



“Give Me Five”: The Case for 5 Days of Antibiotics as the Default Duration for Acute Respiratory Tract Infections

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Acute respiratory tract infections (ARTIs) account for most antibiotic prescriptions in pediatrics. Although US guidelines continue to recommend ≥ 10 days antibiotics for common ARTIs, evidence suggests that 5-day courses can be safe and effective. Academic imprinting seems to play a major role in the continued use of prolonged antibiotic durations. In this report, we discuss the evidence supporting short antibiotic courses for group A streptococcal pharyngitis, acute otitis media, and acute bacterial rhinosinusitis. We discuss the basis for prolonged antibiotic course recommendations and recent literature investigating shorter courses. Prescribers in the United States should overcome academic imprinting and follow international trends to reduce antibiotic durations for common ARTIs, where 5 days is a safe and efficacious course when antibiotics are prescribed.

Key words. acute bacterial rhinosinusitis; acute otitis media; acute respiratory tract infection; antimicrobial stewardship; duration of therapy; pharyngitis.

INTRODUCTION

Antibiotics are life-saving medications, but also lead to resistance, adverse drug events, and other patient harms. Antimicrobial stewardship efforts have targeted inappropriate prescribing, optimal diagnostic testing, and strategies such as “watch and wait” or delayed prescribing. These strategies have all been successful in reducing overall inappropriate antimicrobial use. One other strategy that is more recently being examined is optimizing the duration of antibiotic treatment to reduce overall antibiotic exposure.

However, the data focusing on treatment durations are incomplete and robust literature does not exist to support commonly used long antibiotic durations. Acute respiratory tract infections (ARTIs) in children account for the majority of antibiotics prescribed, making them a high-yield target to optimize treatment durations [1]. Shifting common drug durations from 10 to 5 days for most uncomplicated ARTIs could minimize consequences such as diarrhea, microbiome disruption, *C. difficile* infection, healthcare system costs, and potentially drug shortages, which have been frequently

encountered in the last few years and lead to less appropriate therapy [2].

In this review, we will focus on available data regarding duration of treatment for common, uncomplicated ARTIs. Because complications of bacterial ARTIs are rare in the United States, eg, acute rheumatic fever (ARF) after group A streptococcal (GAS) pharyngitis, randomized controlled trials (RCTs) are often unavailable with enough power to definitively answer the question of optimal treatment. Additionally, there is wide variation internationally on recommended durations of therapy for common ARTIs (Table 1). Therefore, we sought to review the strength of the medical literature supporting durations of treatment for common ARTIs, including GAS pharyngitis, acute bacterial rhinosinusitis (ABRS), and acute otitis media (AOM).

Clinicians commonly prescribe longer courses of antibiotics to err on the side of caution and avoid complications of common infections. This article explores the significance of focusing on durations of antibiotic therapy and highlights the need to overcome “academic imprinting,” which refers to the tendency of healthcare professionals to adhere to long-standing practices, even when evidence supporting these practices is limited [17]. Long-standing practices often are not based on strong evidence relevant to modern clinicians. Advances in related fields (eg, pharmacokinetics) and changing epidemiology of infection due to medical advancement (eg, vaccines) should be considered in current practice. Overcoming academic imprinting and challenging the historical mindset is crucial to drive positive change in medical practices, as it allows healthcare professionals to adapt to emerging evidence and provide optimal patient care.

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Table 1. Duration of Penicillin-Class Antibiotics for Treatment of Group A Streptococcal (GAS) Pharyngitis, Acute Otitis Media (AOM), and Acute Bacterial Rhinosinusitis (ABRS) in US Guidelines Compared to Select International Guidelines

Duration in Days	GAS Pharyngitis	AOM	ABRS
United States	10 d [3]	>6 y: 5–7 d 2–5 y: 7 d <2 y or severe symptoms: 10 d [4]	10–14 d (7 d from symptom resolution) [5–7] Redbook: 5–7 d [8]
United Kingdom (NICE) [9]	5 d for symptomatic cure 10 d for microbiologic cure	5–7 d	5 d
The Netherlands	Forego antibiotics If treating, 5–7 d to shorten symptom duration [10]	<2 y or perforation: 7 d >2 y: forego antibiotics [11]	Antibiotics only if severe course or immune compromised: “no reasons to recommend a longer than usual duration of use of the antibiotic” [12]
Australia	High-risk groups: 10 d Low-risk groups: forego antibiotics [13]	7 d [14]	5 d [15]
WHO [16]	High-risk groups: 10 d Low-risk groups: forego antibiotics. If treating: 5 d	5 d	5 d

