Since the early 1980s the reported incidence of pertussis in the United States has gradually risen with superimposed cyclical peaks occurring at approximately 3-year intervals [1]. In 1990, pertussis was responsible for 350,000 deaths worldwide. The morbidity and mortality for this disease are highest in children less than 6 months of age, and both decline with increasing age [2]. Moreover, 70% of children less than 6 months of age require hospitalisation and fully 15% develop radiographically confirmed pneumonia [1].

Several authors have previously described severe refractory pulmonary hypertension leading to progressive shock and death in pertussis [3, 4] and it has recently been suggested that extracorporeal circulatory life support (ECLS) may be a worthwhile therapy to consider for such infants [3]. We describe our experience where ECLS was provided to a 3.8-kg, 5-week-old male, and review the above suggestion in the light of our experience, post-mortem findings and ECLS registry data review.

Case report

A 5-week-old twin boy was admitted at the referring hospital with a 2-day history of lethargy, poor feeding, tachypnoea and cough. He was afebrile with a respiratory rate of 60 breaths/min, heart
rate of 160 beats/min and had a percutaneous arterial oxygen saturation of 95% in room air. Chest X-ray showed bilateral infiltrates with consolidation of the right middle and upper lobes. Full blood count showed haemoglobin 11.1 g%, total white cell count 9200 × 10^9/l and platelet count 298 000 × 10^9/l. A clinical diagnosis of bronchiolitis was made although respiratory syncytial virus (RSV) immunofluorescence of a nasopharyngeal aspirate was negative, as was immunofluorescence for chlamydia. *Bordetella pertussis* serology and nasopharyngeal swab were collected.

Our patient’s twin brother was admitted to hospital at the same time with a similar history of intermittent tachypnoea and cough. Neither of the twin’s cough was paroxysmal and there were no episodes of apnoea. Neither twin had yet received any immunisations. There was a history of persistent cough for 6 weeks in an 8-year-old sibling and for 3 weeks in their mother, both of whom were fully immunised against *B. pertussis*. Over the following 4 days the infant initially seemed to improve symptomatically with satisfactory breast feeding and only occasional coughing. However, on day 5, he developed more respiratory distress, persistent tachycardia > 190 beats/min and an increased oxygen requirement. He was intubated and transferred to Sydney Children’s Hospital. Arterial blood gas prior to intubation was pH 7.26, arterial carbon dioxide tension (PaCO₂) 71 torr, arterial oxygen tension (PaO₂) 61 torr and bicarbonate (HCO₃⁻) 27 mEq/l [in a fractional inspired oxygen (FIO₂) of 0.5].

On admission to hospital the infant’s weight was 3.8 kg, he was ventilated at a peak inspiratory pressure of (PIP) 28 cmH₂O, positive end-expiratory pressure (PEEP) 7 cmH₂O, rate 40/min, IT 0.5 s, FIO₂ 0.5 and mean airway pressure Pₐₗₜ. 17 cmH₂O, and the arterial blood gas was pH 7.39, PaCO₂ 45 torr, PaO₂ 116 torr and HCO₃⁻ 27 mEq/l. Peripheral perfusion was barely adequate with a pulse rate of 200/min and blood pressure 70/40 mmHg. An echocardiogram showed a small pericardial effusion with minimal tri- cuspid regurgitation. At this time, full blood count showed a haemoglobin of 9.9 g%, total white cell count 114 000 × 10⁶/l (71% lymphocytes, 13% monocytes, 6% eosinophils, 3% neutrophils, 13% eosinophils and 6% bands) and platelet count 575 000 × 10⁶/l. Cleaved lymphocytes were present on the blood film. Baseline biochemistry, LFTs and coagulation screen were otherwise unremarkable. Treatment with intravenous cefotaxime and erythromycin was started. The patient was isolated and all family members were given oral erythromycin.

