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Review

Pertussis in the Newborn: certainties and uncertainties in 2014

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EDUCATIONAL AIMS

- This review summarizes the most recent literature and addresses the most important aspects that pediatricians and neonatologists must be familiar with, when treating a newborn' *pertussis* infection.
- Clinical aspects, laboratory diagnosis, treatment, epidemiology over the last years, and vaccination aspects are highlighted.

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SUMMARY

Bordetella pertussis infection remains a serious potential health risk to infants, specially in those too young to be vaccinated. Over the recent years, numerous sources highlighted a widespread resurgence, making it, again, a challenging disease. Globally, pertussis is ranked among the 10 leading causes of childhood mortality. This review summarizes the most recent literature and will address the most important aspects that pediatricians and neonatologists must be familiar with, when treating a newborńs *pertussis* infection.

INTRODUCTION

Pertussis, or whooping cough, is caused by the organism *Bordetella pertussis* and remains a serious potential health risk to infants, specially in those too young to be vaccinated [1]. Although removed from the list of notifiable diseases in many countries once apparentely conquered after routine vaccination, over recent years, numerous sources highlighted a widespread resurgence making it, again, a challenging disease [2,3].

Severe respiratory failure complicated by pulmonary hypertension is associated with high mortality which may develop in the newborn and young children [4]. Globally, pertussis is ranked among the 10 leading causes of childhood mortality [5]. Macrolide resistance has been documented and is an essencial point when investigating individual treatment failures [6]. New vaccination strategies have been suggested in the last decade, predominantly to protect infants younger than two months of age [7].

This review summarizes the most recent literature and will address the most important aspects that pediatricians and neonatologists must be familiar with when treating a *pertussis* infection in a young infant.

PATHOPHYSIOLOGY, CLINICAL PRESENTATION AND DIFFERENTIAL DIAGNOSIS

Bordetella pertussis is a small aerobic Gram-negative coccobacillus that infects only humans. It causes irritation and inflammation by infecting the ciliated respiratory tract epithelium. The bacterium has several virulence factors and toxins that are important in the pathogenesis of the disease and also play a role in inducing protective response. Filamentous hemagglutinin and fimbriae are adhesins required for tracheal colonization. The ensuing tissue necrosis and epithelial cell damage recruits macrophages, and reactive lymphoid hyperplasia of peribronchial and tracheobronchial lymph nodes occur. Other virulence factors such as pertactin and *pertussis* toxin can act as adhesins as well [8].

Pertussis toxin can inactivate or supress signaling pathways of the immune system in the lung, which delays recruitment of neutrophils. The role of *pertussis* toxin in the pathogenesis of *pertussis* is not fully understood. The toxin has been shown to cause leukocytosis with lymphocytosis and possibly the rare encephalopathy seen in clinical disease. Other direct effects of *pertussis* toxin include sensitization of the beta-islet cells of the pancreas. This effect can lead to hyperinsulinemia with a resistant hypoglycemia,

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and sometimes occurs in young infants who have poor feeding. Adenylate cyclase toxin inhibits migration and activation of phagocytes and T cells [8].

Pertussis is spread by aerossol droplets expelled while coughing or sneezing. Infants get pertussis from older siblings, parents, or caregivers who may have only mild symptoms [9]. After an incubation period of seven to 14 days, the natural history of *pertussis* tends to follow a relatively predictable clinical course, although disease severity and prognosis are quite variable, and a high degree of suspicion may be necessary to make a timely diagnosis. A child suspected of having pertussis should be placed in appropriate isolation until the infection is confirmed or ruled out [8].

The catarrhal phase lasts one to two weeks, and includes nonspecific complaints. The absent or mild fever, cough and nasal signs are similar to those seen in many viral upper respiratory tract infections, which often delays the suspicion of the diagnosis. The cough worsens as the patient progresses to the paroxysmal phase. This phase of illness lasts from weeks two to six, and is characterized by paroxysms of typical cough. The paroxysms may occur several times per hour and can be associated with cyanosis, salivation, lacrimation, and post-tussive emesis. They can be exhausting and often interfere with sleep and nutritional intake. Newborns and young infants often have a less typical presentation. The classic "whoop" following the paroxysm of cough may be absent, and gasping, gagging, and apnea can occur. The clinical picture of the most severely affected newborns and young infants may be dominated by marked respiratory distress, cyanosis, and apnea, rather than significant cough. Lymphocyte counts are frequently in excess of 30 $x10^{9}$/L [10]. Leukocytosis, together with an absolute lymphocytosis on a peripheral complete blood count, is a laboratory finding suppotive of *Bordetella pertussis* infection. This finding often correlates with disease severity, specially in very young patients. White blood cell counts as high as 30 to 60 $x10^{9}$/L can be seen [8].

The convalescent phase follows the paroxysmal phase with improvement in respiratory tract integrity and function, decreasing frequency and severity of the coughing episodes, and may last from weeks to months [8].

