Pediatric Antibiotic Stewardship

Shorter vs. longer duration of therapy: a review of the evidence.

ABSTRACT: With the rise of antibiotic resistance, antimicrobial stewardship programs can now be found in the ambulatory setting, where nearly 95% of antibiotic prescriptions originate. Judicious use of antibiotics is of particular importance to the ambulatory pediatric provider, as the annual antibiotic prescription rate is highest among children ages two and younger and inappropriate early-life antibiotic use is associated with elevated childhood risk of several medical conditions. While most ambulatory antibiotic stewardship programs have focused on shaping clinician behaviors to prevent unnecessary antibiotic prescribing, duration of antibiotic therapy has been found to be a critical, yet underexamined, facet of antibiotic use. In the past, duration of antibiotic therapy was largely based on convention and expert opinion, with little scientific evidence supporting many of the recommendations. Research suggests that many common pediatric infections such as acute otitis media, community-acquired pneumonia, streptococcal pharyngitis, and urinary tract infections can be effectively and safely treated with reduced courses of antibiotic therapy. In addition to reducing the incidence of antibiotic resistance, a shorter duration of antibiotic therapy may help prevent many adverse effects associated with antibiotic treatment. Current studies on the duration of antibiotic therapy, especially in pediatrics, are limited as they often rely on data extrapolated from adult studies that fail to consider the effects of age-related growth and development on both pharmacokinetics and pharmacodynamics. Future investigation into this topic is also limited by researchers' reliance on subsidies from pharmaceutical companies; clinicians' fear of undertreating infection; and hesitancy to deviate from current standards of care, even when such standards are not evidence based. Despite these challenges, the dangers of inappropriate antibiotic use in the pediatric population warrant further evaluation.

Keywords: antibiotics, antibiotic stewardship, infection, pediatrics

Inappropriate antibiotic use has a well-established association with the rise of antibiotic resistant organisms and has prompted a global rise in antibiotic stewardship initiatives.[1] While antibiotic stewardship programs were initially confined to the realm of acute care and long-term care facilities, the recognition that in many developed countries 86% to 95% of antibiotics are dispensed in community care centers[2] has inspired researchers to evaluate and improve antibiotic usage in outpatient settings. For example, in 2016, the Centers for Disease Control and Prevention (CDC) published *Core Elements of Outpatient Antibiotic Stewardship* (available for download at www.cdc.gov/antibiotic-use/core-elements/outpatient.html) to guide antibiotic treatment in ambulatory care facilities in the United States.[3] In these facilities, based on the rate of ambulatory care visits in which antibiotics are prescribed to treat conditions for which they are not indicated or are overused, it's estimated that 30% of antibiotic prescriptions are inappropriate.[4]

THE FOCUS ON PEDIATRICS

Appropriate use of antibiotics is particularly important in pediatric practice. An analysis of the 2010–2011 National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care

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Survey found that the annual antibiotic prescription rate was highest among children ages two and younger, for whom 1,287 antibiotic prescriptions were written per 1,000 population.[4] The diagnoses commonly associated with antibiotic prescriptions were sinusitis, suppurative otitis media, and pharyngitis. Although national guidelines recommend antibiotic therapy for streptococcal pharyngitis,[5] the mean annual rate of antibiotic prescriptions for pharyngitis in children (91 per 1,000 population) was more than 50% higher than the estimated appropriate annual rate (60 per 1,000 population).[4]

Additionally, emerging research shows that inappropriate use of antibiotics early in life is associated with disturbances in the gastrointestinal microbiome, which puts children at elevated risk for medical conditions such as juvenile idiopathic arthritis, celiac disease, inflammatory bowel disease, diabetes, obesity, and food allergies.[3]

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NURSES' ROLE IN PEDIATRIC ANTIBIOTIC STEWARDSHIP

While antibiotic prescribing was initially thought to be the sole responsibility of providers, there is a growing recognition that nurses are integral to responsible antimicrobial use.[6] Given the increasing number of antibiotic-resistant organisms, evidence-based education of both health care professionals and the public at large on the appropriate use of antibiotics is critical to public health and safety, and nurses are the most qualified professionals to provide this information. In U.S. Gallup polling, nurses have repeatedly been identified as the most trusted professionals and are specifically trained in methods of effective communication.[7] Nurses who know the benefits of the currently recommended approach to antibiotic use and stewardship are well suited to teach patients the importance of appropriate antibiotic use and adherence.

