

AMMI Canada – Position Statement on the Appropriate Duration of Antibiotic Therapy

Abstract:

Introduction: When antibiotics were first introduced, much lower doses and shorter courses were used out of necessity given the rarity and expense of the compounds. Over time, treatment duration has crept up based on perceptions of harmlessness of antibiotics and drug availability. However, antibiotic duration is a subject in which opinion is more prominent than evidence. The force driving longer courses is fear of resistance of any remaining nidus of infection, as well as the potential for clinical failure. However with the advent of our understanding of the microbiome, many experts are questioning the logic that a longer duration of therapy is the best defence against resistance. Most recently experts in the BMJ suggested that patients should stop therapy as soon as they “feel better.” While most professional groups disagreed with the assessment, it is very likely that we treat longer than the available literature would support.

Methods: We examined the recent literature for guidelines, systematic reviews, meta-analysis and subsequent clinical studies comparing shorter and longer durations of therapy for commonly encountered infections. Priority was given to meta-analysis of RCTs with guidelines and individual studies used only in the absence of the former. Special patient populations were examined separately when appropriate.

Results: We have developed a list of recommended duration of antibiotics for routine treatment of commonly encountered infections. We have included the lowest duration studied without evidence of reduced efficacy, suggested time to consider conversion to PO therapy, and any pertinent caveats.

Conclusion: While we don’t feel that patients should be allowed to choose their duration of therapy, clinicians do need to readjust their current practices with respect to duration of therapy based on the available evidence. In many cases, this will substantially reduce duration of therapy, shorten duration of hospitalization and improve patient outcomes.

Table 1 summary of recommendations for adults (except where noted)

Infection	Recommended duration	Excluded patients	Shortest duration	switch to PO*	References
Urinary Tract					
Uncomplicated Cystitis	3-5 days	Applies only to young female patients with normal urinary tracts	3 days	N/A	1, 2
Pyelonephritis and Urosepsis	7 days	Complicated urinary pathology (e.g. stents)	5 days	Day 3	3, 4, 5, 6, 7
Respiratory Tract					

Streptococcal pharyngitis	6 days	Studies limited to pediatrics	4 days	N/A	8
Acute sinusitis	5 days		3 days	N/A	9
Community Acquired Pneumonia (Includes Moderate to Severe)	5 days	Immune suppressed patients, patients with underlying lung disease (e.g. CF), patients requiring mechanical ventilation	3 days	Day 2	10, 11, 12, 13, 14
Ventilator Acquired Pneumonia (VAP)	7 days	Severely immune suppressed patients, CF patients, Patients with collections or abscesses, patients with S. aureus bacteremia associated with VAP	3 days†	N/A	15, 15a
Acute Chronic Obstructive Pulmonary Disease (COPD) exacerbation	5 days	Only for patients meeting criteria for antibiotic treatment	5 days	N/A	16
Intra-Abdominal Infection (IAI)					
Uncomplicated IAI	No more than 24 hours post-operatively	N/A	Pre-op only, no post-op dose	N/A	17
Complicated IAI	4 days after adequate source control	Immune competent patients	3 days	N/A	17, 18, 19
Traumatic bowel perforation	No more than 24 hours post-operatively	So long as operated on within 12 hours	N/A	N/A	17
Gastroduodenal perforation	No more than 24 hours post-operatively	So long as operated on with 24 hours	N/A	N/A	17
Necrotizing pancreatitis	None	Antibiotic prophylaxis not recommended in absence of infection	N/A	N/A	17, 20, 21
Skin and Soft Tissue Infections (SSTI)					
Uncomplicated cellulitis	7 days	Patients worsening on therapy or with	5 days	N/A	22

		uncontrolled source excluded			
Bone and Joint Infections					
Osteomyelitis	6 weeks	N/A	6 weeks	None‡	23, 24, 25
Meningitis					
Community associated acute Meningitis	7 days	Children only, only <i>N. meningitidis</i> , <i>H. influenzae</i> and <i>S. pneumoniae</i>	3 days (single IM dose Rx possible)	N/A	26, 27
Bacteremia					
Bacteremia	7 days	Assumes source controlled and not associated with clinical syndrome requiring longer Rx., excludes <i>S. aureus</i> and <i>Candida</i> Spp.	5 days	As per syndrome	28

