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Community-acquired pneumonia in children ☆

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ABSTRACT

Community-acquired pneumonia (CAP) remains a frequent cause of morbidity and mortality worldwide even in industrialised countries, and its incidence is highest among children aged <5 years. Over the last two years, three international guidelines have been updated with new evidence concerning the incidence, aetiology and management of childhood CAP, but there are still some major problems in standardisation. The main aim of this review is to consider the available data concerning the aetiology, diagnosis, evaluation of severity, and treatment of paediatric CAP. Analysis of the literature shows that there are a number of unanswered questions concerning the management of CAP, including its definition, the absence of a paediatric CAP severity score, the difficulty of identifying its aetiology, the emergence of resistance of the most frequent respiratory pathogens to the most widely used anti-infectious agents, and the lack of information concerning the changes in CAP epidemiology following the introduction of vaccines against respiratory pathogens. More research is clearly required in various areas, and further efforts are needed to increase vaccination coverage with the already available vaccines in order to reduce the occurrence of the disease.

1. Introduction

Community-acquired pneumonia (CAP) remains a frequent cause of morbidity and mortality worldwide, even in industrialised countries, and its incidence is highest among children aged <5 years [1]. It is estimated that CAP is responsible for one-fifth of the deaths of young children, with two million deaths per year in the developing and developed world: the incidence of CAP among children aged <5 years in developing countries is 0.29 per child-year, with a mortality rate of 1.3-2.6% and, in North America and Europe, its incidence in preschool children is still approximately 36 per 1,000 child-years [2]. Extensive infant vaccinations with pneumococcal conjugate vaccines in developed countries have significantly decreased the rates of hospital admissions due to childhood CAP (1,3,4), but concerns have been raised by the increase in complicated CAP cases due to *Streptococcus pneumoniae* serotypes 1, 3, 5 and 19A over the last few years [3,4]. Furthermore, an increase in deaths due to Staphylococcal pneumonia has been reported in North America, mainly following influenza infection [5].

During the last two years, three international guidelines have been updated with new evidence concerning the incidence, aetiology and management of childhood CAP [1,6,7]. However, there are still some major problems in standardising the management of paediatric CAP, including the lack of a true diagnostic standard and the difficulty in identifying the causative micro-organisms before selecting antibiotics.

The definition of CAP varies widely worldwide depending on whether chest radiography is used or not; furthermore, although chest radiography is still the main means of confirming a clinical suspicion of CAP in everyday practice, its diagnostic accuracy is limited by significant intra- and inter-observer differences in interpreting plain chest radiographs [8]. Furthermore, as the recent international guidelines for the management of paediatric CAP do not recommend routine radiological investigations in patients suspected of having uncomplicated CAP or CAP not requiring hospitalisation [1,6,7], it is difficult to establish the real incidence of childhood CAP.

In terms of therapy, the first-line antimicrobial approach varies from country to country, and there is no clear consensus concerning second-line treatment [1,6,7].

The main aim of this review is to consider the available data concerning the aetiology, diagnosis, evaluation of severity, and treatment of paediatric CAP.

2. Aetiology

The use of molecular methods to detect microbial products in biological fluids has greatly improved our knowledge of CAP aetiology. New respiratory pathogens have been discovered over the last ten years, including human metapneumovirus, bocavirus and some coronaviruses [9], and new data concerning the importance of the different pneumococcal serotypes and the impact of the use of pneumococcal conjugate

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vaccines have been collected using polymerase chain reaction [3,4]. However, determining the aetiology of CAP is still difficult in routine clinical settings because appropriate lower respiratory tract specimens can rarely be obtained from children; the evaluation of upper respiratory tract secretions is only useful for viruses and atypical bacteria because typical bacteria are part of the normal flora colonising the upper respiratory tract [1]; and the detection of bacterial antigens in urine is related to the same flora and cannot be considered an aetiological marker of infection in children [2].

