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Viewpoint

Macrolides (alone or in combination) should be used as first-line empirical therapy of community-acquired pneumonia in children: myth or maxim?

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Whether macrolides should be used as a first-line empirical therapy in children with community-acquired pneumonia (CAP) remains debated. This debate is clearly reflected in the international and national management guidelines by incorporating vague recommendations when to use or add a macrolide antibiotic. In this viewpoint, the arguments feeding into the question of whether the statement "Macrolides should be used as first-line empirical therapy of CAP in children" is a myth or maxim, will be discussed.

To define first-line empirical therapy, *e.g.* treatment provided on the basis of an "educated guess" in the absence of complete information about the cause of the disease, the epidemiology of causative pathogens is highly relevant. Despite the fact that respiratory viruses are the most commonly detected causes of pneumonia in children, CAP is one of the most common reasons for prescribing antibiotics among paediatric patients [1, 2]. Childhood CAP is a clinical diagnosis and in the majority of the cases no causative diagnosis is obtained.

Epidemiological studies in Europe and the USA have shown that up to 10% of childhood CAP is caused by *Mycoplasma pneumoniae*, with lower rates in infants (3%) and higher rates in children aged >10 years (19%) [1, 3–6]. In comparison, in the post-pneumococcal and *Haemophilus influenzae* B vaccine era the incidence of CAP caused by *Streptococcus pneumoniae*, non-typeable *H. influenzae* and *Streptococcus* species is between 8 and 30% [1, 5] with comparable rates across paediatric age groups. The threshold for when to cover a specific causative pathogen with empirical therapy based on prevalence rates is not straight forward and other aspects need to be taken into account as well.

The expected disease severity and the risk of complications, especially when possibly delaying antibiotic treatment against a specific pathogen is also important. A severe disease course and development of complications (pleural empyema) is more frequently observed with the typical respiratory bacterial pathogens than with *M. pneumoniae* [4]. Pneumonia caused by *M. pneumoniae* usually progresses slowly and presents with self-limiting and benign disease. A recent study showed that the outcome of proven *M. pneumoniae* was not different between those who received empirical *versus* targeted treatment with a macrolide, supporting the notion that upfront treatment is not indicated [3].

While the majority of the common bacterial respiratory pathogens are susceptible to aminopenicillins, *M. pneumoniae* is not. Although macrolides have activity against the common bacteria causing CAP in children, increasing antimicrobial resistance is a huge concern.

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Macrolides should not be used as first-line therapy for community-acquired pneumonia in children as no clinical benefit is shown and widespread use is associated with an emerging increase in macrolide resistance amongst *S. pneumoniae* and *M. pneumoniae* https://bit.ly/3yQuedF

Macrolides are extensively used worldwide in children due to their ease of administration and favourable safety profile, but this has come at a cost. Pneumococcal resistance to macrolides is between 3% and 30% in European countries [7] and reported to be almost 50% amongst paediatric isolates in the USA [8]. The concerning increase in macrolide-resistant *M. pneumoniae* with close to 100% resistance rates reported in Asia, questions the use of macrolides as first-line empiric treatment for CAP in children [9].

International and national management guidelines strongly recommend the use of narrow-spectrum antibiotics (aminopenicillins) as first-line treatment for CAP in children [10]. Recommendations when to prescribe a macrolide do differ and range from when an atypical pneumonia is suspected or confirmed, to if no response to amoxicillin, and for its use as monotherapy or in combination with a β-lactam antibiotics [10]. While these recommendations do reflect the limited quality and paucity of the data available, multiple observational studies and clinical trials have failed to show a clear benefit of macrolides over narrow-spectrum antibiotics or in combination in the empirical treatment of children with CAP [11]. In addition, there is a lack of data concerning the role of macrolide therapy in children with proven atypical pneumonia [12].

