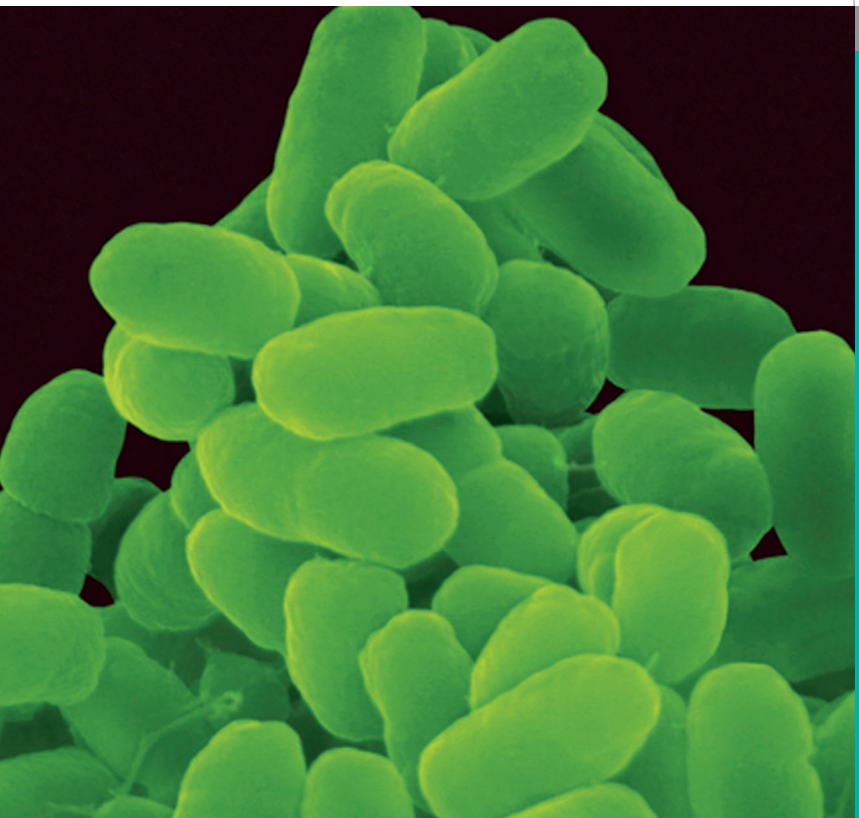
SWISS SOCIETY OF NEONATOLOGY

Fatal pertussis infection – an emerging disease?



April 2013

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Before the widespread implementation of vaccination strategies, pertussis caused large epidemics and was responsible for an estimated 10‘000 annual deaths in the United States (1). As a result of successful vaccination programs, the public awareness of this disease in most developed countries at present is low, and most neonatologists will not get confronted with severe pertussis infections during their training. However, over the past decade, several countries including Australia have reported outbreaks of pertussis infections, and there is concern about an increasing number of potentially preventable deaths, particularly in neonates and young infants (2). In Switzerland, approximately 50 infants with confirmed pertussis are hospitalized each year (3). We present the case of an infant with severe pertussis infection requiring extracorporeal membrane oxygenation (ECMO).

CASE REPORT

A four-week-old boy was brought to the emergency department after his parents had observed a cyanotic episode at home that had responded to stimulation. The baby had been born through spontaneous vaginal delivery at 39 2/7 weeks, and the early neonatal period had been uneventful. The child and his family, including a two year old, fully vaccinated sibling, had all had cough and coryza for the past days.

On arrival to the emergency department, the patient was saturating 100% in 2 L/min of oxygen, but showed signs of respiratory distress with a respiratory rate of 66/min and moderate subcostal and tracheal recessions. The heart rate was 216/min with a capillary refill time of 3 to 4 seconds. Pulses were palpable on all four limbs, the liver was of normal size, and no cardiac murmur was audible. The fontanel was soft, but the child was irritable. Suspecting sepsis, a fluid bolus was given and intravenous antibiotic treatment with cefotaxime and gentamycin was started. A venous blood gas showed a mixed acidosis with a pH of 7.19, pCO2 7.5 kPa (56 mmHg), a base excess of -8.1 mmol/l and a lactate of 5.7 mmol/l. The full blood count revealed a severe leukocytosis with a white blood cell count (WCC) of 94.4 $x10^9$/L, 44.3 $x10^9$/L neutrophils, and 36.3 $x10^9$/L lymphocytes. The hemoglobin level was 108 g/L, and platelets count was 758 $x10^9$/L. Suspecting pertussis, intravenous treatment with azithromycin was added.

