

REVIEW ARTICLE

Keeping It Short and Simple: Duration of Antibiotic Therapy for Common Pediatric Bacterial Infections

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INTRODUCTION

“If you use penicillin, use enough.” – a previous warning from the inventor of penicillin, Alexander Fleming regarding antibiotics.¹ In the early 1940s, penicillin resulted to favorable outcomes within 4 to 5 days, yet the belief that longer antibiotic use is necessary is still being practiced even in these modern days. The 7-day use of these medicines was based on the code by a Roman Emperor in AD 321 that there are 7 days in a week. Surprisingly, even in the era of evidence-based medicine, this belief and practice has remained to be the basis of antibiotic duration.²

The objective of this article is to review the current guidelines and updates on the duration of treatment of common bacterial infections in children.

DISCUSSION

Recently, there are clinical trials that have challenged the standard duration of antimicrobial therapy to a shorter duration due to the risk of antibiotic resistance. The inappropriate use—including extension of antibiotic use is one of the causes of antimicrobial resistance, now considered an urgent global public health threat. More than 2.8 million antimicrobial infections occur each year. As per Centers for Disease Control and Prevention, antimicrobial resistance has already killed 1.27 million people worldwide and is associated with nearly 5 million deaths since 2019. One in five of those deaths occurred among children under 5 years old.³

Locally, the Philippines has also experienced the burden of antimicrobial resistance, ranking 128th

highest across 204 countries. In 2019, more than 15,000 deaths were attributed to antimicrobial resistance and ranked 5th as to the cause of death, even higher than respiratory, maternal and neonatal diseases.⁴

For the past year, in a local tertiary government hospital, it has been alarming that approximately 50% of the cultures from pediatric units have drug-resistant isolates. This is a reminder that we should improve antimicrobial stewardship that includes antibiotic prescription for the shortest duration necessary. Clinical trials are being conducted regarding shorter versus longer antimicrobial use in different pediatric bacterial infections, such as neonatal sepsis, community-acquired pneumonia, urinary tract infections and central nervous system infections – which are all common in our local setting and relevant to review.

Neonatal Sepsis

Neonatal sepsis is one of the most common causes of neonatal mortality with the highest burden observed in developing countries. Unfortunately, these neonates can be affected by multi-drug resistant organisms. Moreover, along with irrational and prolonged use of antibiotics, they are prone to acquiring secondary bacterial and fungal infections that leads to changes in their microbiome and a more prolonged hospital stay.

The American Academy of Pediatrics (AAP) guidelines recommend that antibiotics may be discontinued if cultures are negative after 36 to 48 hours unless there is proven infection on a specific site in newborns.⁵

International studies have reviewed using short versus standard course of antibiotic duration. A 10 versus 14 days antibiotic therapy in culture-proven sepsis study by Reddy was done which used a randomized-clinical trial to evaluate outcomes of neonates more than 32 weeks of age and at least 1.5 kg. There was no difference with readmissions to NICU between the 2 groups.⁶

In another study by Rohatgi et al., a much shorter duration with 7 versus 10 days of antibiotics were analyzed. The 2 groups had met clinical remission by day 5 and were randomized thereafter. Follow-up after 28 days of completion of antibiotics showed that the 7-day course of antibiotics was as effective as the 10-day course.⁷

For the culture-negative neonatal sepsis, one retrospective population-based study from Norway reported data that showed neonates may be treated safely with 7-10 days of antibiotics for culture-confirmed sepsis, while 5-7 days for those with negative cultures given the low mortality. However, its limitation is that the diagnosis of culture-negative sepsis was not universally followed. The duration of 5 days may still need further evidence.⁸ It is important to note that in these clinical trials, neonates were in clinical remission prior to allocation to a shorter course.