THE FUNDAMENTALS OF ANTIBIOTIC STEWARDSHIP

Antibiotic stewardship is often viewed as the practice of preventing unnecessary antibiotic overuse, but it also encompasses the following critical components[3]:

- appropriate diagnosis
- timely initiation of indicated antibiotics
- optimization of antibiotic selection, that is, identifying the best drug, dose, and duration to treat an infection effectively while reducing the risk of adverse reactions

ANTIBIOTIC DURATION: WHY SHORTER IS BETTER

Our understanding of pediatric pharmacokinetics and pharmacodynamics, properties of antimicrobial agents, and etiologies of common infectious conditions have produced a vast amount of information to guide appropriate drug selection and dosage, but research on duration of therapy is scant. For both adults and children, studies of therapy duration have been performed for only some common infectious conditions and, in most cases, there is limited evidence to support a specific duration of treatment.[8]

Historically, recommendations for duration are based largely on clinical anecdotes and expert opinion, though research from as far back as 1998 suggests that a shorter duration of antibiotic therapy can effectively treat such conditions as acute otitis media and community-acquired pneumonia without compromising clinical outcomes.[9-11]

It's widely acknowledged that the commonly prescribed duration of antibiotic therapy—ranging from seven to 14 or five to 10 days—was adopted simply because, for purposes of calculation, it's convenient to prescribe medications in terms of weeks or in multiples of five days.[8, 12]

Even a week may be too long. While much research on the duration of antibiotic therapy has used a week as a convenient measure of a short course (less than seven days) or a long course (more than seven days), recent preliminary research indicates that even a seven-day duration may be longer than necessary to adequately treat many common infections.[13] An approach of "shorter is better" is becoming a more common evidence-based paradigm for the use of antibiotics. Pharmacological research has demonstrated that many antibiotic courses may be shortened without clinical compromise, while also reducing risk of adverse effects.[14]

In pediatric practice, it's estimated that one in 14 children treated for acute otitis media with antibiotics experiences an adverse drug reaction, such as vomiting, diarrhea, or rash, suggesting that management should stress the importance of appropriate analgesia and limit the use of antibiotics.[15]

Shortened antibiotic courses likewise reduce the risk of promoting antibiotic-resistant organisms by shortening the period during which bacteria are exposed to the antibiotic, thereby lowering bacterial selection pressure.[14] For example, an antibiotic that kills susceptible bacteria also allows bacteria that are resistant to the agent to survive and multiply. A shortened duration of antimicrobial therapy, therefore, not only reduces adverse effects in patients receiving the therapy but also tends to preserve the antibiotic's effectiveness for the treatment of future infections in those patients as well as in others.

COMMON PEDIATRIC INFECTIONS

While data regarding reduced antibiotic courses for specific pediatric conditions are limited, recent research has examined shorter versus longer courses of antibiotic treatment for common pediatric infections such as acute otitis media, community-acquired pneumonia, streptococcal pharyngitis, and urinary tract infections. For a summary of current and alternate treatment duration recommendations, see Table 1.[9, 16-22]

Acute otitis media. Recent research on the reduction of antibiotic duration in acute otitis

Table 1. Current and Alternate Treatment Durations for Common Conditions

Condition	Current Treatment Duration Guidelines[22]	Studied Alternate Treatment Durations	Comparison
Group-A streptococcal pharyngitis	10 days of penicillin-based antibiotic or cephalosporin	3 to 6 days of macrolide or cephalosporin[19]	No significant difference in late clinical recurrence or development of complications such as acute rheumatic fever or glomerulonephritis between current and alternate treatment durations.
			Lower risk of early treatment failure in shorter duration of therapy.
		7 days of penicillin-based antibiotic[20]	No significant difference in adverse outcomes (recurrent or persistent infection) between shortened and standard treatment groups.
Community-acquired pneumonia	7 days of amoxicillin, ampicillin, or penicillin (or 5 days in uncomplicated cases)	The variable etiology of community-acquired pneumonia makes treatment recommendations challenging. Current tools may not effectively capture children with bacterial pneumonias, forcing providers to treat empirically in many cases.[18]	
Urinary tract infections	7 to 10 days of bacteria-specific antibiotic for children > 2 years; no duration recommendation for children < 2 years	< 10 days of bacteria-specific antibiotic[21]	No significant difference between patients treated for a median of 8 days and for > 10 days (median, 11 days) with respect to the odds of treatment failure and the development of drug-resistant pathogens with subsequent infections.
Acute otitis media	10 days of amoxicillin	< 10 days of penicillin-based antibiotic	Variable after 30 days. Treatment courses of < 10 days are as effective as courses > 10 days, with no significant increase in adverse events.[9] No increase in treatment failure or rate of adverse events through 30 days occurred in long or short durations of treatment.[16] Higher failure rate of therapy occurred in shorter treatment duration groups.[17]