During the initial 6 h in hospital good gas exchange was achieved on moderate ventilator settings (PaCO₂ 40 torr, PaO₂ 70–90 torr), but tachycardia and prolonged capillary refill persisted. Colloid infusion (20 ml/kg of 4% albumin) was administered during hours 8 and 9, which increased central venous pressure from 7 to 10 mmHg but did not otherwise improve haemodynamics. Adrenaline infusion was commenced at this time and was gradually increased to 2 μg/kg per min. The colloid infusion was repeated at 12 h with little effect on haemodynamics and clinical signs and, at 16–18 h after admission, hypotension [mean arterial pressure (MAP) < 30 mmHg] and metabolic acidosis occurred for the first time. At 20 h a repeat echocardiogram confirmed acute severe pulmonary hypertension with right atrial and right ventricular dilatation with the septum encroaching into the left ventricular cavity and compromising left ventricular filling during diastole. Pulmonary pressures were estimated to be suprasystemic. Inhaled nitric oxide was administered (commenced at 8 parts/million and increased to 80 parts/million). There was some improvement in oxygenation; however, haemodynamics remained poor despite continued inotropic support. Methaemoglobin levels always remained < 3%.

At this time oxygenation index [MAP (cmH₂O) × FIO₂ ÷ PaO₂ (torr)] was 0.22 and ventilation index [PaCO₂ (torr) × RR × PIP (cmH₂O) ÷ 1000] was 66. Although these values do not justify ECLS for respiratory support in our institution, refractory hypotension and acidosis suggested a requirement for ECLS which was established by 24 h following admission. Arterial blood gas prior to initiating venoarterial ECLS was pH 7.12, PaCO₂ 34 torr, PaO₂ 94 torr and HCO₃⁻ 11 mEq/l on ventilator settings of PIP 39 cmH₂O, PEEP 7 cmH₂O, rate 50/min, FIO₂ 1.0. The Pediatric Risk of Mortality score was 41 and the lung injury score 3.3.

Despite achievement of satisfactory pump flow rates (> 350 ml/min) and satisfactory oxygenation, poor circulatory function and profound acidosis persisted. A follow-up echocardiogram demonstrated severe myocardial dysfunction with a dilated poorly contractile left ventricle and some moderate aortic and mitral regurgitation. Apart from the acidosis and severe disturbance of LFTs, biochemistry was normal. Haemofiltration with a bicarbonate-supplemented predilution fluid was unable to ameliorate the acidosis (base deficit of > 20 mEq/l for > 24 h) and laboratory studies confirmed that disseminated intravascular coagulopathy was now present. Between 30 and 36 h on ECLS, the infant became clinically unresponsive to stimulation, an electroencephalogram confirmed absence of electrical activity and after 48 h on ECLS, in consultation with the family, support was withdrawn.

Subsequent to his death, culture results became available. *B. pertussis* was grown from the infant, his twin and mother and enzyme-linked immunosorbent assay IgA-specific for *Bordetella* was positive in the mother and 8-year-old sibling.

**Post-mortem report**

Post-mortem examination of the lungs revealed a large amount of intra-alveolar oedema fluid, haemorrhages and macrophages. There was alveolar leucocytoclastic granular material with foci of fibrin but no organisms seen. Some areas showed breakdown of alveolar walls suggestive of early pulmonary infarction. Small and medium-sized pulmonary veins were solidly packed with dense leucocyte thrombi. Marked generalised lymphoid depletion was noted.
Discussion

Pertussis is a non-invasive bacterial colonisation of ciliated cells in the respiratory epithelium [2]. The clinical features of pertussis are mediated by toxins produced by the *B. pertussis* organism. It is this phenomenon which leads to the disease continuing unabated despite eradication of *B. pertussis* from the patient’s respiratory tract [2]. The course can be altered if these organisms are eradicated with antibiotics early in the disease [6].

A recent review of deaths from pertussis demonstrated that 90% were younger than 12 months and risk factors included young maternal age and preterm delivery but, most importantly, inadequate immunisation [7]. The importance of a high level of community immunisation cannot be overstressed and there is evidence to support an expedited immunisation programme during an epidemic [8]. The value of isolation of the patient and erythromycin prophylaxis of contacts is well documented.