Over the next two hours, the condition of the baby deteriorated despite high-flow nasal cannula oxygen support with persistent grunting and frequent desaturations. A repeat venous blood gas now showed a severe respiratory acidosis with a pH of 7.03 and a pCO2 of 14.1 kPa (106 mmHg). The infant was therefore intubated and retrieved to our tertiary pediatric intensive care unit (PICU). On arrival to the PICU, the chest X-ray showed bilateral consolidations with areas of hyperinflation (Fig. 1). Echocardiography showed a morphologically normal heart with normal function but increased pulmonary pressures. Due to high peak ventilatory pressures and persistent hypercarbia, high-frequency oscillatory ventilation (Sensormedics 3100A) was initiated, and a milrinone infusion was started. Inhaled nitric oxide was added at 20 ppm.

Blood cultures were negative, but the polymerase chain reaction (PCR) in the nasopharyngeal aspirate tested positive for Bordatella pertussis. The WCC confirmed hyperleukocytosis of 111 $x10^9$/L. Given the critical conditions of the infant with acute cardiorespiratory failure, it was decided to perform a double blood volume exchange transfusion. Based on the protocol published by the Great Ormond Street Hospital (GOSH) (4), 200 ml/kg of blood were removed and continously replaced with packed red blood cells and 4% albumin over four hours. The procedure was hemodynamically well tolerated, and the WCC dropped to 24.8 $x10^9$/L.

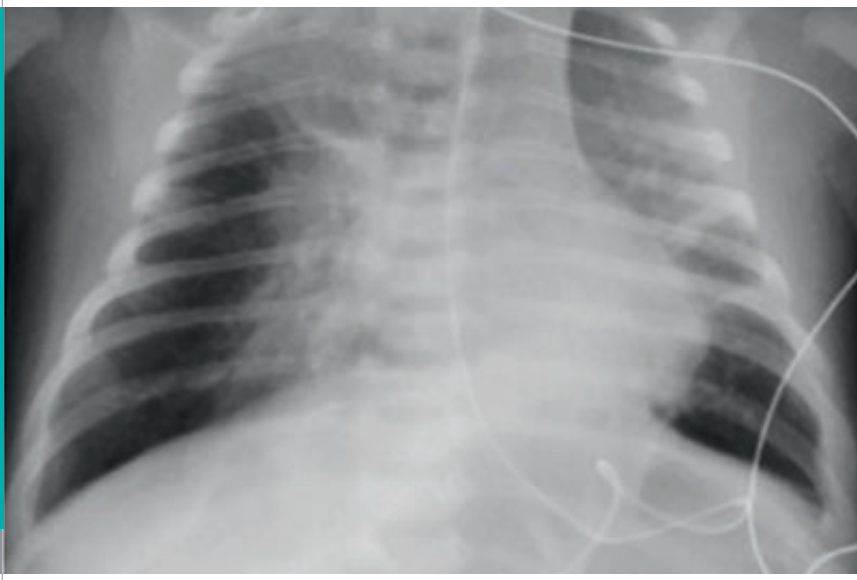

Fig. 1

Chest X-ray on admission to the PICU: bilateral patchy infiltrates with partial consolidation of the right and left upper lobes alternating with hyperinflated areas.

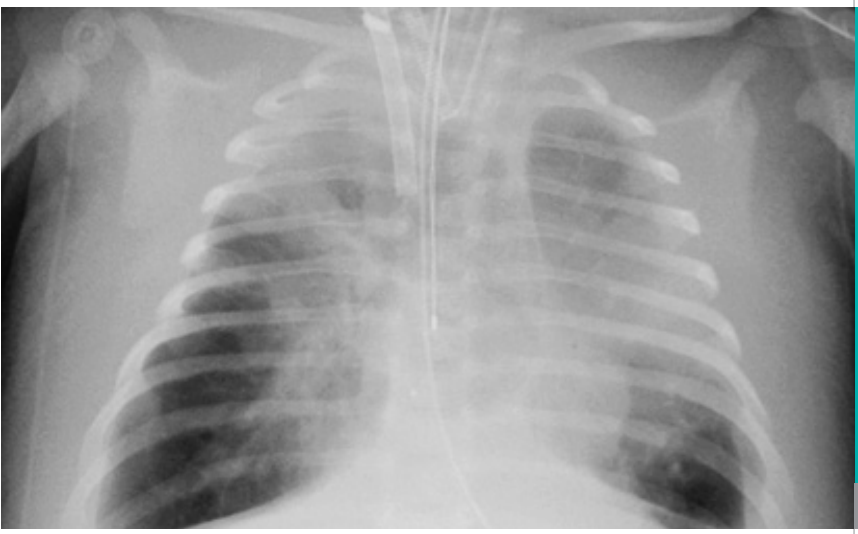

Fig. 2

Chest X-ray after cannulation for VA ECMO on HFOV: the pulmonary radiographic changes noted on admission have progressed.

