The New Antibiotic Mantra—"Shorter Is Better"

Brad Spellberg, MD

In AD 321, Roman Emperor Constantine the Great codified that there would be 7 days in a week. Even in the modern era of evidence-based-medicine, this 1695-year-old decree remains a primary reference for duration of antibiotic therapy: it leads physicians to treat infections in intervals of 7 days. Thus, it is gratifying when clinical trials challenge the standard antibiotic duration of 7 to 14 days.

In the past, community-acquired pneumonia was treated with a 7- to 14-day course of antibiotics. However, clinical trials in the early 2000s demonstrated that 3 or 5 days of protocol-specified antibiotics are as efficacious as longer courses of therapy for patients with mild to moderately severe community-acquired pneumonia.[1,2] To this body of literature is now added a new randomized trial, in this

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issue of *JAMA Internal Medicine*, by Uranga et al,[3] comparing short-course vs longer courses of therapy for hospitalized patients with community-acquired pneumonia. The trial used a pragmatic design in that treating physicians were allowed to select their preferred antibiotic for the first 5 days of therapy. Patients were randomized such that on day 5 those in the control group continued the therapy selected by their treating physicians and those in the experimental group had their antibiotics stopped if they were afebrile for 48 hours and had no more than 1 sign of clinical instability (eg, hypotension, tachycardia, tachypnea, or hypoxia). These criteria for stopping the antibiotic applied to 70.1% of patients in the experimental arm. Although patients admitted to the intensive care unit were excluded from the trial, a substantial number (approximately 40%) of patients in both arms had Pneumonia Severity Index scores of IV to V, indicative of severe illness. In contrast, prior studies of short-course antibiotic therapy have focused primarily on patients with mild to moderate illness.

The study arms were well matched, and the results were compelling. The intervention worked, as patients who were administered the short-course regimen received a median of 5 days of antibiotics vs 10 for the standard regimen. Across all end points, time points, and populations, short-course therapy was as effective as longer courses of therapy. Point estimates of success favored short-course therapy across most end points and time points. In the sickest cohort (Pneumonia Severity Index scores of IV-V), 30-day rates of clinical success in the intention-to-treat population were significantly higher for short-course vs standard therapy (93.1% vs 80.3%; P = .04). Furthermore, the readmission rate was significantly lower for patients receiving the short-course regimen (1.4% vs 6.6%; P = .02). Overall, the data are convincing that 5 days of anti-

biotic therapy is at least as effective as 10 days for the treatment of community-acquired pneumonia.[3]

In his keynote address at an annual meeting of the Infectious Diseases Society of America, Louis B. Rice, MD, pointed out that pneumonia was successfully treated with short durations of antibiotics as long ago as the 1940s.[4] Physicians considered "pioneers" of penicillin customized the duration of therapy depending on the patient's response and found that a range of 1½ to 4 days of therapy resulted in high cure rates. The modern concept that we should continue treating bacterial infections past the time when signs and symptoms have resolved can be traced to 1945. Meads et al wrote that they administered penicillin to patients with pneumonia, "until there was definite clinical improvement and the temperature had remained below 100°F for 12 hours…then given for another two to three days."[5(p748)] The perceived need to treat beyond resolution of symptoms was driven by a desire to prevent relapses. However, the recurrent infections seen in the case series were caused by isolates with distinct bacterial serotypes, indicative of reinfection rather than relapse. It is unclear how this confused desire to prevent reinfections subsequently transformed into the illogical dogma that antibiotic resistance could be prevented by continuing therapy beyond resolution of symptoms.[4]

Nevertheless, this dogma has been reinforced by the equally illogical, often-heard statement that to prevent antibiotic resistance, it is necessary for patients to complete the entire prescribed course of therapy, even after resolution of symptoms. There is no evidence that taking antibiotics beyond the point at which a patient's symptoms are resolved reduces antibiotic resistance. To the contrary, specifically for pneumonia, studies have shown that longer courses of therapy result in more emergence of antibiotic resistance,[6,7] which is consistent with everything we know about natural selection, the driver of antibiotic resistance.[8] In only a few types of infections does resistance emerge at the site of infection; rather, resistance typically emerges off target, among colonizing flora away from the site of infection.[9] Thus, all that is achieved by treating an infection with antibiotics for longer than the patient has symptoms is increased selective pressure driving antibiotic resistance among our colonizing microbial flora.