Locally, the current available Clinical Practice Guideline (CPG) on neonatal sepsis recommends otherwise. It does not recommend a 5-day over a 7-day course of intravenous antibiotics for newborns with clinical sepsis who improve after initial therapy, as the shorter duration may show an apparent risk for harm and had indirect and inconclusive findings on review of experts. The recommended duration is in line with United Kingdom guidelines and Integrated Management of Childhood Illness (IMCI) which supports at least 7 days treatment for infants less than 2 months with serious bacterial infection.⁹

In a study by Mathur and Behera, on blood procalcitonin levels and duration of antibiotics in neonatal sepsis in 2019, a prospective observational study design determined the time to normalization of procalcitonin and duration of antibiotics in the

different types of neonatal sepsis. This included >34 weeks neonates with different clinical features of sepsis and positive markers. Results showed that specifically for neonates with positive cultures, recommended duration was 9.6 ± 3.1 days, while 6.4 ± 3.1 days for neonates with culture-negative sepsis.¹⁰

The mean procalcitonin levels has decreased significantly before 10 days in culture-positive sepsis and before 7 days for culture-negative sepsis. All types of sepsis had a recommendation of less than 9 days or even shorter if procalcitonin was used as parameter for shorter duration of antibiotics, after clinical correlation. This decrease in inflammatory marker supports the clinical evidence that antibiotics may be given as short as 7 days for both culture positive and culture-negative sepsis.¹⁰

Community Acquired Pneumonia (CAP)

In the management of CAP in infants and children older than 3 months of age as per Infectious Diseases Society of America (IDSA) guidelines, the recommendation is a treatment course of 10 days, however, it also stated that short courses may be just as effective, particularly those with milder disease managed on an outpatient basis.¹¹ The guideline emphasize the importance of research to identify the shortest effective duration of therapy to minimize patient harms, including the development of antibiotic resistance and drug-related toxicities.

The local 2021 CPG on the Evaluation and Management of Pediatric CAP for infants aged 3 months to 18 years old with bacterial pneumonia states that the recommended empiric therapy and duration of treatment if a bacterial etiology is considered is as follows:

For non-severe pneumonia, amoxicillin and amoxicillin-clavulanate may be given as short as 5 days using the high dose. While for uncomplicated severe bacterial pneumonia, shortest duration is 7 days. Longer duration may be required depending on clinical response. The guideline recommends future research for lowest effective antimicrobial dose and

shortest optimal duration of therapy to decrease risk of toxicity and development of resistance.¹²

A more recent systematic review and meta-analysis of randomized clinical trials of antibiotic duration for CAP in outpatient children in high-income countries showed evidence that a shorter duration is equally effective compared with the current recommendation of 7 to 10 days. Short course antibiotics 3-5 days was equally effective and safe compared to 7-10 days in children 6 months or older with CAP. In this meta-analysis, 3 out of 4 studies used amoxicillin, while 1 study used both amoxicillin and amoxicillin-clavulanic acid.¹³

A comparative retrospective cohort study including children >6 months old hospitalized at John Hopkins Hospital who received short course (5-7 days) versus prolonged (8-14 days) antibiotic therapy for uncomplicated CAP, showed that a short course of antibiotics, approximately 5 days, does not increase the odds of 30-day treatment failure compared with longer courses for hospitalized children with uncomplicated CAP.¹⁴

In the treatment of bacterial pneumonia, 3-5 days duration may be an option for outpatient therapy while as short as 5 days for hospitalized patients with pneumonia can be considered.

Urinary Tract Infection (UTI)

The current guidelines available for the optimal duration of antibiotic treatment for infections involving the urinary tract have changed throughout the years, with the more recent studies leaning towards a shorter course therapy.

The previous 2011 AAP CPG recommended and affirmed in 2016 the use of 7 to 14 days antibiotic therapy for febrile infants and children from 2 to 24 months who presents with initial urinary tract infection.¹⁵

Comparable to the local National Antibiotic Guidelines in 2018, the recommendations from the Consensus on Urinary Tract Infection in Children from the societies of Pediatric Nephrology and Urology where treatment duration of acute uncomplicated UTI is 10-14 days for infants less than 2 months, while

it is 7 to 14-day antibiotic coverage for older than 2 months to 18 years of age.^{16,17} For patients with recurrent, catheter-related UTI or with other comorbidities, treatment duration is 7-14 days depending on the response.¹⁷

Along with this recommendation are reports of growing concern about antimicrobial resistance. Factors include inadequate urine testing, poor prescribing practices and non-selective use of prophylaxis that may have contributed to resistance.