media has been the most variable. A 2010 systematic review found that, up to one month after treatment, short courses of antibiotics had not increased the rate of treatment failure compared with long courses, and that the risk of adverse effects, such as diarrhea, rash, and vomiting, was significantly lower in patients receiving short courses of antibiotics than in those receiving long courses.[16] This study also suggested that shorter courses of antibiotics did not increase the risk of recurrent acute otitis media or persistent middle ear effusion at one to three months after the initial treatment.

In contrast, a 2016 study demonstrated that children with acute otitis media who received a five-day course of antibiotic therapy experienced treatment failure at significantly higher rates than those who received the standard 10-day course.[17] Variability in study findings regarding acute otitis media treatment may be attributed to a number of factors, including temporal and geographic differences between the studies, though etiology of infection is likely a significant contributing factor as well.

Streptococcal pharyngitis. For the past 60 years, the near universal treatment of pediatric streptococcal pharyngitis has consisted of penicillin-based antibiotics for a duration of 10 days.[8] But the 10-day guideline, born largely out of fear of rheumatic fever, has never been scientifically substantiated, and nonpenicillin antibiotics taken for fewer than 10 days has produced equivalent eradication rates.[8] Furthermore, it's estimated that nearly 10,000 people in the United States would need to be treated for group A streptococcal pharyngitis to prevent a single case of rheumatic fever.[24]

A 2012 Cochrane review of 13,102 cases of acute group A β-hemolytic streptococcal pharyngitis found that when children who received a three-to-six day course of a nonpenicillin antibiotic were compared with children treated with the standard 10-day penicillin course, those receiving the shorter treatment course had a lower risk of early treatment failure; moreover, no significant difference was found between the groups in late clinical recurrence or in development of glomerulonephritis or acute rheumatic fever.[19]

An approach of 'shorter is better' is becoming a more common evidence-based paradigm for the use of antibiotics.

Community-acquired pneumonia. Globally, the consensus for treating children with mild to moderate community-acquired pneumonia has been to prescribe seven days of oral antibiotic therapy, though the benefits and risks of this approach have not been studied in randomized controlled trials.[18] While some studies suggest shorter courses of therapy for uncomplicated cases are as effective as seven-day courses, more research is needed in this area.[18]

Evaluating the data regarding duration of therapy for uncomplicated community-acquired pneumonia is particularly challenging, as existing guidelines may not capture children with true bacterial pneumonia. World Health Organization guidelines for the diagnosis of community-acquired pneumonia are notably sensitive, but not specific.[23] Complicating the data surrounding community-acquired pneumonia is its variable etiology. Determining viral versus bacterial origin is incredibly difficult because of the time-consuming nature of respiratory cultures and the high interobserver variation associated with diagnosis by chest radiograph, which may lead to overtreatment.[18]

Additionally, a retrospective analysis of 2,845 cases of children presenting to an ED with group A streptococcal pharyngitis found no significant difference in the rate of return to the ED with a persistent or recurrent infection between those who received a shorter course (seven days) of antibiotics and those who received a standard 10-day course.[20]

Urinary tract infections. A retrospective observational study of children with pyelonephritis found no significant difference between children treated with a short course of antibiotics (six to nine days; median, eight days) and a prolonged course (10 or more days; median, 11 days) in the odds of treatment failure (11.2% versus 9.4% of children, respectively) or in the development of a drug-resistant uropathogen in those with subsequent urinary tract infection within 30 days (40% versus 64% of children, respectively).[21]

SUPPORT FOR SHORTER ANTIBIOTIC COURSES IN ADULTS

As with research involving antibiotic treatment in children, an overview of nine systematic reviews comparing the effectiveness of short and long

courses of oral antibiotics in adults treated in outpatient settings demonstrated no statistically significant difference in clinical cure rates between shortened and standard courses of antibiotic treatment for the following infections[25]:

- acute bacterial sinusitis
- uncomplicated cystitis in nonpregnant women
- acute pyelonephritis
- community-acquired pneumonia