Durations of therapy for common infections have been anchored in historical literature. Dr Michael Radetsky has published detailed reviews on the historical basis of current-day treatment durations [18]. The “7-10-14-day rule,” historically the default for treatment duration decisions for common pediatric infections, has appeared in literature since antibiotics were discovered in the late 1930s. This duration rule was supported by early pediatric textbooks and published guidance despite lack of scientific investigation to define default durations. Historical defaults have remained in national guidance despite an increasing number of large retrospective and observational studies for common pediatric infections which challenge the benefits of longer durations of therapy.

GROUP A STREPTOCOCCAL PHARYNGITIS

The prevalence of GAS pharyngitis is approximately 20% [19]. GAS pharyngitis in children is diagnosed primarily by symptoms and physical exam findings. The use of testing for diagnosis and antibiotics for treatment for GAS pharyngitis vary between countries [20, 21]. In the United States, GAS pharyngitis is typically treated for 10 days; other international bodies recommend shorter durations or no antimicrobial therapy (Table 1). In this section, the duration of antibiotic therapy will be discussed when the decision has been made to treat. Clinicians should consider the optimal duration for GAS pharyngitis needed to improve clinical symptoms, prevent suppurative (eg, abscess) and nonsuppurative (eg, ARF) complications, and reduce transmission to close contacts.

Antipyretics and anti-inflammatory medications are the most effective treatment for symptom relief for pharyngitis. Antibiotic treatment of GAS pharyngitis reduces symptoms of sore throat and fever by a mean of 16 h compared to patients receiving no antibiotic treatment, with the greatest reduction in symptoms seen on day 3 of illness [22]. Symptoms of sore throat and fever resolve with no antibiotic treatment by day 3 of illness in 40% and 85% of patients with pharyngitis,

respectively, and there is no significant difference in symptoms between antibiotic and no antibiotic treatment by 1 week of illness [22]. A recent RCT comparing 5 vs 10 days of penicillin for GAS pharyngitis showed resolution of sore throat at day 4 of illness for both groups [23]. For the goal of symptom reduction and shortened duration of illness for GAS pharyngitis, current literature supports the use of no more than 5 days of antibiotic treatment.

Suppurative complications of GAS pharyngitis (abscess, sinusitis, otitis media, or cellulitis) are rare and occur in ~1% of patients with pharyngitis regardless of treatment with or without antibiotics [24]. An RCT of 433 pediatric patients in Sweden comparing short (5 days) vs long (10 days) duration of oral penicillin showed no difference in relapse (4.5% vs 3.9%, percent difference 0.6 [–4.1 to 5.3]), recurrence (3% vs 6.9%, –3.8 [–8.7 to 1.0]), or suppurative complications (0 vs 2.1%, –2.1 [–4.7 to 0.5]) [23]. Similarly, a retrospective study in Spain of 350 pediatric patients receiving long (8–10 days) vs short (5–7 days) treatment courses found no difference in recurrence (9.8% vs 9.5%, odds ratio, OR 0.97 [0.46–2.03]) or suppurative complications (4% vs 2.4%, OR 0.58 [0.15–2.19]) [25]. The rarity of suppurative complications from GAS pharyngitis regardless of treatment supports a 5-day duration for treatment of GAS pharyngitis.

Longer durations for treatment of GAS pharyngitis have higher rates of microbiological eradication compared to shorter durations of treatment with oral penicillin [26]. To determine the optimal duration of therapy for treatment of GAS, clinicians should consider the clinical significance of microbiological eradication. It is historically believed that bacterial eradication of GAS in the oropharynx is linked to lower rates of ARF. However, the scientific basis of this belief hinges on a retrospective secondary data study without statistical analyses of WWII military recruits during a scarlet fever outbreak [27]. Modern-day studies show persistent culture positivity in 5–10% and PCR positivity in 20% of patients treated for GAS with 10 days of penicillin or amoxicillin [28]. Despite lack of microbiologic

eradication with long durations of therapy, ARF is a rare outcome in low-risk populations.