Complications of *pertussis* include apnea, pneumonia, pulmonary hypertension, seizures, encephalopathy, pneumothorax, pneumomediastinum, subcutaneous emphysema, rib fracture, emesis and dehydration, hypoglycaemia, rectal prolapse, superficial petechial hemorrhage, and even intracranial hemorrhage. Bacterial and viral superinfection such as influenza or respiratory syncytial virus may occur, and can lead to a more severe clinical course [8,10]. *Bordetella pertussis* pneumonia may progress rapidly and pulmonary hypertension may result in right-sided heart failure or fatal cardiac arrythmias [10]. Malignant *pertussis* is defined by a rapidly evolving combination of pneumonia, respiratory failure, severe leukocytosis, neurologic envolvement, and finally, severe pulmonary hypertension leading to death in 75% of cases, despite intensive therapeutic measures. The mortality rate of all infant *pertussis* infection is about 1%, with more than half of the deaths occurring in infants below two months age [11].

Respiratory tissue samples obtained at autopsy from 15 infants aged below four months who had polymerase chain reaction- or culture-confirmed *pertussis* pneumonia were evaluated by multiple histochemical stains, immunohistochemical evaluation, and electron microscopic examination, by *Paddock CD et al* [4]. The pulmonary histopathologic examination of the samples revealed a descending infection dominated by necrotizing bronchiolitis, intra-alveolar hemorrhage, and fibrinous edema. All samples had marked leukocytosis and most showed luminal aggregates of abundant leukocytes in small pulmonary arteries, veins, and lymphatics. A novel immunohistochemical stain for *Bordetella pertussis* revealed abundant extracellular *Bordetellae* in cilia of the trachea, bronchi, and bronchioles, as well as intracellular bacteria and antigens in alveolar macrophages and ciliated epithelium.

Encephalopathy associated with *pertussis* infection is rare, occurring in 0.5–1% of all cases, and the diagnoses is suggested by seizures with *pertussis* infection, in the absence of other diagnosis. It may be the result of the direct neurologic actions of toxins, effects of hypoxia, hemorrhages, vascular occlusions and latent virus infection. However, the aetiology of central nervous system complications are not fully understood [12,13]. The syndrome of innapropriate secretion of antidiuretc hormone (SIADH) including hyponatremia and decreased urine output, although rare, has already been decribed in association with *pertussis* infection [14,15].

The differential diagnosis includes infections from other respiratory pathogens, as Respiratory Syncitial Virus, influenza, adenoviruses, and Chlamidia trachomatis. Rapid viral antigen testing and specific serologies will help these diagnosis [8].

PERTUSSIS-RELATED HYPOXEMIA, HYPERLEUKOCYTOSIS, AND PULMONARY HYPERTENSION

Bordetella pertussis infection may develop a fulminant course in very young, unimmunized infants, and is characterized by pneumonia that rapidly evolves to respiratory failure with refractory hypoxemia, extreme leukocytosis and cardiogenic shock requiring cardiovascular support [4,8,15–19]. The main risk factors for high mortality are high white blood cell (WBC) count and severe pulmonary hypertension (PH), age below six months, prematurity, and incomplete immunization [17].

The setting up of refractory hypoxemia characteristically is rapid and responds inadequately to advanced ventilation maneuvers, including high-frequency oscillatory ventilation, inhaled nitric oxide, and extracorporeal membrane oxygenation (ECMO) [18,19]. There are some hypotheses for this poor outcome. An association between high WBC count and increase in severity led to the theory that vascular infiltration or hyperviscosity may be a factor in inducing PH and heart failure [16,20].

The mechanism for the induction of intractable PH by *pertussis* infection is unknown. Hypoxia contributes to PH, but other factors such as toxin production or pulmonary venous leukocyte thrombi demand additional investigation [21]. Though, the lack of PH in some cases lead to the theory that primary ventricular dysfunction may be a separate contributory entity and could also be the focus of therapeutic intervention [16].

Histological examination of the lungs of fatal cases of *pertussis* infection exhibited histopathologic features of necrotizing bronchiolitis, bronchopneumonia, pulmonary hemorrhage and edema, angiolymphatic leukocytosis, and revealed numerous bacteria in intracellular and extracellular compartments of airways and airspaces. The association between vascular obstruction (blood viscosity, and the consequent tendency for microthrombus formation) and bronchial obstruction (mucus plugs) could be responsible for hypoxemic respiratory failure, acidosis, and PH causing right ventricular failure [16,22]. Some *post-mortem* studies in patients aged below four months found pulmonary leukocyte thrombi obstructing the lumen of the arteries, veins and lymphatics [23]. In the youngest infants with reactive pulmonary arterioles and immature coagulation and fibrinolytic systems, severe leukocytosis contributes directly to severity of disease through a hyperviscosity syndrome and pulmonary arteriolar thrombosis. This microvascular thrombotic obstruction to pulmonary blood flow is resistant to conventional management of pulmonary hypertension with pulmonary vasodilators; in fact, inhaled nitric oxide may worsen the effects of the *pertussis* tracheal cytotoxin [24]. Founded on the assumption that the pulmonary