ANTIBIOTIC DURATION IN COMPLEX PEDIATRIC INFECTIONS

While most research in reducing the duration of pediatric antibiotic therapy has involved children with low-risk infections, evidence suggests that shorter antibiotic courses may be appropriate for some more complex infections. A 2014 cohort study at Johns Hopkins Hospital compared outcomes among 170 pairs of score-matched pediatric patients with uncomplicated gram-negative bacteremia who received antibiotic treatment for either seven to 10 days or 10 or more days.[26] The number of deaths among the children in each of the two groups was comparable, six in the short-course and five in the long-course treatment groups. Similarly, the longer course of antibiotic treatment did not reduce the risk of bacteremic relapse.

ORGANIZATIONS ADVOCATING ANTIBIOTIC STEWARDSHIP

Organizations around the globe have mobilized to address the judicious use of antibiotics, with several making recommendations that directly affect outpatient practice and the treatment of pediatric patients. The CDC has developed recommendations for treating pediatric outpatients to help facilities and providers improve antibiotic prescribing practices and patient outcomes (available online at www.cdc.gov/antibiotic-use/clinicians/pediatric-treatment-rec.html), as well as a "Be Antibiotics Aware Partner Toolkit" (available online at www.cdc.gov/antibiotic-use/week/toolkit.html), which includes educational resources for patients and their families. While the current recommendations for duration of therapy follow the conventional 10 to 14 days of treatment for most pediatric bacterial infections, the CDC's "Be Antibiotics Aware" campaign highlights the importance of ongoing work to identify the shortest effective duration of antibiotic therapy that reduces resistance and minimizes harm to patients.

The American Academy of Pediatrics has also engaged providers in conversation about antibiotic stewardship by partnering with the Pediatric Infectious Diseases Society and Health Care Without Harm to produce the Pediatric Antibiotic Stewardship Program tool kit for all health care settings, (available online at https://pids.org/pediatric-asp-toolkit).The tool kit highlights the risk of adverse drug reactions and growing drug antibiotic resistance in children.

LIMITATIONS OF CURRENT STUDIES

Pharmacological industry-sponsored research on antibiotics has inherent limitations. Pharmaceutical companies have little incentive to perform additional studies that would reduce the volume of antibiotics they supply, and both time and monetary investments in new antibiotics is notably high.[27] These factors force clinicians to extrapolate from the findings of existing studies, which have been largely performed on adults, in developing pediatric treatment practices, which subsequently fail to account for the age-related metabolic differences of children or to address predominantly pediatric conditions.[18, 28] Finally, the etiology and prevalence of infectious conditions play a critical role in the determination of treatment and its success, limiting the ability of studies to make universal recommendations, particularly when resources vary dramatically within countries and across the globe.[23]

RESEARCH CHALLENGES

Despite studies suggesting that reducing the duration of antibiotic therapy may be efficacious and ethical, systemic issues present challenges to future research. Children, by nature, are a protected group within research, and failure to administer pharmacological therapy exactly as recommended in current clinical guidelines may be viewed by prominent health organizations as a deviation from the standard of care. Additionally, while antibiotic stewardship guidelines suggest reducing antibiotic use, inclusive of duration, organizational and association policy often limits the means to do so effectively.

To overcome these challenges, some clinicians have proposed that just as pediatric antibiotic dosing is based on age and size, so too should pediatric antibiotic duration of treatment, which necessitates additional research.[28] Some groups have proposed alternatives to conventional randomized controlled trials, including the use of progressive multiarm trials, in order to maximize valuable data while minimizing potential risk to pediatric patients.[29] ▼

For four additional nursing continuing professional development activities on the topic of antibiotic stewardship, go to www.nursingcenter.com.