At the time of these seminal studies on GAS pharyngitis, ARF rates of 3% occurred in untreated WWII military recruits with pharyngitis. Children were first included in studies on GAS pharyngitis in the early 1960s when healthy children in Chicago were found to have a 0.33% incidence rate of ARF in untreated pharyngitis [29]. It was clear that ARF rates differed between high-risk (crowded military barracks) and low-risk (healthy children in urban settings) populations. Today, nonindigenous persons from high-income countries are considered low risk for developing ARF; certain Indigenous populations and persons from low- and middle-income countries are considered high risk [30]. Current studies indicate that incidence rates of ARF in children in low-risk settings is as low as 0.6 per 100 000 [31]. Rates in the United States are difficult to estimate as ARF has not been a reportable condition since 1995, when ARF rates fell below 2 in a million persons [32]. The outcome of ARF is not estimable in studies after 1962 given the rarity of ARF. A meta-analysis of RCTs (39 studies, 14 081 patients) reporting adverse events of short vs long courses of antibiotics for GAS pharyngitis reported no cases of ARF in high-income countries [33].

Reduction of contact transmission should be considered when determining the optimal duration of therapy for GAS pharyngitis. Antibiotics quickly decrease the bacterial burden in GAS pharyngitis. GAS was not detectable by culture in 91% of children 11–23 h after 1 dose of amoxicillin 50 mg/kg [34]. The American Academy of Pediatrics (AAP) therefore states that children can return to school after 12 h of treatment for GAS pharyngitis [35] and concern for contagion is low after 1 dose of antibiotic.

In considering the risk of antibiotics against the negligible benefit of prolonged antibiotics, several countries recommend no antibiotic or shorter durations of therapy for GAS pharyngitis in low-risk populations (Table 1). If choosing to treat GAS pharyngitis with antibiotics, historical and current evidence supports choosing antibiotic durations of no more than 5 days when considering reductions of symptoms and contagion, and prevention of suppurative and nonsuppurative complications in low-risk populations.

ACUTE BACTERIAL RHINOSINUSITIS

ABRS is a condition that is typically prescribed long durations of antibiotic therapy (US guidelines continue to recommend 10–14 days or longer for treatment of ABRS in children), yet it is also easily over-diagnosed [5–7]. Its diagnosis relies on clinical symptomatology and includes (1) persistent symptoms (nasal discharge, cough) of ≥ 10 days without clinical improvement, (2) severe symptoms (high-grade fever, purulent nasal discharge, or facial pain) of ≥ 3 days, or (3) worsening symptoms with new onset fever, headache, or increased nasal discharge following a

typical viral upper respiratory infection that lasted 5–6 days and was initially improving [5–7]. US guidelines attempt to limit over-diagnosing by asking clinicians to differentiate between sequential episodes of uncomplicated viral ARTI and ABRS and establish whether symptoms are clearly not improving [7]; in practicality, this is much more difficult than on paper, particularly in the pediatric population. A meta-analysis of 16 studies of ABRS in adults and children found that only 31% of patients clinically diagnosed with ABRS have abnormal imaging consistent with the diagnosis [36].

In addition to diagnostic uncertainty, prolonged antibiotic courses are often prescribed for ABRS. Traditionally, RCTs used empiric durations of 10–14 days for treating ABRS [37], with some experts recommending continuing antibiotics for 7 days beyond symptom resolution. Following a meta-analysis that showed no difference in effectiveness and safety of short- (3–5 days) and long- (7–10 days) course antibiotic therapy in adults [38], the Infectious Diseases Society of America guidelines reduced the recommended duration for ABRS in adults to an arbitrary number of 5–7 days [5, 6]. However, a duration of 10–14 days was still recommended for children as “data in children was found to be inconclusive.” The AAP guidelines that followed in 2013 did not provide a duration but reported wide variation in clinical observations (10–28 days of therapy) and suggested 7 days after patient becomes free of signs and symptoms as a “reasonable” alternative [7]. Clinicians familiar with rhinitis symptomatology and duration of illness understand that viral rhinitis may take up to 14 days or longer to resolve [7]; the symptom duration is in fact depicted in a figure included in these same guidelines. Where does that place us in the duration of 7 days beyond complete resolution of signs and symptoms?