The aetiology of CAP varies significantly depending on the age of the patient. Respiratory viruses are the most frequent pathogens in children aged between four months and five years (with syncytial virus and rhinovirus the main viruses), and are responsible for approximately 40% of the CAP episodes in hospitalised children [1,10,11]. *S. pneumoniae* accounts for one-third of the cases of all ages, and *Mycoplasma pneumoniae* is the main pathogen in children aged 5-15 years [1–3,12] and also accounts for 30% of the cases in children aged 2-5 years [13]. Untypeable *Haemophilus influenzae*, *Staphylococcus aureus* and *Chlamydiophyla pneumoniae* are much less frequently observed, partly because of the lack of reliable diagnostic tests [1,2,6,7]. However, many studies published over the last ten years have recorded mixed viral/bacterial infections in up to 45% of cases of childhood, with *S. pneumoniae* being the most frequently involved bacteria [14,15]. Dual viral infections have also been reported, with two or three viruses being detected in 10-20% of cases [11,16]. Some viruses (e.g. bocavirus) are detected more frequently than others in such multiple infections, but it is not clear what this means in clinical practice or whether viral infection always precedes bacterial infection or not.

Although some clinical and radiological pictures and laboratory findings are more characteristics of particular etiological agents (e.g. "paroxysmal" cough in viral or atypical bacterial infections, necrotising pneumonia in infections due to *S. aureus* or *S. pneumoniae*, with the latter also inducing a significant increase), none is sufficiently sensitive or specific to identify them definitely.

3. Assessing severity

Many factors are associated with a complicated CAP course, including microbial load; the type and virulence of the pathogen, and its susceptibility to anti-infective drugs; and host susceptibility to infections [1]. Individual susceptibility to CAP is also related to the presence of comorbidities, pre-existing lung disease (such as bronchodysplasia, bronchiectasis or adenomatoid cystic malformations), previous vaccinations against respiratory pathogens, and genetic susceptibility to infections [1].

This last may play an under-estimated role in the incidence and clinical course of CAP in patients of all ages. The risk of CAP is five times higher in adult patients discharged after being hospitalised because of CAP than in those discharged with any other diagnosis [17] and, in primary care settings, it seems that subjects with CAP are also more likely to have experienced previously recurrent upper respiratory infections [18]. Moreover, studies of adopted patients have shown that the risk of a fatal outcome is greatly conditioned by genetic factors [19], which seem to confirm their major role in determining individual susceptibility [20]. Single nucleotide polymorphisms (SNPs) in many of the genes involved in innate and adaptive immune responses have been associated with host susceptibility [21–26], and some of these genes have also been associated with protection against [27] or susceptibility to infectious diseases other than CAP [28].

The international guidelines have suggested various criteria for assessing the severity of CAP in infants and older children [1,6,7]. In general, signs and symptoms suggesting a respiratory distress, such as age-adjusted tachypnea, SpO2 levels of less than 90-92% in room air, cyanosis, chest retractions, nasal flaring or grunting, suggest a need for hospitalisation [1,6,7] but, unlike in the case of adults, there is no validated scoring system that is sensitive and specific enough to predict which children have sufficiently severe CAP to warrant such a course [10]. The guidelines also point out that a child's overall clinical appearance and behaviour may predict severity, and so any child with a "toxic" appearance (including a temperature of >39 °C and tachycardia, a capillary refill time of >2 s, dehydration and respiratory distress) should be admitted to hospital [1,6,7]. Further criteria for hospitalisation include a younger age (i.e. <3-6 months), pre-existing comorbidities, suspected infection due to methicillin-resistant *S. aureus*, feeding difficulties, an inability to take oral medication because of vomiting, or the possibility of non-compliance with oral treatment because of the family environment [1].

Some interesting perspectives have been opened up by the discovery of some new blood biomarkers of CAP severity in adults, including natriuretic peptide [29], mid-regional pro-adrenomedullin [30], and the triggering receptor expressed on myeloid cells (TREM-1) [31]. However, there are still no data concerning the role of these biomarkers in paediatric CAP.