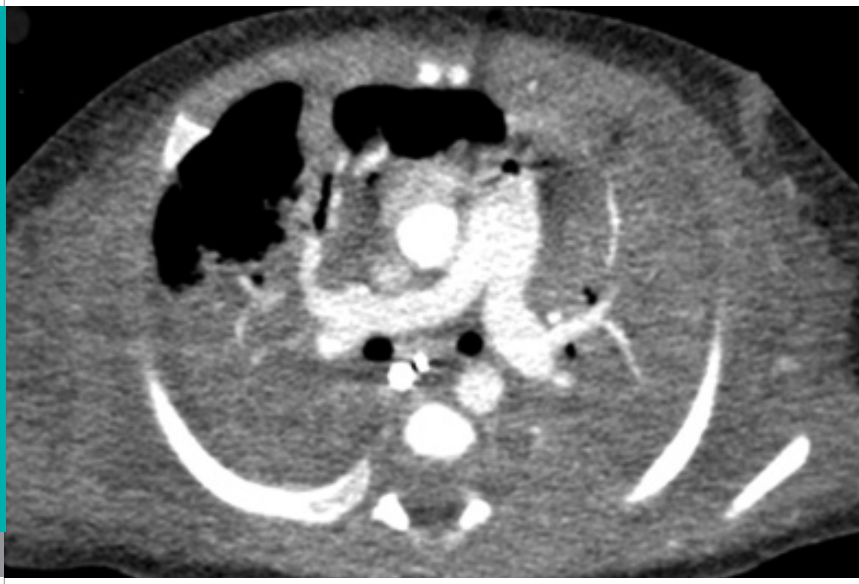

Fig. 3

Chest CT on day 7 of ECMO: dense consolidations in both lungs with partial residual aeration of the right lung.

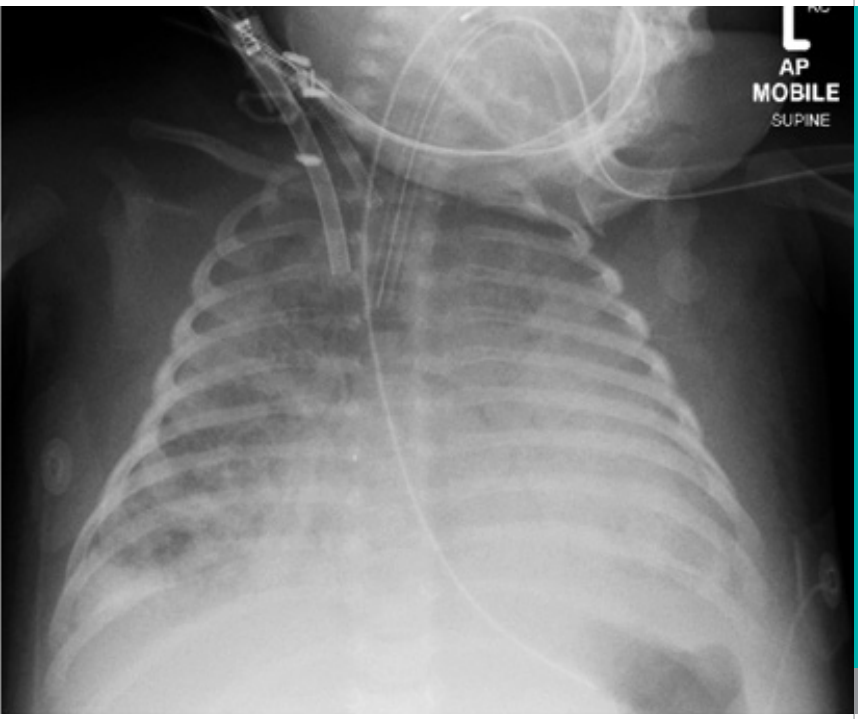

Fig. 4

Chest X-ray on day 25 of ECMO: diffuse interstitial and alveolar opacifications in both lungs.

