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Review

Childhood community-acquired pneumonia: A review of etiology- and antimicrobial treatment studies

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Educational aims

The reader will be able to

- Understand the epidemiology of childhood CAP and effects of universal Hib- and pneumococcal vaccination.
- Identify problems with establishing the causative pathogen for childhood CAP.
- Recognize CAP in under-fives is often viral in origin, thus not needing antibiotics.
- Prescribe adequate antimicrobial treatment (spectrum, route and duration) for uncomplicated and complicated childhood CAP.
- Realize that the evidence for macrolide treatment in childhood CAP is scarce.

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ABSTRACT

Community acquired pneumonia (CAP) is a leading cause of childhood morbidity worldwide. Because of the rising antimicrobial resistance rates and adverse effects of childhood antibiotic use on the developing microbiome, rational prescribing of antibiotics for CAP is important. This review summarizes and critically reflects on the available evidence for the epidemiology, etiology and antimicrobial management of childhood CAP. Larger prospective studies on antimicrobial management derive mostly from low- or middle-income countries as they have the highest burden of CAP. Optimal antimicrobial management depends on the etiology, age, local vaccination policies and resistance patterns. As long as non-rapid surrogate markers are used to distinguish viral- from bacterial pneumonia, the management is probably suboptimal. For a young child with signs of non-severe pneumonia (with or without wheezing), watchful waiting is recommended because of probable viral etiology. For children with more severe CAP with fever, a five-day oral amoxicillin course would be the first choice therapy and dosage will depend on local resistance rates. There is no clear evidence yet for superiority of a macrolide-based regimen for all ages. For cases with CAP requiring hospitalization, several studies have shown that narrow-spectrum IV beta-lactam therapy is as effective as a broad-spectrum cephalosporin therapy. For most severe disease, broad-spectrum therapy with or without a macrolide is suggested. In case of empyema, rapid IV-to-oral switch seems to be equivalent to prolonged IV treatment.

Introduction

Pneumonia is a leading cause of childhood morbidity and mortality worldwide. The annual worldwide incidence of pneumonia in children <5 years old is estimated 120 million approximately, of which ~1.3 million cases lead to death [1]. The world-wide case fatality ratio is estimated to be around 8.7% for severe pneumonia. Most mortality occurs in the younger age group. Specifically, 81%

Abbreviations: BD, bis in die/(two times a day); (RC)CAP, radiologically conformed community acquired pneumonia; HiB, *Haemophilus influenza* type B; HIV, human immunodeficiency virus; HRV, human rhinovirus; ICU, Intensive Care Unit; IV, intravenous; LMIC, low- and middle-income countries; LRT, lower respiratory tract; MIC, minimal inhibitory concentration; PCR, polymerase chain reaction; PCV, pneumococcal conjugate vaccine; RSV, respiratory syncytial virus; SP, *Streptococcus pneumoniae*; TID, ter in die (3 times a day); WHO, World Health Organization; URT, upper respiratory tract.

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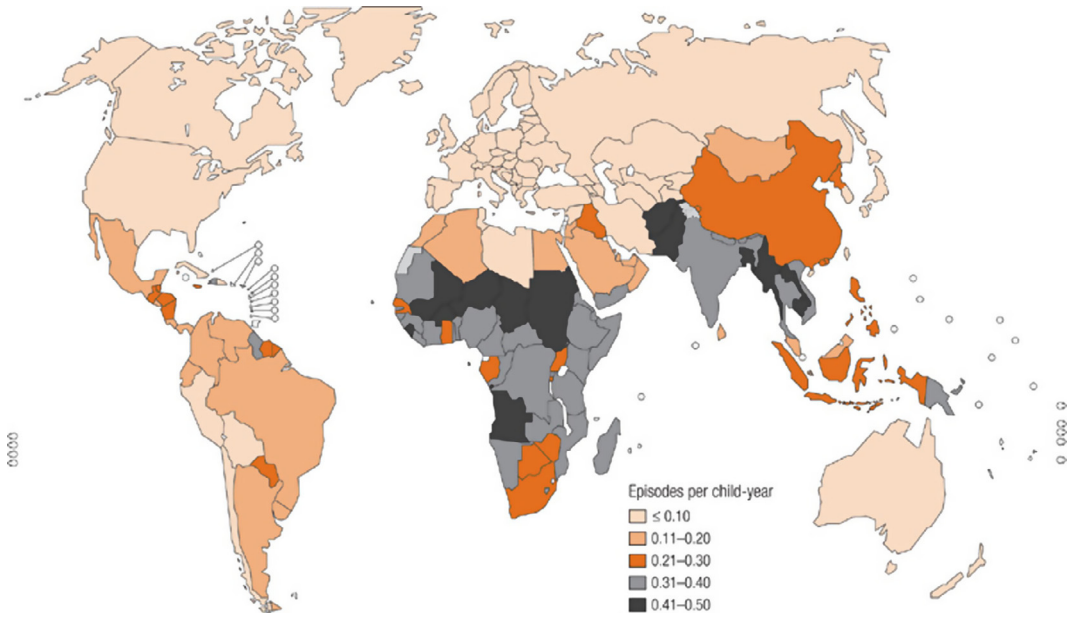