The AAP report of the Committee on Infectious Diseases now includes a table with recommended antibiotic durations of 5–7 days for ABRS in children [8]; however, most clinicians continue to prescribe prolonged antibiotic courses while awaiting further guidance. A recent study evaluating trends in antibiotic dispensations for new ABRS diagnoses among commercially insured children between 2003 and 2020 found that among approximately 3.2 million children dispensed an antibiotic for ABRS, 80% were dispensed 10 days and 14% were dispensed ≥ 11 days of antibiotics [39]. The authors concluded that, with an estimated 65 antibiotic prescriptions for ABRS per 1000 pediatric population in the United States annually, if all US children prescribed an antibiotic for sinusitis were prescribed 5 days, 24.4 million fewer days of antibiotics per year would be prescribed [39].

Complications of ABRS in children are rare. A study evaluating 10 years of discharge data estimated rates of orbital complications (eg, preseptal cellulitis, orbital cellulitis, and subperiosteal abscess) up to 17.2 per 100 000 children, and rates of intracranial complications (eg, meningitis, subdural/epidural

empyema, intracranial abscess, or cavernous sinus thrombosis) up to 3.8 per 100 000 children [40].

It is unclear whether children with ABRS benefit from antibiotics [41, 42]; although this finding is likely tied to the diagnostic uncertainty and inability to easily differentiate viral from bacterial rhinosinusitis. Many European guidelines recommend against antibiotic use, including the 2020 European position paper on rhinosinusitis which concluded that, as opposed to adults where a short course of antibiotics appears to be effective, data on the effect of antibiotics on ABRS in children is very limited with no significant difference over placebo [43]. Therefore, a 5-day antibiotic course for ABRS is sufficient and supported by various guidelines (Table 1). An additional consideration would be to apply more stringent diagnostic criteria to identify true ABRS.

ACUTE OTITIS MEDIA

The commonly used treatment duration for AOM has traditionally been 10 days. The AAP guidelines recommend a 10-day antibiotic duration for children 2 years or younger or those with severe symptoms, 7 days for children 2–5 years with mild symptoms, and 5–7 days for children 6 years and older with mild symptoms. However, data demonstrate that 5-day treatment regimens provide similar rates of clinical cure and bacterial eradication for children 2 years and older as compared to traditional 10-day regimens [44–46]. One prospective observational study of 2172 children with AOM demonstrated no overall difference in outcomes comparing 5-day to 10-day regimens (84.3% vs 84.8%, respectively) [46]. A Cochrane Review found a modest increase in risk of treatment failure at 1 month in patients treated with 5 days of antibiotics compared to those treated with 10 days of antibiotics (21% in the 5-day group vs 18% in the 10-day group) but noted that the difference is likely not clinically significant [44]. While the odds ratio of treatment failure within 1 month was 1.34 for short-course treatment (number needed to treat: 34), the odds ratio for gastrointestinal side effects was 0.72 with short-course treatment (number needed to treat: 29), highlighting the trade-off between nonclinically significant cure rates and protection from antibiotic side effects. Furthermore, treatment failure at 20–30 days or within 3 months was not significantly different between the short- and long-course groups. A recent systematic review and network meta-analysis also demonstrated similar rates of clinical improvement when comparing 5-day to 10-day regimens, with a relative risk of clinical improvement of 0.86 (95% confidence interval 0.8–0.93) for amoxicillin-clavulanate and a relative risk of 0.93 (95% confidence interval 0.88–0.98) for third-generation cephalosporins [45]. Again, although the authors concluded that a 10-day regimen resulted in statistically significantly more clinical cure, they note that a 5-day regimen is likely sufficient to obtain clinical improvement for most patients.

One well-designed RCT demonstrated statistically significantly higher rates of clinical failure for children younger than 2 years when using 5-day regimens as compared to 10-day regimens (34% vs 16%) [47], so it is generally accepted in the United States that this age group needs longer durations. However, in a subanalysis of 5 studies with 570 participants younger than 2 years in the Cochrane Review referenced above, there was no significant difference in treatment failure with 5-day treatment as compared to longer courses [44]. Similarly, many European countries recommend 5-day regimens for children of all ages with AOM [48] (Table 1).

Patients with AOM have similar clinical outcomes regardless of antibiotic duration because (1) approximately 25% of AOM is caused by a viral etiology [49], (2) about 35% of AOM due to *S. pneumoniae*, *H. influenzae*, or *M. catarrhalis* will self-resolve without antibiotic therapy [50], and (3) studies evaluating bacterial eradication from middle ear fluid in AOM demonstrate eradication within 3–6 days after starting antibiotic treatment [45, 51]. Additionally, complications such as mastoiditis and hearing loss from untreated AOM are exceedingly rare [52]. Because 60% of AOM episodes will self-resolve, prescribers should observe, reevaluate, and utilize delayed prescribing for patients who fail to improve within 2–3 days.