The recommendations with respect to when to use a macrolide might be perceived as being relatively narrow, studies assessing antibiotic prescriptions for CAP in children indicate that the interpretation of these guidelines might lead to more use of macrolides as intended. In a retrospective cohort study of 252177 children aged 0–18 years diagnosed with CAP at the outpatient or emergency department in the USA, macrolide monotherapy was the most frequently used antibiotic regimen (43.2%) [13]. Aminopenicillins and broad-spectrum antibiotics were prescribed to 26.1% and 24.7% of children, respectively. A lower proportion of children aged 1–4 years received macrolides (32.9%) as empiric treatment. Over the study period (2010 to 2016), a favourable trend was seen as aminopenicillin prescriptions (20.1% to 31.8%) increased and prescriptions for macrolides decreased (45.8% to 40.5%) ($p<0.001$ for all trends). Decrease in macrolide monotherapy was highest in the youngest children (10.1%) compared with 4.4% in teenagers [13]. A similar prescribing behaviour was observed by Costenaro *et al.* [14], who assessed the antibiotic prescribing by 147 paediatricians to 6409 children aged 3 months to 14 years, suffering 7260 episodes of CAP over a period of 10 years in Italy. Overall, macrolides were prescribed in 30%, aminopenicillins in 16.7%, and 53.3% received broad-spectrum antibiotics. Of the 20% prescribed combination therapy, half of these received a combination with a macrolide. Children aged >5 years and those who had received antibiotic therapy in the previous 3 months were more likely to receive either a macrolide or broad-spectrum antibiotic. Another three studies assessing antibiotic used for childhood CAP in outpatients and emergency department settings in the USA showed that the majority of children received macrolides (38.7–47%) compared with 23–42% receiving a prescription for amoxicillin [15–17]. Factors associated with macrolide prescriptions included age >5 years, previous antibiotic receipt, and private insurance [17].

These antibiotic prescribing studies indicate that macrolides are more often prescribed for childhood CAP than aminopenicillins, and at a much higher frequency than one would expect based on the prevalence of *M. pneumoniae* pneumonia. A reason for this behaviour might well be a common belief that macrolides should be used in the empiric treatment of CAP in children. Another aspect we have to consider is that guidelines alone will not result in the expected behaviour, that drivers of prescription behaviour include nonclinical characteristics, and that the current guidelines do leave room for different interpretations. Based on clinical characteristics, the differentiation between a so-called "typical" and "atypical" CAP in children is a very challenging one, and this might increase the addition of a macrolide as alluded to in many guidelines: "add a macrolide when an atypical pneumonia is suspected".

Guidelines alone will not change prescription behaviour, as nicely illustrated in two studies focused on the role of antimicrobial stewardship in the management of CAP in children. The impact of the 2011 national guidelines for the management of childhood CAP (aged <18 years) was assessed in three US hospitals in the period 2010–2021 [18]. In two hospitals (B+C) educational conferences were held, and at one of these all staff received an e-mail that the recommendation for aminopenicillins was endorsed by the Infectious Disease Division. At the third hospital (A), no additional activities were undertaken after the publication of the guidelines. A remarkable difference was observed in the prescribing of antibiotics for childhood CAP between hospitals B+C and A. An absolute decrease in the prescription of macrolides in combination with either aminopenicillins or third generation cefalosporins of 21% and 22.3% *versus* 6.7% was observed in hospitals B+C and hospital A, respectively [18]. Another study assessed the changes in antibiotic prescriptions before and after implementation of a clinical pathway for CAP in children aged 3 months to15 years in an Italian paediatric emergency department [19]. Three clinical pathway training sessions were held. A statistically significant increase in the use of amoxicillin (54.5% *versus* 71.1%) and decrease in the use of macrolides (21.3% *versus* 6.4% was observed ($p<0.0001$) [19].

Summarising the data discussed, I have to come to the conclusion that it is a myth that macrolides should be used as a first-line antibiotic

to treat CAP in children, with the main argument that there is no data to support that the use of macrolides (either mono- or combination therapy) for CAP in children is more effective than aminopenicillins. For completeness, macrolides are recommended as an alternative in case of aminopenicillin allergy. Although some reductions in the use of macrolides have been shown [13], more efforts are needed to rationalise antibiotic use for childhood CAP. More clarity could be aimed for in the international and national guidelines on when to use a macrolide to cover *M. pneumoniae* and to prevent its overuse. More specific recommendations to prescribe a macrolide when no response to aminopenicillins is observed [20], or in case of proven *M. pneumoniae* infection [21], will be of value to optimise antibiotic use for childhood CAP. Unfortunately, real-time microbiological testing for atypical pathogens is not widely performed and differentiation between colonisation and infection is challenging [21]. Future research employing clinical prediction and decision algorithms may identify a subgroup of children more likely to benefit from macrolide therapy [22]. Another highly relevant argument in this discussion is the emerging antimicrobial resistance, urging us to use our antibiotics in the most appropriate way. The emerging resistance against macrolides amongst pneumococci as well as *M. pneumoniae* is of huge concern. Antimicrobial stewardship (AMS) programmes aim to promote a rational use of antibiotics resulting in improved patient outcomes, to prevent over- and misuse to minimise unintended consequences, and to reduce the development of antimicrobial resistance. Paediatric AMS programmes have already been shown to be successful in delivering these goals [19, 23, 24] and dedicated AMS teams are needed to optimise a rational antibiotic prescribing behaviour for childhood CAP.

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Conflict of interest

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