Fig. 1. Incidence of pneumonia in children <5 years. Rudan et al, WHO 2008 [4]. Reprinted with permission [4].

of all pneumonia deaths occur in children <2< years old [2]. These figures have largely improved since the eighties, when childhood respiratory tract infections accounted for 4–5 million childhood deaths per year [3].

The epidemiology of childhood pneumonia varies widely between different regions of the world related to prevalence of risk factors and causative pathogens [4]. Most pneumonia episodes occur in Southeast Asia and Africa. Importantly, sub-Saharan Africa accounts for 43% of pneumonia deaths, despite only constituting 19% of the world's under-5 population [2,5]. In low- and middle-income countries (LMIC), the incidence has been reduced to 25% over the last decade, now being ~0.22 episodes per child year [6]. Figure 1 shows the worldwide incidence of pneumonia in children <5 years old.

Increased hygiene, antibiotic therapy and vaccination against *Streptococcus pneumoniae* (SP) with pneumococcal conjugate vaccine (PCV), and *Haemophilus influenzae* type B (HiB) have largely decreased the morbidity in children in the developed world [7]. Especially the contribution of HiB CAP is falling quite rapidly because of widespread vaccination in the majority of LMIC. Only a few countries do not vaccinate against HiB; in 2012, 180 countries introduced HiB-vaccine and 86 countries PCV [1]. The estimated reduction of the HiB- and PCV on radiologically confirmed (RC) pneumonia is ~18% and ~26% respectively [8]. A recent Asian study noted a 39% decline in RCCAP in young children after HiB vaccination [9]. However, the HIV-epidemic has increased the incidence of childhood CAP again [1,6].

Because of the large burden of pneumonia on child health and mortality, the optimal management of pneumonia is a 'hot topic'. Optimal management comprises good accessibility to health care services, adequate diagnosis, and rational easily available inexpensive antimicrobial therapy. These lead to a fast resolution of symptoms in the majority of children with pneumonia. Resistance must be prevented by restricted use in general, and use of narrow-spectrum antibiotics. This review will describe the available evidence for the etiology and management of CAP in otherwise healthy children beyond the neonatal period.

Etiology of community acquired pneumonia in childhood

Methods

Microbiological methods to study the etiology are culture, polymerase chain reaction (PCR), direct immunofluorescence, antigen tests and (paired) serology. Upper respiratory tract (URT) samples (naso- or oropharyngeal swabs) are often used as surrogate markers for the lower respiratory tract (LRT) (sputum, pleural fluid, lung tap, broncho-alvealor lavage fluid, and biopsy). The positive predictive value and specificity of the URT samples might be limited for LRT, since many potential pathogenic organisms also colonize the URT [10].

Blood cultures

Blood cultures rarely add to the diagnosis of CAP (1–10%), and might lead to a prolonged hospitalization [11]. A targeted approach of identifying the patients with CAP at risk for bacteraemia might aid in the yield of positive blood cultures [12].

Lung aspirates, biopsy- and empyema studies

In the pre-vaccine era, 62% of pre-treated children from LMIC had bacteria detected in their lung aspirates, mainly SP and HiB. Viruses were present in 23% [3]. A post-mortem study of lung tissue samples from 98 Mexican children younger than 2 years who died of pneumonia, showed respiratory syncytial virus (RSV) in 30% of patients [13]. Bacterial PCR on post-mortem stored Chinese lung tissue samples from a 50-year period showed HiB as a causative pathogen for fatal CAP in 18% of children [14]. A recent systematic review series on incidence and pathogens in childhood CAP found HiB responsible for 16% of fatal cases, adjusted for HiB vaccination [6]. More data will be available in the future as the PERCH (Pneumonia Etiology Research for Child Health) project will study post-mortem samples combined with ante-mortum samples with modern techniques to define the cause of death in children with pneumonia in the vaccine-era [10,15].

In recent childhood empyema studies PCR aided in the yield of pathogens. The majority of severe pneumonia cases were still