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Rightsizing Treatment for Pneumonia in Children

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Antibiotics are the double-edged swords we love to wield. They save lives, but they also cause harm with adverse drug events and the promotion of antibiotic resistance. Antibiotic stewardship is the effort to optimize the use of antibiotics to the right antibiotic at the right time and for the right duration. Stewardship encourages us to ask ourselves: can we decrease the biological costs of using these powerful tools, even a little, if we put them away earlier? Evidence has accumulated that we can give shorter courses of antibiotics, at least to adult patients, for many conditions, including for pneumonia, urinary tract infections, sinusitis, and cellulitis.[1] This is welcome news to anyone who has taken antibiotics themselves or given their child an antibiotic and experienced diarrhea or a yeast infection; adverse events and effects are common, especially in children.[2] However, in children, evidence regarding the efficacy of shorter antibiotic courses is lacking for most common conditions. At least in part because of this uncertainty, most antibiotic courses prescribed to children in the US for common infections, including pneumonia, are 10 days in duration.[3] This may be owing in part to the lack of strong evidence to guide recommendations for duration of therapy for many infections.

Is 10 days of antibiotics for pediatric pneumonia too long? Globally speaking, the answer is probably yes. The World Health Organization recommends 3 to 5 days of therapy.[4] A recent Cochrane review[5] that evaluated antibiotic therapy for nonsevere community-acquired pneumonia (CAP) globally in children aged 2 to 59 months found that 3 days was as effective as 5 days, although notably, there was no comparison with 10 days. Beyond the pediatric population, 5 days of antibiotic therapy is recommended for most adults with CAP in the US, even those requiring hospitalization, if they are showing improvement.[6] However, guidelines from the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America[7] do not recommend a specific duration of antibiotic therapy for

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pediatric CAP, when antibiotics are recommended, based on a lack of evidence supporting the optimal duration.

Pneumonia in children is considered one of the most common, serious infections of childhood, leading to an estimated 1 million outpatient antibiotic courses annually.[8] High vaccination rates for pneumococcal conjugate vaccine have reduced disease caused by *Streptococcus pneumoniae* since introduction in the US in 2000.[9] The advent of advanced molecular diagnostics that can rapidly identify respiratory viruses has also highlighted the role these viruses play in pediatric pneumonia. Indeed, in the large multicenter, population-based Etiology of Pneumonia in the Community (EPIC) study,[10] researchers identified viruses in 70% of children, whereas bacteria were identified in 15%, with *S pneumoniae* accounting for only 4%. Although there are limitations to these diagnostics, viruses clearly play an important role in pediatric pneumonia, a fact that furthers the impetus for reevaluating how we use antibiotics to treat this condition.

Considering these viral causes added to the current recommendations for treatment of pneumonia in global and adult populations, the evidence suggests recommending a shorter duration of therapy for pediatric pneumonia when antibiotics are indicated. Even so, randomized clinical trials should ask this question within the population of interest. In this issue of *JAMA Pediatrics*, Pernica and colleagues[11] in the SAFER study set out to help do just this, in evaluating the noninferiority of 5 vs 10 days of amoxicillin therapy for children presenting with pneumonia to 2 academic pediatric emergency departments in Ontario, Canada.

In this study, participants aged 6 months to 10 years were included if they were well enough to be treated as outpatients and if they met several criteria for the diagnosis of pneumonia, including evidence on chest radiography. Exclusions aimed to eliminate those with predisposition to severe disease or atypical organisms (eg, congenital heart disease, malignant neoplasms, immunodeficiency); however, children with conditions such as asthma were included. Participants were randomized to receive either 5 days of amoxicillin plus 5 days of placebo or 10 days of amoxicillin, and they were blinded to this intervention. The primary outcome was clinical cure at 14 to 21 days, which required defervescence within the first 4 days, no more than 1 additional fever spike after day 4, improvement in work of breathing, resolution of tachypnea, and no need for additional antibiotics or hospital admission due to worsening symptoms. Secondary outcomes sought to measure duration of absence from school or daycare, caregiver work disruption, mild drug adverse reactions, serious drug reactions, adherence, and recurrence. The noninferiority margin was set at 7.5% (1-sided confidence limit, 97.5%, with $\alpha = .025$).