In a retrospective cohort analysis, of children 2-17 years old with uncomplicated UTI, there was also no statistical significance when 7 days was used compared to 10 and 14 days in terms of relapses and re-infections.¹⁸

A study on an even shorter duration of therapy for urinary tract infection in children was conducted using randomized clinical trial, comparing the efficacy of standard 10-day course versus short 5 day-course therapy. Participants included children aged 2 months to 10 years with UTI who had clinical improvement after 5 days of antimicrobials. Another 5 days of antimicrobials was added to the standard course group, while the short course group completed another 5 days of placebo. Outcome was defined as having symptomatic urinary tract infection on or before their follow-up after 2 weeks. Results showed that there were no differences between groups in rates of UTI after the first follow-up visit, incidence of adverse events, or incidence of gastrointestinal colonization with resistant organisms. Standard course therapy had lower rates of treatment failure than children assigned to short-course therapy. However, the low failure rate of the short-course group suggests that it can still be an option for children exhibiting clinical improvement after 5 days of antimicrobial treatment.¹⁹

Based on a more recent review article from AAP in 2021, Contemporary Management of Urinary Tract Infection in Children, uncomplicated febrile urinary tract infections may be adequately managed with oral antibiotics for 7 to 10 days, and that this is as safe and effective as conventional longer treatment duration.²⁰

For pyelonephritis, AAP recommends 7-14 days of antibiotics. In a retrospective observational study that included 6 months to 18 years of age children, they compared using short (6-9 days) versus a prolonged course (10 days or more) of treatment. Primary outcome of treatment failure was measured that includes unanticipated emergency department or outpatient visit related to UTI, hospital readmission related to UTI symptoms, prolongation of the planned initial antibiotic treatment course and death. The study concluded that shorter course is as effective as the prolonged course.²¹

Central Nervous System (CNS) Infection

Recommendations for neurologic infections' duration of treatment based on AAP, National Antibiotic Guidelines and from the Pediatric Infectious Disease Society of the Philippines CPG on Acute Bacterial Meningitis varies, but it may be as short as 5 days for *Neisseria meningitidis* to as long as 28 days depending on the isolated pathogen.^{17, 22, 23} While for culture-negative bacterial meningitis, 10-14 days of empiric therapy is recommended.^{17,23} While for other complicated CNS infections such as brain abscess, ventriculitis and others, antibiotic duration may be as long as 6-8 weeks as per local national guidelines.¹⁷

A previous double-blind randomized equivalence study was done more than a decade ago, for which the researchers compared 5 versus 10 days of treatment with ceftriaxone for bacterial meningitis in children. The study showed that beyond neonatal age group with meningitis caused by *Streptococcus pneumoniae*, *Haemophilus influenzae type b* and *Neisseria meningitidis*, and are stable, they can receive 5-day antibiotic course. The primary endpoint of the equivalence study was the rate of bacteriologic failure defined as positive cultures of cerebrospinal fluid or blood on days 6-40 for the originally identified pathogen or isolation of *H. influenzae*, *S. pneumoniae* or *N. meningitidis* from whom the first sample of CSF culture was negative. The secondary endpoints included neurologic, audiologic and visual

complications, and death during the study period. The outcomes of the study showed that there was no bacteriologic failures with both 5-day or 10-day treatment.²²

SUMMARY

The table below shows a quick overview based on studies on shortened duration of antibiotic therapy for the most common bacterial infections in children. However, there are lack of recent literatures for shorter treatment duration for CNS infections. This may be attributed to nature of the disease that still requires the standard treatment course. Most bacterial infections showed equivalent outcomes comparing standard duration to the short-course therapy. Thus, short-course treatment can be an option to improve antibiotic prescription, a critical element to address the antimicrobial resistance we are experiencing at present.

Though these reviewed studies may have their limitations and may need further studies and larger populations, it is a step forward to improve our practices guided by evidence-based medicine.

Table 1. Summary of Duration of Therapy Recommendations

DISEASE	SHORT COURSE (DAYS)	STANDARD COURSE (DAYS)	OUTCOME
Neonatal Sepsis			
Culture-positive	7	10-14	equivalent
Culture-negative	7	10	equivalent
Community-Acquired Pneumonia (uncomplicated)			
Outpatient	3-5	7-10	equivalent
Inpatient	5-7	8-14	equivalent
Urinary Tract Infection			
Uncomplicated UTI	5	10	equivalent
	7	10-14	
Pyelonephritis	6-9	≥10	equivalent

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CONFLICT OF INTEREST

None declared.

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