* If patient is improving clinically, can absorb oral intake and there is an appropriate oral drug for identified organism(s), N/A if all oral or IV only
† applies to VAP with no derangement in oxygen exchange. ‡ Highly bioavailable drugs excluded

Notes on specific infections:

Urinary tract: The data on short therapy for uncomplicated cystitis in otherwise healthy, young women has the most robust data and guideline support, and is the most generally clinically accepted. Despite relatively strong data, the use of 7 days for pyelonephritis is less commonly accepted and has not been included in many guidelines,²⁹ even more so in the case of bacteremic urosepsis. There is a significant lack of data in complicated cystitis (i.e. cystitis in populations other than healthy, reproductive age women) and in special patient populations such as the immune compromised and those with structurally abnormal urinary tracts. However there are sufficient data to make a recommendation.

Respiratory tract – CAP: The data on short course therapy for pneumonia are well elucidated. Original data from the 1940s confirmed shorter durations of therapy, and more recent clinical trials and meta-analysis have confirmed efficacy, even in severe disease and bacteraemia. Five day duration in guidelines has been confirmed by meta-analysis and confirmatory clinical trials. Shorter courses of 3 days also have randomized, blinded control trial data, but these are less well accepted. In children, shorter courses are becoming the standard of care, especially in less developed countries where costs for longer duration of antibiotics is cost prohibitive for many patients.

Respiratory tract – Sinusitis: The duration of 5 days is based on a meta-analysis of 12 RCTs comparing <7 to >7 days using multiple different classes of antibiotics. The 3 day course, of note, was performed with Azithromycin and as such represents a longer exposure to antibiotics than the actual duration suggests.

Respiratory tract – COPD: Shorter duration of 5 days has been extensively studied using multiple different drug classes, in in-patient and out-patient populations with consistently equivalent results. However there is still no comment on duration in major society guidelines. Duration of antibiotic

therapy recommendation pre-supposes that the exacerbation qualifies for antibiotic therapy due to severity or suspicion of bacterial cause.

Respiratory tract – VAP: The conventional wisdom on duration of therapy for VAP has made a sea-change in the past 10 years moving from long therapy (up to 21 days) to 7 day therapy as a generally accepted norm with European guidelines recommending 7-8 depending on patient improvement. Sentinel RCT studies have been followed by confirmatory analysis and guideline endorsement.^{30 31} Previous concerns about requirements for longer therapy have been reassessed in light of the understanding that most “relapse” was recolonization and likely not true disease. More recent studies of shorter durations (3d) have been limited to mild disease and likely are not applicable to more severe VAP.

Intra-abdominal infections: The data supporting shorter course therapy (essentially peri-operative only) is well supported with a systematic literature review classifying the evidence as grade 1A in community-associated bowel perforations. While the data for more complicated infections are less robust it is based on RCTs and has been studied as low as 3 days, with the most robust data for 4 days. Duration of therapy for uncontrolled sources is not clear and there is insufficient data to make a recommendation even though there is the suggestion that courses as short as 5 days may be effective. The data regarding reserving antimicrobials for pancreatitis with clear evidence of infection is supported by robust RCTs that show no impact on outcome.

Skin and Soft Tissue infections: Despite its ubiquity, there is a single published RCT and one published protocol³² looking at shorter term treatment of cellulitis. The single trial used levofloxacin and excluded patients with undrained abscesses. Additionally, patients who had primary clinical failure (10%) were not included. This is intuitively obvious, but needs to be considered when arranging follow-up and counselling patients. While it is very probable that there is no substantial difference in outcomes between different drug classes, we are recommending a slightly longer than studies course, until further data are available.

Bone and joint infections: The data regarding limiting duration to 6 weeks comes from several well done RCTs on disparate patient populations including vertebral osteomyelitis, Diabetic foot infections and prosthetic joint infections with retained hardware. The similarity of the data in all these patient populations suggests that it is likely that 6 weeks is more than adequate. A cohort study suggested that even shorter durations may have equivalent outcomes,²⁵ however this needs further support from adequately powered RCTs.