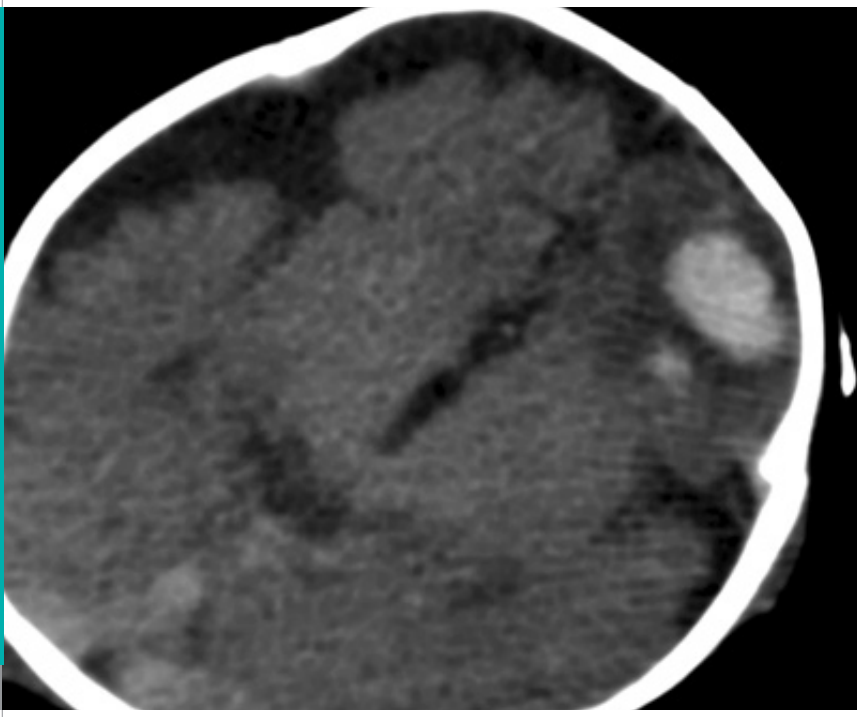

Fig. 5

CT scan of the brain on day 25 of ECMO: several foci of intracerebral hemorrhages with associated edema; in addition, cerebral atrophy with widened extracerebral spaces is noted.

Twelve hours after admission to the PICU, the infant developed arterial hypotension requiring support with noradrenaline and dobutamine. Echocardiographic assessment now revealed suprasystemic pulmonary hypertension and a dilated failing right ventricle with bulging of the interventricular septum to the left. The decision to support the child with extracorporeal membrane oxygenation (ECMO) was made. Venoarterial (VA) ECMO was initiated through neck cannulation. While on VA ECMO, the patient was kept on HFOV (Fig. 2). Echocardiography showed significantly reduced right ventricular dimensions and a decompressed left atrium and ventricle. Since the WCC decreased to values between 5 and 20 $x10^9$/L no additional leukodepletion was performed.

On day seven, given the absence of any improvement in pulmonary status, a thorough bronchoscopy was performed, and several mucous plugs were removed. A computed tomography (CT) of the head was normal, while the CT of the chest showed extensively consolidated lungs but no signs of necrotizing pneumonia (Fig. 3).

Over the next two weeks, different strategies to recruit the consolidated lungs were applied, including repeated broncoscopies with DNAse washouts, and surfactant application. Lung function tests showed minimal compliance, and chest x-ray showed persistent diffuse opacifications of the lungs (Fig. 4). Conversion

of venoarterial to venovenous ECMO and weaning of ECMO was not possible since reduction of ECMO flows rapidly led to increased pulmonary pressures with right ventricular dilatation. At 25 days on ECMO, hyperechogenic changes were noted on cranial ultrasound. A subsequent CT of the head confirmed the presence of several intracerebral bleedings and cerebral atrophy with widened extracerebral spaces (Fig. 5). As there were no signs of pulmonary recovery, and given the evidence for permanent brain damage, continuation of life support was considered futile by the team and the parents. The infant died upon cessation of ECMO.

The postmortem MRI confirmed multiple hemorrhagic foci throughout the cerebral hemishperes and the basal ganglia. The postmortem pathology showed extensive lung injury with totally consolidated lungs. In histopathology, highly inflamed alveoli with a mononuclear cellular infiltrate of the airspaces were found side-to-side with focally necrotizing pneumonia with fibrous scarring (Fig. 6). Multiple small arteries with thromboses were noted (Fig. 7).

