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Recurrent, protracted and persistent lower respiratory tract infection: A neglected clinical entity

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Summary Community-acquired pneumonia is a potentially life-threatening disease affecting children worldwide. Recurrent pneumonia episodes can lead to the development of chronic respiratory morbidity. Chronic wet cough, a common pediatric complaint, is defined as a wet cough indicating excessive airway mucus that lasts for a minimum of 4 weeks. Most children with a chronic wet cough do not suffer from underlying debilitating pulmonary disorders. Rather, chronic wet cough is generally associated with neutrophilic airway inflammation and bacterial infections of the conducting airways. Failure to characterize endobronchial infections has led to under-recognition of chronic wet cough as an important clinical entity in children. Under-recognition and under-treatment of protracted bacterial bronchitis (PBB), a diagnosis made by the presence of isolated cough >4 weeks that resolves with appropriate antibiotic treatment, may lead to the development of chronic suppurative lung disease (CSLD) and bronchiectasis. The burden of bronchiectasis is highest in developing countries and in specifically vulnerable populations in developed countries, in particular indigenous children living in remote communities. The incidence, hospitalization rates and risk of long term sequelae of childhood pneumonia in indigenous children are higher than in non-indigenous children residing in the same area.

The overlapping clinical and pathophysiological characteristics of PBB, CSLD and bronchiectasis are the presence of a chronic wet cough, impaired mucociliary clearance of the conducting airways, the presence of endobronchial bacterial infection (mainly non-typeable *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Moraxella catarrhalis*) and

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neutrophilic airway inflammation. The principles of managing PBB, CSLD and bronchiectasis are the same. More research and public health interventions are required to improve the awareness, diagnosis and management of these causes of chronic wet cough in children.

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Global burden and causes of childhood pneumonia

It has been claimed that there is a global mismatch between the research and development activities that are needed and those that are carried out. This was first demonstrated in 1990, when it was shown that less than 10% of the global health research is devoted to conditions that make up 90% of the global disease burden, the so-called '10/90-gap'.¹ From 2007 until 2012, bacterial pneumonia and meningitis received 1–3% of the total global research and development funding² while in 2010 lower respiratory infections and meningitis together accounted for >15% of the global child deaths.³ In 2010, a total estimated number of 2,031,474 children died worldwide and over 25% (515,994) of these deaths were attributed to lower respiratory infections or meningitis.³ The greatest proportion of pneumonia deaths are observed in the African region, closely followed by Southeast Asia.⁴

Definitions of pneumonia vary widely. Especially in young infants that experience high prevalence rates of both pneumonia and bronchiolitis it is generally difficult to distinguish these two clinical entities. In addition, the features of other conditions often affecting children such as malaria or bacterial sepsis overlap with pneumonia signs and symptoms.^{5,6} The World Health Organization has defined case definitions of non-severe, severe and very severe pneumonia based on clinical signs and symptoms observed by healthcare workers.⁷

The identification of the causative pathogen in a child presenting with pneumonia is challenging. Asymptomatic colonization of the human nasopharynx by respiratory bacteria and viruses is common.^{8,9} Furthermore, bacteraemia is observed in less than 10% of bacterial pneumonia cases and children generally do not cough up sputum representing lower-airway secretions. With an extensive etiological workup including sensitive polymerase chain reaction (PCR), antigen and serology methods, a potential cause of community-acquired pneumonia was identified in 86% of 99 Swiss children aged 2 months to 5 years. Evidence of bacterial infection was shown in 53% of patients, with *Streptococcus pneumoniae* documented in 45%. A virus was demonstrated in 67% of the children, mainly rhinovirus and human metapneumovirus (hMPV), while 33% had a mixed bacterial and viral infection.¹⁰ The most likely causes of pneumonia differ by age group. If pneumonia occurs in the first three weeks of life, it is often caused by perinatally transmitted pathogens. *S. pneumoniae* appears as a common cause after the age of 3 weeks throughout childhood. *Staphylococcus aureus* can cause severe pneumonia, often with complicated effusion, in children 3 weeks to 3 months of age whereas *Haemophilus influenzae* is more common in children of 4 months to 4 years. Among the viral causes, the respiratory syncytial virus (RSV) is the most observed cause of pneumonia in younger children, with a peak incidence at

2–7 months of age.¹¹ In a sample of Kenyan infants and children, RSV was significantly more often detected in those admitted with severe pneumonia than in healthy controls (adjusted odds ratio (OR) 6.11, 95% confidence interval (CI) 1.65–22.6) whilst collectively, other respiratory viruses were not associated with severe disease.¹² Other viral causes of pneumonia in children aged 4 months to 4 years are parainfluenza virus, influenza virus, adenovirus and rhinovirus.¹¹ Over one-third of the childhood pneumonia cases that require hospitalization are thought to be caused by atypical organisms, eg, *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*.^{13–15} However, findings from a recent study in Dutch children suggest that the burden of respiratory tract infections attributable to *M. pneumoniae* may be overestimated because currently used diagnostic tests are unable to differentiate between asymptomatic carriage and symptomatic infection.¹⁶

Risk factors for (recurrent) pneumonia

In developing countries, the incidence and mortality rate of childhood pneumonia are 10 times higher than in developed countries.¹⁷ Malnutrition is thought to be the underlying cause of approximately half of the fatal acute lower respiratory tract infections. Nutritional determinants of the global acute lower respiratory infection disease burden in children less than 5 years old are macronutrient undernutrition, low birthweight (<2500 g), zinc deficiency and a lack of exclusive breastfeeding in the first 6 months.^{4,18} In addition to malnutrition, inadequate healthcare, crowded living conditions, a lack of running water, poor maternal education and insufficient vaccination rates are related to the higher frequency of (recurrent) lower respiratory tract infections in the developing world.¹⁹ Furthermore, a systematic review and meta-analysis by Dherani et al. demonstrated that exposure to unprocessed solid fuels increases the risk of pneumonia in children aged less than 5 years by a factor of 1.8.²⁰

Specific populations in developed countries show prevalence rates of respiratory infections equal to or higher than those observed in developing countries. Indigenous populations form an example of a particularly vulnerable group of children often living in extreme poverty experiencing high prevalence rates of respiratory infections. In the United States, Canada, Australia and New Zealand indigenous children experience hospitalization rates for acute respiratory tract infections that are at least three times higher than their non-indigenous counterparts.^{21–25} The annual rates of radiographically confirmed pneumonia in Australian indigenous children from the Northern Territory are among the highest reported in the world.²⁶ While *S. pneumoniae* accounts for the majority of pneumonia episodes on a global level,^{10,11} improved detection methods have identified non-typeable *H. influenzae* as a major causative pathogen in recurrent pneumonia.²⁷

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