Meningitis: There is a single meta-analysis of trials looking at common causes of community associated meningitis (*N. meningitidis*, *S. pneumoniae* and *H. influenzae*) in children which shows no difference in numerous outcomes. Mortality is excluded because of the low number of events in all studies (all of which occurred prior to discontinuation of antibiotics). The efficacy of shorter course therapies is in keeping with WHO recommendations for a single dose of oily chloramphenicol or 5 days of ceftriaxone for children in developing countries (excepting children <2 months of age). Since this recommendation is in keeping with current recommendations for *N. meningitidis* in adults, for that indication, we are

comfortable. Longer durations of therapy for other organisms should be based on clinical improvement and other indicators. There are few data to support any recommendation in adults.

Bacteremia: The question of bacteremia is more complicated than other categories since the cause of bacteremia determines the duration of therapy in most cases. For example, transient bacteraemias, or those thought to be clinically irrelevant, may not need any therapy. For bacteraemias associated with a clinical syndrome for which a shorter duration of therapy is indicated (e.g. intra-abdominal infection with controlled source), that duration should be considered the appropriate therapy. Similarly, those syndromes or organisms that require longer therapy (e.g. *S. aureus*), should be treated accordingly. However for patients with bacteremia that do not fall into either category, it is reasonable to default to 7 days of therapy, unless there are clinical reasons to extend (e.g. failure to improve). This recommendation is based on observational trials and meta-analysis. There is an ongoing RCT to confirm these observations that has not yet been reported.

References:

1. Katchman, Chrisiaens, Baerheim, Leibovici. Duration of antibacterial treatment for uncomplicated urinary tract infection in women (review). Cochrane Collaboration. 2(CD004682). 2005.
2. Gupta, Hooton, Naber et al., International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the infectious diseases society of America and the European society for microbiology and infectious diseases. *Clinical Infectious Diseases*. 1(52):e103-120. 2010.
3. Sandberg, Skoog, Bornefalk et al., Ciprofloxacin for 7 days versus 14 days in women with acute pyelonephritis: a randomized, open label and double-blind, placebo-controlled, non-inferiority trial. *The Lancet*. 380(aug 4):484-490. 2012.
4. Kyriakidou, Rafailidis, Matthaïou et al., Short- versus long-course antibiotic therapy for acute pyelonephritis in adolescents and adults: A meta-analysis of randomized controlled trials. *Clinical Therapeutics*. 30(10):1859-1868. 2008.
5. Drekonja, Rector, Cutting et al., Urinary tract infection in male veterans. *JAMA Internal Medicine*. 173(1):62-68. 2013.
6. Eliakim-Raz, Yahav, Paul, Leibovici, Duration of antibiotic treatment for acute pyelonephritis and septic urinary tract infection – 7 days or less versus longer treatment: systematic review and meta-analysis of randomized controlled trials. *Journal of Antimicrobial Chemotherapy*. 68(10):2183-91. 2013.
7. Talan, Stamm Hooton et al., Comparison of ciprofloxacin (7days) and trimethoprim-sulfamethoxazole (14 days) for acute uncomplicated pyelonephritis in women. *JAMA*. 283(12):1583-90. 2000.
8. Altamimi S, Khalil A, Khaliawi K et al., Short-term late-generation antibiotics versus longer term penicillin for acute streptococcal pharyngitis in children (Review), *Cochrane Database of Systematic Reviews*, Issue 8. Art. No.: CD004872. 2012

