates lymphocytosis and prevents the migration of lymphocytes and macrophages to areas of infection, negatively affecting phagocytosis and intracellular killing.

Mortality rates of infants with pertussis admitted to intensive care units reach 50–70% in many centers [12], and therefore different modalities of treatment have been utilized. Among these, based on the fact that NO increases intracellular cGMP, which produces smooth muscle relaxation and vasodilation, inhaled NO and other vasodilators have been utilized [13] with varying results. Pertussis toxin blocks the release of NO by some endothelium-dependent vasodilators, both endogenous and exogenous. Another action of this toxin is to block α2 adrenergic receptors and some dopamine receptors from the heart and blood vessels, which may explain the catecholamine resistance observed in some severe pertussis cases [13].

Extracorporeal life support (ECLS) has been utilized for critical pertussis during the last three decades, with variable outcomes [7,12,14–17]. An updated review of the role of ECLS in pertussis by Halasa and colleagues analyzing the period January 1986–July 2002 revealed that mortality rates for pediatric pertussis undergoing ECMO reached 71% [15]. Therefore, issues concerning the benefit of ECMO for pertussis should be discussed in detail by treating physicians and the parents of affected infants.

Following the first report in 2004 of a double-volume exchange transfusion for treating severe pertussis in PHT [11], other investigators have recommended and successfully utilized this technique [18], especially following reports of infants with pertussis undergoing ECMO. On the other hand, the first report of leukopheresis for severe infantile pertussis was published in 2006 [19]; since then, a lack of reports makes the paper under evaluation here very interesting.

Risk factors for death among infants suffering with pertussis include very young age of the infant, young maternal age, no previous vaccination, shorter preadmission illness, pneumonia, marked or extreme leukocytosis and lymphocytosis, and the need for circulatory support [7,9,20–22]. In the largest series of pediatric patients with pertussis requiring PICU management published by Australian investigators, pneumonia seemed to be a poor prognostic factor [21]. The extensive damage and necrosis of the bronchiolar and alveolar epithelium, and the presence of hyaline membranes, contribute to plugging of secretions, which leads to increased perfusion abnormalities.

The results of the study by Rowlands et al. [6] discussed here are of great interest in an era in which mortality rates are still high in developing parts of the world for infants requiring PICU admission where improved critical care strategies for treating the very sick infant with pertussis may not be available. Although this study offers new hope on the horizon in the management of these patients and is the largest series of leukodepletion for pertussis, the results should be interpreted with caution. As the authors acknowledged, the study had some limitations. First, the small number of patients should be kept in mind; however, it is unlikely that any huge randomized clinical trials will be performed in the future for many reasons, including the limited availability of leukodepletion technique for only a minority of hospitals. Second, this study was performed at only a single center, albeit the one managing the majority of patients for ECMO support in southern England. Third, the attempts to predict case mix-adjusted mortality including cases from 10–15 years ago should be interpreted cautiously. However, we pediatricians caring for very sick infants with pertussis often have no further options other than managing these patients with high-frequency oscillatory ventilation, NO or exchange transfusion. For this reason, leukodepletion seems to be another option for the child with extreme leukocytosis who will otherwise develop refractory PHT and cardiopulmonary collapse.

In conclusion, the paper described in this analysis shows promising data in the critical care management of infants who are critically ill with pertussis. The authors should be applauded for their original contribution, and their decision to adopt new therapeutic options reminded us of what we [23] and many other clinicians around the world have experienced when dealing with these critically ill babies. Is there a ‘magic number’ of leukocytes to help us decide whether exchange transfusion, plasmapheresis or rapid leukodepletion should be started? Or should leukodepletion be initiated very early before the effects of hyperviscosity syndrome occur? The answers are difficult to ascertain and multiple factors should be considered. However, what we do know for sure is that increasing vaccination coverage rates among infants and children, and immunizing adolescents and adults, and post-partum women (‘cocoon strategy’) against pertussis seem to be the best preventive strategies for reducing the impact of the disease.
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Key issues

- Death in pertussis results from a complex cascade of events that involves, among others, necrotizing bronchiolitis and pneumonia, acute respiratory distress syndrome, respiratory failure, pulmonary vasoconstriction, pulmonary hypertension, cardiac failure and shock.
- Intensive care strategies for managing very sick infants with pertussis include conventional mechanical ventilation, high-frequency oscillatory ventilation, inhaled nitric oxide, extracorporeal membrane oxygenation, plasmapheresis, exchange transfusion and leukodepletion.
- For infants younger than 90 days of age with pertussis and secondary extreme leukocytosis, leukodepletion is associated with a rapid decrease in the number of peripheral white blood cells and should be considered in the intensive care management of these patients.
- Despite the availability of newer techniques in the critical care management of these infants, which are actually limited in the majority of countries around the world, vaccination remains the single most effective strategy for preventing the disease, its transmission and secondary outbreaks.
- Although continuous improvements in the management of the child with life-threatening pertussis should be pursued, efforts should focus on increasing vaccination coverage rates of infants and children and targeting vulnerable individuals: adolescents, adults, and pregnant and post-partum women.

References