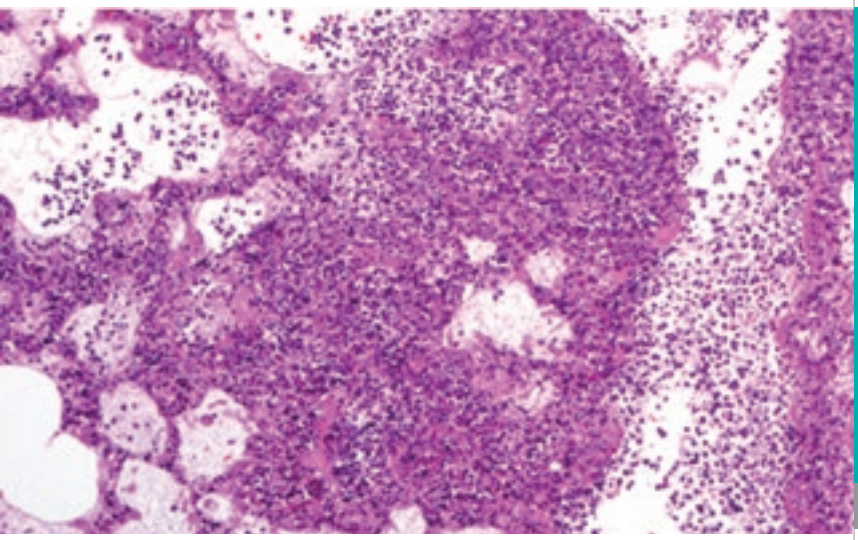

Fig. 6

Postmortem lung histology: acute necrotizing inflammatory infiltrates in a respiratory bronchiolus; the infiltrate is neutrophil-rich, and the background lung architecture is still intact in this area (HE stain, x20 objective).

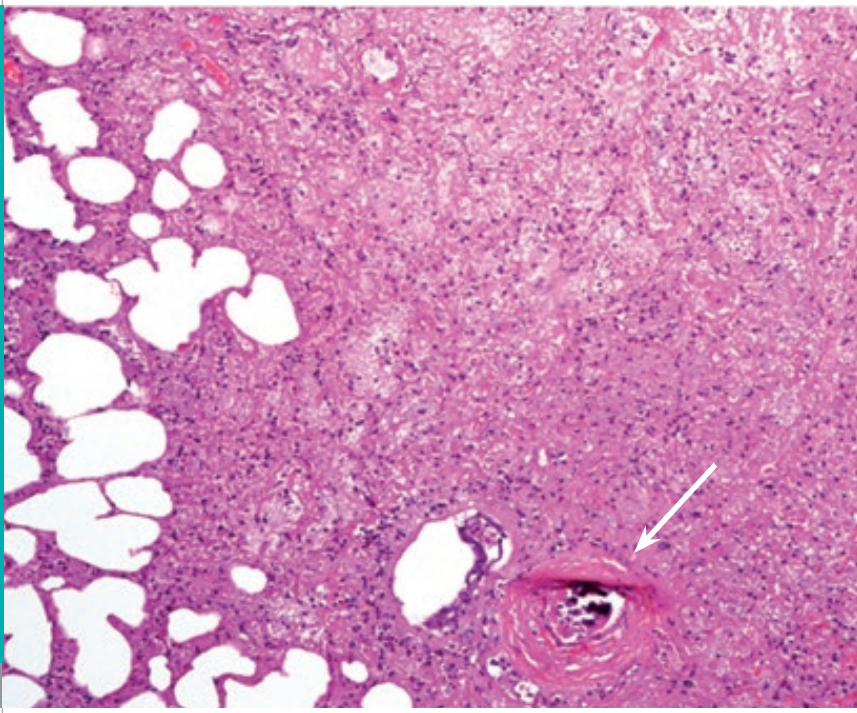

Fig. 7

Postmortem lung histology: here, the lung architecture is mostly lost, and replaced by solid necrotic tissue and fibrin; a thrombosed vessel (arrow) with early calcification can be seen (HE stain, 10x objective).