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REFERENCES

1. King LM, et al. Changes in US outpatient antibiotic prescriptions from 2011-2016. *Clin Infect Dis* 2020;70(3):370-7.
2. Duffy E, et al. Antibacterials dispensed in the community comprise 85%-95% of total human antibacterial consumption. *J Clin Pharm Ther* 2018;43(1):59-64.
3. King LM, et al. Advances in optimizing the prescription of antibiotics in outpatient settings. *BMJ* 2018;363:k3047.
4. Fleming-Dutra KE, et al. Prevalence of inappropriate antibiotic prescriptions among US ambulatory care visits, 2010-2011. *JAMA* 2016;315(17):1864-73.
5. Shulman ST, et al. Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis: 2012 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2012;55(10):e86-e102.
6. Olans RD, et al. Good nursing is good antibiotic stewardship. *Am J Nurs* 2017;117(8):58-63.
7. Olans RD, et al. Nurses and antimicrobial stewardship: past, present, and future. *Infect Dis Clin North Am* 2020;34(1):67-82.
8. Radetsky M. Hostage to history: the duration of antimicrobial treatment for cute streptococcal pharyngitis. *Pediatr Infect Dis J* 2017;36(5):507-12.
9. Kozyrskyj AL, et al. Treatment of acute otitis media with a shortened course of antibiotics: a meta-analysis. *JAMA* 1998;279(21):1736-42.
10. Dunbar LM, et al. High-dose, short-course levofloxacin for community-acquired pneumonia: a new treatment paradigm. *Clin Infect Dis* 2003;37(6):752-60.
11. el Moussaoui R, et al. Effectiveness of discontinuing antibiotic treatment after three days versus eight days in mild to moderate-severe community acquired pneumonia: randomised, double blind study. *BMJ* 2006;332(7554):1355.
12. Spellberg B. The new antibiotic mantra—"shorter is better." *JAMA Intern Med* 2016;176(9):1254-5.
13. Wald-Dickler N, Spellberg B. Short-course antibiotic therapy—replacing Constantine units with "shorter is better." *Clin Infect Dis* 2019;69(9):1476-9.
14. Hanretty AM, Gallagher JC. Shortened courses of antibiotics for bacterial infections: a systematic review of randomized controlled trials. *Pharmacotherapy* 2018;38(6):674-87.
15. Venekamp RP, et al. Antibiotics for acute otitis media in children. *Cochrane Database Syst Rev* 2015(6):CD000219.
16. Gulani A, et al. Efficacy of short course (<4 days) of antibiotics for treatment of acute otitis media in children: a systematic review of randomized controlled trials. *Indian Pediatr* 2010;47(1):74-87.
17. Hoberman A, et al. Shortened antimicrobial treatment for acute otitis media in young children. *N Engl J Med* 2016;375(25):2446-56.
18. Esposito S, et al. Antibiotic therapy for pediatric community-acquired pneumonia: do we know when, what and for how long to treat? *Pediatr Infect Dis J* 2012;31(6):e78-e85.
19. Altamimi S, et al. Short-term late-generation antibiotics versus longer term penicillin for acute streptococcal pharyngitis in children. *Cochrane Database Syst Rev* 2012(8):CD004872.
20. Oliveira Pereira C, et al. [Diagnosis and treatment of acute pharyngitis—is there any benefit on ten-day course of antibiotics?] *An Pediatr (Engl Ed)* 2018;88(6):335-9.
21. Fox MT, et al. Comparative effectiveness of antibiotic treatment duration in children with pyelonephritis. *JAMA Netw Open* 2020;3(5):e203951.
22. Kimberlin DW, et al. Streptococcus pneumoniae (pneumococcal) infections. In: Kimberlin DW, Barnett ED, et al., editors. *Red book: 2021 report of the committee on infectious diseases*. Itasca, IL: American Academy of Pediatrics; 2021. p. 717-27.
23. Ben-Shimol S, et al. Evidence for short duration of antibiotic treatment for non-severe community acquired pneumonia (CAP) in children - are we there yet? A systematic review of randomised controlled trials. *Pneumonia (Nathan)* 2014;4:16-23.
24. McMurray K, Garber M. Taking chances with strep throat. *Hosp Pediatr* 2015;5(10):552-4.
25. Dawson-Hahn EE, et al. Short-course versus long-course oral antibiotic treatment for infections treated in outpatient settings: a review of systematic reviews. *Fam Pract* 2017;34(5):511-9.
26. Park SH, et al. Short versus prolonged courses of antibiotic therapy for children with uncomplicated Gram-negative bacteraemia. *J Antimicrob Chemother* 2014;69(3):779-85.
27. Ventola CL. The antibiotic resistance crisis: part 1: causes and threats. *P T* 2015;40(4):277-83.
28. Le J, Bradley JS. Optimizing antibiotic drug therapy in pediatrics: current state and future needs. *J Clin Pharmacol* 2018;58 Suppl 10:S108-S122.
29. Pouwels KB, et al. Optimising trial designs to identify appropriate antibiotic treatment durations. *BMC Med* 2019;17(1):115.