The researchers found that in 281 participants, with a median age of 2.6 (interquartile range [IQR], 1.6-4.9) years, clinical cure rates were similar in both groups: 88.6% in the 5-day arm vs 90.8% in the 10-day arm for the per protocol analysis. This resulted in a risk difference of −0.016 with a 97.5% confidence limit of −0.087, and thus, they could not conclude noninferiority. However, the intention-to-treat analysis was conclusive in finding 5 days of therapy to be statistically noninferior to 10 days, with clinical cure in 85.7% in the 5-day arm vs 84.1% in the 10-day arm (risk difference, 0.023; 97.5% confidence

limit, −0.061%). Among secondary outcomes, there were no differences, except that median caregiver work absenteeism was 2 (IQR, 0-4) days for those receiving 5 days of therapy vs 3 (IQR, 0-6) days for the standard therapy. This difference was likely owing to chance, because it occurred before 5 days.

As the trial was being conducted, the authors realized some children were being categorized as having clinical failure because they had more than 1 fever spike in the 14 to 21 days after their initial defervescence, but that these children did not require additional treatment. Thus, post hoc, the authors created a variant of the primary outcome termed *clinical cure not requiring additional intervention*. This outcome required improvement and defervescence in the first 4 days and no need for additional antibiotics or hospitalization. The authors believed that this outcome better approximated real-world clinical care delivery. In the post hoc, per protocol analysis, 95.5% of children in the 5-day arm and 95.4% in the 10-day arm achieved the outcome, and noninferiority was reached. Although the authors were unable to formally conclude noninferiority based on their a priori, per protocol analysis, they concluded that strong evidence supports using 5 days of amoxicillin for children with pneumonia.

This study adds to a growing body of evidence that the optimal duration of antibiotic therapy for CAP is shorter than what is traditionally given. Performing a high-quality trial in the specific target population strengthens the finding that 5 days of antibiotic therapy likely works as well as 10 days for most children with pneumonia. Although the study did not officially meet noninferiority criteria with the a priori per protocol analysis, it is worth mentioning that changing clinical practice is not about being unequivocally better; rather, in this case and many others, one weighs the balance of additional harms from more days of therapy against a small risk of clinical failure. Although incidence of mild and severe adverse events was too small in this study to draw conclusions, decreasing the burden of antibiotic therapy could contribute to a speedier return of gut microbiota and decrease complications stemming from this disruption.[12]

Furthermore, shortening the recommended duration of antibiotic therapy for pediatric pneumonia does not prevent clinicians from prescribing for a longer duration when needed. A recommended duration is a behavior change tool: giving a default option nudges a clinician to use that duration and helps change practice.[13] Most treatment failures in the study occurred early (ie, before 5 days) and thus would offer an opportunity to extend or change therapy in these cases. Clinicians can and should check in on their patients and instruct patients to seek medical care if symptoms worsen. The ongoing multicenter, randomized superiority trial Short Course vs Standard Course Outpatient Therapy of Community Acquired Pneumonia in Children (SCOUT-CAP) is investigating this strategy in treating children in the US: if the child is evaluated and improving on day 5, do they need another 5 days of antibiotic therapy, or can they place the therapeutic sword back in its scabbard?[14]

Reevaluating the duration of antibiotic therapy furthers the difficult but necessary work of preserving the usefulness of our current antibiotic arsenal. This study by Pernica and colleagues[11] underscores the importance of finding the right duration of therapy for specific conditions and in specific populations. High-quality data from randomized clinical trials,

such as this one, constitute the first and most important step to changing traditional prescribing practices. As we continue to be confronted with the far-reaching harms of antibiotic overuse both on an individual and population level, we should work toward improving care for our patients with right-sized antibiotic courses, resheathing our swords to keep them sharp for the next battle.

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