4. Diagnosis

Although the radiographic detection of infiltration is currently the gold standard for a diagnosis of CAP, experts agree that routine imaging studies are not essential to confirm the diagnosis in children, at least in those who are well enough to be treated as outpatients and do not present recurrent episodes [1,6,7]. However, they are essential in the management of severe and/or recurrent CAP because, in addition to confirming the diagnosis, they can also document the characteristics of the parenchymal infiltrates and the presence of complications requiring specific therapy [10].

Computed tomography (CT) is usually reserved for patients with CAP complicated by parapneumonic effusions, necrotising pneumonia or lung abscesses, especially when surgery needs to be considered [2]. Chest radiographs are less sensitive in detecting lung abscesses than CT scans, and fail in approximately 20% of cases [2]. Severe parapneumonic effusions and empyema (i.e. with more than half of the chest X-ray opacified) often require a CT scan before the placement of a chest tube, especially when loculated effusion is suspected [2]. In such cases, lung ultrasonography (LUS) may be an alternative as it has the advantage of avoiding radiation exposure, even though it is less accurate and gives rise to more inter-observer disagreement than CT [7]. A recent prospective multicentre study aimed at comparing the accuracy of LUS, plain chest radiography and low-dose CT in diagnosing adult CAP found a sensitivity of 93.4% (95% confidence interval [CI] 89.2–96.3%) and a specificity of 97.7% (95% CI 93.4–99.6%) [32].

Aetiologically, a number of studies have shown that the signs and symptoms of viral and bacterial CAP may be surprisingly similar, that radiological characteristics cannot be used to distinguish different aetiological agents, and that non-microbiological laboratory tests (such as total and differential white blood cell counts, serum C-reactive protein levels and the erythrocyte sedimentation rate) are often not useful for decision making in individual cases [1,2,10]. Procalcitonin levels currently seem to be the best marker for distinguishing bacterial from viral CAP and reducing the duration of antimicrobial therapy [33].

Identifying the aetiology of paediatric CAP is also a problem when microbiological methods are used to detect bacteria. The risk of complications means that punctured lung puncture, bronchoalveolar lavage and thoracoscopic lung biopsy should be reserved for complicated and life-threatening cases that do not respond to theoretically adequate antibiotic therapy [1,2,6,7]. Blood cultures are positive in 13–26.5% of children with complicated CAP, but in fewer than 5% of those with mild or moderate disease [10]. Molecular methods can increase the sensitivity of identifying bacterial pathogens in blood samples, but they are not routinely used in all laboratories [3]. Gram staining and cultured expectorated sputum are widely used to identify the bacteria responsible for adult CAP, but most children (particularly those in the first years of life) cannot provide adequate specimens for

testing. Furthermore, otherwise healthy younger children frequently carry nasopharyngeal bacteria that are the same as those that can cause CAP and so, when sputum is induced, contamination often leads to unreliable results [10].

In relation to atypical bacteria, culturing respiratory secretions in order to identify *M. pneumoniae* is impractical in most laboratories because it requires specific media and its slow growth means that it takes too long to obtain information that is useful for therapeutic decision making. The presence of cold-reacting antibodies against red blood cells in serum was once considered a reliable index of *M. pneumoniae* infection, but its accuracy has never been evaluated in children and so it is not currently recommended in paediatrics [10]. Serological methods (mainly enzyme assays) can detect specific IgM and IgG antibodies, and their sensitivity and specificity are good if two serum samples are evaluated (one taken during the acute phase and one during convalescence) [10]; however, once again, although they are useful for epidemiological studies, the findings cannot be used to make therapeutic decisions. Finally, PCR-based testing is theoretically very sensitive and specific, but it is not readily available or practical, and is not considered a standard means of identifying *M. pneumoniae* CAP [10]. The diagnostic tests used to identify *Chlamydophila pneumoniae* are even more limited because they are unreliable, and the performance of many of the serological assays is poor or inadequately validated [1,10].