Pertussis toxin (PT) is also known as lymphocytosis promoting factor and is known to stimulate lymphocytosis and prevent migration of lymphocytes and macrophages to areas of infection with adverse effects on phagocytosis and intracellular killing. However, whether PT has a decisive role in the generation of symptoms of pertussis remains controversial [9]. Tracheal cytotoxin (TCT) has been implicated in local tissue damage in the respiratory tract [10]. TCT has been demonstrated in in vitro studies to produce changes in human respiratory epithelial cell ultrastructure after just 4 h of exposure and to destroy ciliated cell populations completely in 60–96 h [10].

The precise factor which mediates acute severe pulmonary hypertension in pertussis is unknown. It seems, however, that colonisation of the respiratory epithelium

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**Table 1** Comparison of demographic and gas exchange data between survivors and nonsurvivors of ECLS for pertussis. Values are mean ± SD except for age (A-aDO₂, alveolar-arterial oxygen difference)

|                | Survivors | Nonsurvivors | p     |
|----------------|-----------|--------------|-------|
| Number         | 5         | 17           |       |
| Age (months)   | 4.4 (range 1.1–14) | 6.5 (range 0.7–31) | 0.52a |
| Weight (kg)    | 4.2 ± 0.6 | 4.5 ± 2.4    | 0.82a |
| Pre-ECLS VI    | 73 ± 27   | 105 ± 59     | 0.39a |
| Pre-ECLS A-aDO₂| 609 ± 20  | 599 ± 28     | 0.38a |
| Pre-ECLS severe hypotension | 1/5 | 10/17 | 0.12b |
| Pre-ECLS pH    | 7.4 ± 0.2 | 7.2 ± 0.1    | 0.02a |
| Pressors on ECLS | 0/5 | 7/17 | 0.08b |
| Venovenous (VV) ECLS | 3/5 | 2/17 | 0.02b |

* a Mann-Whitney U test  
* b Chi-square analysis
is important in the development of serious disease, as mice infected intraperitoneally with chambers containing *B. pertussis* remained healthy despite developing antibody responses [11]. It has been suggested that damaged epithelium would compromise mucociliary clearance and so promote further *B. pertussis* proliferation and enhance local delivery of toxins. Whether the ensuing pulmonary hypertension results from a haemodynamic effect of such a locally delivered toxin or results from associated hypoxia, hypercapnia, acidosis, tissue injury or even iatrogenically from vasoactive drugs (or any combination of the above) is not clear.

The rapidity and severity with which severe pulmonary hypertension evolved in our patient was impressive. Increase of pulmonary vascular resistance is known to occur in infants and children with pneumonia of multiple aetiologies [12]; however, this case clearly represented the most severe end of a spectrum of such changes.

Hyperventilation and alkalisation were not able to ameliorate this pulmonary hypertension. Inhaled nitric oxide as a selective pulmonary vasodilator was also unsuccessful. The possible aetiological significance of the pulmonary venous leucocyte thrombi in the genesis of this pulmonary hypertension must remain speculative at this time. The leukocytoclastic bronchopneumonia we found at autopsy is characteristic of fatal pertussis as is a pulmonary leukaemoid reaction [13].

In conclusion, we recognise that drawing conclusions from small numbers of patients in a retrospective analysis is tenuous and that our review of registry data is limited by the information available. As such, the timing and reason for the hypoxic ischaemic cerebral injuries noted among nonsurvivors remain unknown.

Review of ELSO Registry data would indicate that the outcome with ECLS for children with pertussis is poor (overall mortality 78%), particularly in association with profound hypotension (overall mortality 90%). This outcome is worse than that for neonates receiving ECLS with a proven primary diagnosis of sepsis (mortality 27%) [14] or those who developed a septic complication during ECLS (mortality 35%) [15]. The observed mortality with ECLS in pertussis is significantly worse than the mortality observed in other paediatric patients receiving ECLS for respiratory failure.

There appears to be a subgroup of patients suffering from *B. pertussis* infection who have severe, although not life-threatening, respiratory disease but the major problem of an acute myocardial failure. Despite receiving ECLS to maintain perfusion, these infants commonly develop fatal cerebral ischaemia. We conclude that although ECLS may have a role in providing respiratory support in infants with severe *B. pertussis* infection, it is highly likely to be unsuccessful if instituted primarily for cardiovascular indications.

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