9. Falgas M, Karageorgopoulos D, Grammatikos et al., Effectiveness and safety of short vs. long duration of antibiotic therapy for acute bacterial sinusitis: a meta-analysis of randomized trials. *British Journal of Clinical Pharmacology*. 67(2):161-71. 2008
10. El Moussaoui R, de bourgie van den broek 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; 332:13555
11. MASCOT study group, Clinical efficacy of 3 days versus 5 days of oral amoxicillin for treatment of childhood pneumonia: a multicentre double-blind trial. *Lancet*. 360(9336):835-41. 2002
12. Dimopoulos G, Matthaiou D, Karageropoulos D et al. Short- versus Long-Course Antibacterial Therapy for Community-Acquired Pneumonia A Meta-Analysis. *Drugs*, 68 (13): 1841-1854. 2008
13. Ghazipura M, Shorter Versus Longer Duration of Antibiotic Therapy in Patients With Community-Acquired Pneumonia: A Rapid Review. Toronto, ON: Health Quality Ontario; 2013 November. 20 p. Available from: <http://www.hqontario.ca/evidence/publications-and-ohtac-recommendations/rapid-reviews>. 2013
14. Uranga A, Espana P, Bilboa A et al., Duration of Antibiotic Treatment in Community-Acquired Pneumonia A Multicenter Randomized Clinical Trial. *JAMA Intern Med*. 2016;176(9):1257-1265
15. Dimopoulos G, Garaphallia P, Pneumatikos I et al., Short- vs Long-Duration Antibiotic Regimens for Ventilator-Associated Pneumonia, A Systematic Review and Meta-analysis. *Chest*. 144(6):1759-67. 2013
- 15a. Pugh, R., Grant, C., Cooke, R. P. & Dempsey, G. Short-course versus prolonged-course antibiotic therapy for hospital-acquired pneumonia in critically ill adults. *Cochrane Database Syst Rev* CD007577 (2015).
16. El Moussaoui R, Roede B, Speelman P et al., Short-course antibiotic treatment in acute exacerbations of chronic bronchitis and COPD: a meta-analysis of double-blind studies, *Thorax*, 63:415–422. 2008
17. Mazuski JE et al. The Surgical Infection Society revised guidelines on the management of intra-abdominal infection. *Surgical Infections*, 18:1-76. 2017
18. Sawyer RG et al. Trial of short-course antimicrobial therapy for intraabdominal infection. *New England Journal of Medicine* 2015;372:1996-2005
19. Basoli A et al. A prospective, double-blind, multicenter, randomized trial comparing ertapenem 3 or \geq 5 days in community-acquired intraabdominal infection. *J Gastrointest Surg* 2008;12:592-600
20. Wittau M et al. Systematic review and meta-analysis of antibiotic prophylaxis in severe acute pancreatitis. *Scand J Gastroenterol* 2011;46:261-270
21. Villatoro E et al. Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis. *Cochrane Database Syst Rev* 2010;Issue 5:CD002941
22. Hepburn M, Dooley D, Skidmore P, Comparison of Short-Course (5 Days) and Standard (10 Days) Treatment for Uncomplicated Cellulitis, 2004; *Arch Intern Med* 164(23):1669-74, 2004
23. Chaussade H, Uçkay I, Vuagnat A et al., Antibiotic therapy duration for prosthetic joint infections treated by Debridement and Implant Retention (DAIR): Similar long-term remission for 6 weeks as compared to 12 weeks, *International Journal of Infectious Diseases*. 63(2017):37-42, 2017

24. Tone A, Nguyen S, Devemy F et al., Six-Week Versus Twelve-Week Antibiotic Therapy for Nonsurgically Treated Diabetic Foot Osteomyelitis: A Multicenter Open-Label Controlled Randomized Study. *Diabetes Care*, 38 (Feb):302-7. 2015
25. Locke T, Kell M, Bhattacharyya D et al., Spontaneous methicillin-sensitive *Staphylococcus aureus* spondylodiscitis—Short course antibiotic therapy may be adequate: Evidence from a single centre cohort. *Journal of Infection and Public Health* 7:44—49. 2014
26. Karageopolous D, Valkimadi P, Kapaskelis A et al., Short versus long duration of antibiotic therapy for bacterial meningitis: a meta-analysis of randomised controlled trials in children, *Arch Dis Child*, 94:607–614. 2009
27. WHO, Standardized treatment of bacterial meningitis in Africa in epidemic and non-epidemic situations, WHO, 2007 accessed Feb 7, 2018 at: http://www.who.int/csr/resources/publications/meningitis/WHO_CDS_EPR_2007_3.pdf
28. Havey T, Fowler R, Daneman N, Duration of antibiotic therapy for bacteremia: a systematic review and meta-analysis, *Critical Care*, 15:R267. 2011
29. Gupta K, Hooton T, Naber K et al., International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases, *Clinical Infectious Diseases*, 52(5):e103–e120. 2011
30. Torres, A. et al. International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia: Guidelines for the management of hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) of the European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Asociación Latinoamericana del Tórax (ALAT). *Eur Respir J* 50, (2017).
31. Kalil, A. C. et al. Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis* 63, e61-e111 (2016).
32. Cranendonk D, Opmeer B, Prins J, Wiersinga, Comparing short to standard duration of antibiotic therapy for patients hospitalized with cellulitis (DANCE): study protocol for a randomized controlled trial, *BMC Infectious Diseases*, 14:235. 2014