Bordatella pertussis, a gram-negative aerobic bacterium, causes airborne respiratory infections in all age groups, ranging from coryza and persistent cough to apneas and life-threatening complications including pulmonary hypertension and acute respiratory distress syndrome (ARDS)-like presentations. Despite significant reduction in mortality over the past decades, pertussis is still ranking among the 10 leading causes of childhood mortality on a global scale with an estimated 195'000 annual deaths (www.who.int/immunization_monitoring/diseases/pertussis/en/index.html).

Pathogenicity is related to different virulence factors including adhesins allowing binding to epithelial cells, cytotoxins which inhibit ciliary clearance, and Pertussis toxin. Pertussis toxin affects cellular signalling and causes lymphocytosis, which is pathognomonic for the disease (5). Traditional teaching on pertussis in textbooks mainly refers to the paroxysmal coughing spells which may last up to several minutes and which can lead to intermittent hypoxemia, apneas, hypertensive encephalopathy and seizures.

In 1993, Gouldin et al. reported refractory pulmonary hypertension in fatal pertussis (6). In fact, the majority of fatal pertussis cases that have been reported in recent series from developed countries were associated with hyperleukocytosis, severe pulmonary hypertension and ARDS-like refractory respiratory failure (7, 8). The extreme leukocytosis may exceed 100 $x10^9$/L and

results in a hyperviscosity syndrome which can lead to impaired microcirculation and organ failure. In addition to hyperviscosity, obstruction of pulmonary arterioles by leukocyte thrombi may result in severe pulmonary hypertension as a prominent feature (5). Furthermore, pertussis toxin can mediate an increase of cAMP levels which contributes to pulmonary vasoconstriction. Finally, aggregation and activation of lymphocytes and neutrophils in the pulmonary vascular bed may aggravate acute lung injury. Postmortem studies have found cilia loss in airway mucosa, necrotizing bronchiolitis, and focal or diffuse bronchopneumonia (5). Aggregates of leukocytes in pulmonary arterioles, small arteries and venules and occlusive thrombi are frequent postmortem findings, as observed in the presented case.

The management of severe pulmonary hypertension in pertussis patients is extremely challenging, since classic approaches at reducing pulmonary vascular resistance such as iNO may fail due to hyperviscosity and vascular obstruction. The observation of a high mortality in infants presenting with hyperleukocytosis has therefore lead to strategies for leukoreduction (4). The GOSH protocol recommends leukofiltration in patients requiring ECMO for cardiorespiratory failure with WCC above 50 $x10^9$/L. In patients that do not require ECMO, urgent double-volume blood exchange transfusion is advocated if the WCC is above 100 $x10^9$/L, or above 70 $x10^9$/L and cardiorespiratory failure or se-

vere pulmonary hypertension are present. Comparing a historical cohort of nine infants under 90 days of age with severe pertussis managed without leukoreduction versus a recent group of ten infants treated according to this protocol, the group at GOSH observed improved survival from 55% to 90%. To date, this small non-randomized study remains the only report on a significant treatment benefit for severe pertussis.

ECMO is a valid treatment option in the setting of refractory pulmonary hypertension due to a potentially reversible cause (such as meconium aspiration syndrome or sepsis), and has therefore been used in patients with pertussis-induced cardiorespiratory failure (9). The Extracorporeal Life Support Organisation (ELSO) registry recorded 169 pertussis cases that were treated with ECMO between 1992 to 2009 (4). The prognosis of severe pertussis requiring ECMO was worse compared to other indications for respiratory ECMO (mortality of 70% compared to a mortality of 20% for respiratory syncytial virus bronchiolitis). The highest case fatality rate (84%) was observed in infants below 6 weeks of age. ECMO may be required for several weeks, which leads to a high risk of ECMO-related life-threatening complications such as sepsis, major bleeding or thromboembolic events.

Recent serological follow-up data from vaccine centers suggests that the protection after full immunization using the acellular pertussis vaccine wanes faster

compared to whole-cell pertussis vaccines (1). In fact, adolescents and adults currently represent the main epidemic reservoir, leading to infection of non-vaccinated neonates and infants (10). Therefore, the Swiss Federal Office of Health (BAG) recently issued new recommendations that include a dTpa booster every ten years for all adolescents and adults with regular contact with infants less than 6 months of age (11). Obviously, decreasing adherence of parents to vaccination programs remains a major concern.

In summary, the present case illustrates that pertussis can lead to rapid cardiorespiratory failure and refractory pulmonary hypertension in neonates and young infants. Hyperleukocytosis is associated with a high mortality, and rescue strategies including exchange transfusion for leukodepletion, or leukapheresis in patients on ECMO should be considered early.

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