Observation and delayed prescribing are not always feasible in the real-world setting, however. In prescriber focus groups, clinicians noted fewer concerns regarding loss to follow-up, time spent educating families, and parent satisfaction with 5-day antibiotic durations for AOM compared to observation or delayed prescribing [53]. Caregivers are also more comfortable with short durations than with delayed prescribing. In a caregiver study on preferences for AOM management, most surveyed respondents (77%) stated that they would immediately fill a prescription written as delayed, but 86% favored whichever duration was recommended by their child's clinician or the shortest duration necessary [54]. Given the burden of antibiotic prescriptions written for AOM annually in the United States, decreasing the “default” antibiotic duration to 5-days could have significant impact on overall outpatient antibiotic use.

OTHER CONSIDERATIONS

Clinicians should consider several other potential issues that favor limiting the prescribing of antibiotics to shorter durations. It should not be assumed that antibiotics are being taken as directed, particularly for children. A study that conducted telephone interviews with adults and mothers of children aged 0–12 years who were prescribed antibiotics in Europe in the 1990s found that 82% of participants stopped antibiotics on day 3 because of symptom improvement [55]. In a German study of pediatric ambulatory patients, nonadherence with antibiotic prescribing for ARTI was greater than 30%. Adherence to

regimens was improved for those receiving <7 days of treatment [56]. In an RCT involving 10 days of treatment for skin/soft tissue infections, full adherence with the treatment regimen was less than half in all groups, but lower at 37%–39% in children as compared to 46% in adults [57]. Rates of full adherence were lowest in children provided liquid formulation of the medication. In 1 Israeli study of children with GAS pharyngitis, most children had antibiotics discontinued 1 or 2 days after the fever subsided and the incidence of complications was not affected by the poor compliance [58]. So, it is likely that patients have been using short durations with good clinical outcomes, despite being prescribed longer courses, for decades.

Leftover antibiotics may result in improper circulation of antibiotics either incorrectly disposed of, given to others, or used in the future without an antibiotic prescription [59, 60]. In a cross-sectional survey in metropolitan Atlanta, 16% of pediatric caregivers reported having stored antibiotics currently in the home. The most common source of those with currently stored antibiotics was residual from a prior prescription [61]. Parents said they intended to use the antibiotics in the event of future illness without clinical directive.

Additionally, drug shortages of common antibiotics have been reported in the United States, Europe, and other areas of the world [62]. The 2022 amoxicillin shortage in the United States resulted in treatment with broader therapy than necessary for AOM, such as amoxicillin-clavulanate and cefdinir [2]. Decreased drug availability is partially due to decreased production and low profitability of manufacture, but considerations for shorter durations of treatment could affect the overall demand and could conserve antibiotics for children that most critically need the medication.

Children living in rural counties are prescribed antibiotics at higher rates and are more likely to have inappropriate drugs prescribed [63]. Limiting the duration of treatment to these children would decrease their overall exposure to unnecessary antibiotics. These children may have less access to medical care, and the importance of re-assessment would be potentially an issue for areas with less clinician volume. However, most children would be adequately treated with shorter courses. Future studies could assess the number of days of excess antimicrobials needed to be prescribed to prevent 1 complication for ARTIs in children. In addition, future studies may consider examining differences in duration of treatment prescribed by race, ethnicity, and geographic location [64]. It is important for clinicians to educate families about a contingency plan in case their child worsens, and this could be emphasized with shorter treatment courses as well.

Finally, the “one health” approach to combating antimicrobial resistance should be considered. Excess antimicrobials in the environment can contaminate sewage and water systems with low amounts of antimicrobials potentially contributing to resistance [65]. By limiting the excess volume of commonly

prescribed antimicrobials that circulate, this could potentially help prevent further antimicrobial resistance.

In conclusion, quality of data informing the duration of treatment recommendations, considerations of adherence, availability of drugs, and the goal in antimicrobial stewardship of zero inappropriate dosing of antibiotics should call into question common practices. We favor the 5-day choice for most antimicrobial drug regimens for acute respiratory tract infections.

Notes

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