It used to be thought that identifying CAP-causing viruses in upper respiratory secretions was more reliable because it was believed that they could not be carried by healthy children. However, this assumption is now widely questioned because it has been shown that it is not true of some viruses; furthermore, viral/bacterial co-infections are frequent, and bacterial pathogens may play a more important role in conditioning clinical signs and symptoms, and patient outcomes [10].

In conclusion, identifying the aetiology of paediatric CAP is frequently not possible, particularly in mild or moderate cases, and this may lead to the unnecessary prescription of antibiotics.

5. Therapy

In the absence of reliable markers capable of distinguishing viral and bacterial CAP or CAP caused by common and atypical bacteria, treatment remains largely empirical. However, the distinction seems to be somewhat artificial as 25-60% of childhood CAP cases have a mixed aetiology. Some guidelines suggest that antimicrobial therapy should not be routinely started in preschool-aged children with CAP because viral pathogens may be responsible in some cases [1,7], although another guideline states that all children with a clear clinical diagnosis of CAP should receive antibiotics because bacterial and viral pneumonia cannot be reliably distinguished [6].

Different antibiotics should be used for mild/moderate and severe/complicated CAP. Other factors to bear in mind are the patient's age, the presumed aetiology of the disease, the prevalence of antimicrobial resistance, and pneumococcal vaccination status.

During the first four weeks of life, the traditionally used combination of ampicillin (or amoxicillin) and aminoglycosides (mainly gentamicin) remains the treatment of choice, with a broad spectrum parenteral cephalosporin as a potential alternative [1]. In patients aged 1-3 months, *S. pneumoniae* is the main bacterial cause of CAP, and a β-lactam antibiotic is the proposed first-line treatment. *Chlamydia trachomatis* and *Bordetella pertussis* should be considered, especially in the presence of little or no fever and severe cough when macrolides should be proposed [1].

In children aged between four months and five years, the main bacterial causative agent of CAP is still *S. pneumoniae*, but atypical bacteria (particularly *M. pneumoniae*) may play a significant role, especially in children aged >2 years. The proposed drugs are penicillin G or an aminopenicillin, of which the most widely used is amoxicillin. Clinical failures and children who are not fully immunised against *S. pneumoniae* and/or *H. influenzae* type b could be treated with amoxicillin-clavulanate or third-generation cephalosporins. Second-generation cephalosporins can be proposed in areas with a low prevalence of *S. pneumoniae* penicillin resistance. In cases of severe CAP or suspected atypical bacteria, consideration can be given to combined therapy with a β-lactamase-resistant drug plus a macrolide [1].

The main cause of CAP in children and adolescents aged 5-18 years is *M. pneumoniae*, although *S. pneumoniae* still plays a significant aetiological role, particularly in more severe cases [1]. Macrolides are the first-line drugs in mild and moderate cases, whereas combined β-lactam and macrolide therapy can be considered in more severe cases [1].

In all age groups, an anti-staphylococcal antibiotic should be considered in critically ill patients [1]. As they are not approved for the regular treatment of children and can lead to the selection of resistant strains, quinolones should only be used in selected cases if there are no other effective alternatives (e.g. macrolide-resistant *M. pneumoniae* infections with persistent symptoms), or in children with immunoglobulin E-mediated allergy to ß-lactams [1].

The recommended duration of antimicrobial therapy is 7-10 days for mild/moderate CAP, but longer (e.g. ≥14 days) in cases of severe and/or complicated CAP [1].

6. Conclusions

Although CAP is one of the most frequent paediatric infectious diseases, the findings of this review indicate that there are a number of unanswered questions concerning its management, including the definition of CAP, the lack of a paediatric CAP severity score, the difficulty of identifying the aetiology of the disease, the resistance of the most frequent respiratory pathogens to the most widely used anti-infectious agents, and the lack of information concerning the changes in CAP epidemiology following the introduction of vaccines against respiratory pathogens. More research is clearly required in various areas, and further efforts are needed to increase vaccination coverage.

Conflict of Interest

The authors have no conflict of interest to declare.

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