Treatment of *Mycoplasma pneumoniae* in Pediatric Lower Respiratory Infection

In this issue of *Pediatrics*, Biondi et al[1] present a rigorous systematic review and meta-analysis of the literature on the use of antibiotics to treat community-acquired (CA) lower respiratory infections (LRIs) secondary to *Mycoplasma pneumoniae* (MP). Consistent with previous studies, but on a larger scale, the evidence is deemed insufficient to support or refute such treatments for MP.

The following comments, although largely addressed in the article, are intended to highlight the caution that is required on the part of the reader when attempting to implement these conclusions to everyday practice. In particular, we must point out that lack of evidence of efficacy is not evidence of inefficacy when addressing current treatment paradigms. The problems of this and previous studies lie in the lack of uniformity of diagnostic methods, complicated by the fact that mixed infections with other microorganisms often go undiagnosed and contaminate any analysis of treatment efficacy. The small number of studies and their heterogeneity add to our inability to conclude either way, and therefore statements about results of MP-oriented antibiotic treatment are difficult to substantiate, particularly when applied to individual cases.

MP is a common cause of CA LRI, particularly in school-aged children and adolescents. It is responsible for at least 40% of cases of CA pneumonia (CAP) and as many as 18% of cases requiring hospitalization in children.[2] The diagnosis of MP infection is difficult and nonuniform, and serology and nucleic acid amplification (polymerase chain reaction) are mostly used. Few commercial serologic assays have been shown to have appropriate sensitivity and specificity.[3] Conversely, polymerase chain reaction may overestimate the incidence of MP and cost considerations limit its use. These factors frequently limit or delay diagnosis and introduce arbitrariness to therapeutic decisions.

Even when the diagnosis is made, there is evidence that MP infections are often mixed; Korppi et al[4] reported >50% of MP CAP to be mixed infections, with *Streptococcus pneumoniae* identified in two-thirds of cases. MP may precede and intensify subsequent infections with various respiratory viruses and bacteria.[5] Such data raise the question of how statements on efficacy of therapies for MP can be made when there is not even the knowledge of which organisms are being targeted.

Patients with MP infections mostly recover spontaneously, and it is difficult to assess how intervention and the timing thereof within the course of the infection can be factored in when studying the results of therapies. In human studies, antibiotics have been shown to shorten the clinical course of MP infection,[6] but at the same time carriage of organisms in the upper respiratory tract may not be eliminated.[7] It is therefore difficult to assess the effect of medication when organism eradication is not achieved, and thus the response of MP, unlike bacterial infections, is inherently more subtle and variable. Biondi

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KEY WORDS
mycoplasma, *Mycoplasma pneumoniae,* child

ABBREVIATIONS
CA—community-acquired
CAP—community-acquired pneumonia
LRI—lower respiratory infection
MP—*Mycoplasma pneumonia*

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et al[1] correctly allude to the fact that no study included in the analyses of this article ever considered the timing of the antibiotic intervention relative to the start of the symptoms. Indeed, timing constitutes an added layer of complexity, namely that treatment response may be a moving target in the context of MP. Slotkin et al[8] support the observation of antibiotics efficacy but suggest that the timing of the intervention may have an effect on the outcome; and although not directly stated, it is possible that delayed intervention may reduce efficacy. The authors comment that the data suggest that antibiotics benefit the clinical expression of MP disease by mechanisms other than reduction in or elimination of the organism.[8]

As shown in early studies in environments that were the closest to pure MP infections,[9–11] macrolides are the antibiotics of choice for treating MP infections in both adults and children. Therefore, suggestions to limit the use of these antibiotics that are based on meta-analyses such as the current analysis or the Cochrane review,[12] which point to insufficient evidence for efficacy of these treatments, are conclusions that are based on far less well established diagnoses and should be treated with caution. On the other hand, pneumococcal resistance to macrolides is currently so common in many countries that the use of macrolides alone is not justified anymore, even for respiratory infections, because of the risk of mixed infections.

We conclude that the current study further buttresses the uncertainty of the antibiotic treatment of presumed MP LRI. However, it falls short of guiding the practicing physician in daily decision-making about such treatments, and by no means should it be construed as evidence against the use of macrolide (or other appropriate) antibiotics in bona fide cases of MP. The concluding statement of the article that prospective controlled studies are needed has by now become a truism; our comments above, in agreement with the authors, set the parameters of what would be required from such a prospective study, a colossal undertaking indeed.

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