Given the large number of bacterial infections that occur every year, overtreating patients who have established infection is likely a major source of selective pressure that drives antibiotic resistance in society. Other than tuberculosis—which is caused by a very slowly replicative organism that spends much of its time in a nonreplicating state—for every bacterial infection for which trials have compared short-course with longer course antibiotic therapy, short-course

Table. Infections for Which Short-Course Therapy Has Been Shown to Be Equivalent in Efficacy to Longer Therapy

Disease	Treatment, Days	
	Short	Long
Community-acquired pneumonia[1-3]	3-5	7-10
Nosocomial pneumonia[6,7]	≤8	10-15
Pyelonephritis[10]	5-7	10-14
Intraabdominal infection[11]	4	10
Acute exacerbation of chronic bronchitis and COPD[12]	≤5	≥7
Acute bacterial sinusitis[13]	5	10
Cellulitis[14]	5-6	10
Chronic osteomyelitis[15]	42	84

Abbreviation: COPD, chronic obstructive pulmonary disease.

therapy has been just as effective, and with reduced selective pressure driving resistance (**Table**).[1-3,6,7,10-15] Use of shorter courses of antibiotic therapy is therefore greatly preferable to longer courses of therapy.

Of course, the ultimate goal is to customize duration of therapy to the patient's response. So what should we do when patients are given a prescription for a fixed duration of therapy and their symptoms resolve before they complete the course? Here we need to change the dogma: patients should no longer be told to keep taking the antibiotic. Patients should be told that if their symptoms resolve before completing the antibiotic they should communicate with their physician to determine if they can stop therapy early. Health care professionals should be encouraged to allow patients to stop antibiotic treatment as early as possible on resolution of symptoms of infection. Ultimately, we should replace the old dogma of continuing therapy past resolution of symptoms with a new, evidence-based dogma of "shorter is better."

REFERENCES

1. el Moussaoui R, de Borgie CA, van den Broek P, 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.

2. Dunbar LM, Wunderink RG, Habib MP, et al. High-dose, short-course levofloxacin for community-acquired pneumonia: a new treatment paradigm. *Clin Infect Dis*. 2003;37(6):752-760.

3. Uranga A, España PP, Bilbao A, et al. Duration of antibiotic treatment in community-acquired pneumonia: a multicenter randomized clinical trial [published online July 25, 2016]. *JAMA Internal Med*. doi:10.1001/jamainternmed.2016.3633.

4. Rice LB. The Maxwell Finland Lecture: for the duration-rational antibiotic administration in an era of antimicrobial resistance and clostridium difficile. *Clin Infect Dis*. 2008;46(4):491-496.

5. Meads M, Harris HW, Finland M, Wilcox C. Treatment of pneumococcal pneumonia with penicillin. *N Engl J Med*. 1945;232:747-755.

6. Chastre J, Wolff M, Fagon JY, et al; PneumA Trial Group. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. *JAMA*. 2003;290(19):2588-2598.

7. Singh N, Rogers P, Atwood CW, Wagener MM, Yu VL. Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit: a proposed solution for indiscriminate antibiotic prescription. *Am J Respir Crit Care Med*. 2000;162(2, pt 1):505-511.

8. Spellberg B, Bartlett JG, Gilbert DN. The future of antibiotics and resistance. *N Engl J Med*. 2013;368(4):299-302.

9. Russo TA, Spellberg B, Johnson JR. Important complexities of the antivirulence target paradigm: a novel ostensibly resistance-avoiding approach for treating infections. *J Infect Dis*. 2016;213(6):901-903.

10. Eliakim-Raz N, Yahav D, Paul M, Leibovici L. 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. *J Antimicrob Chemother*. 2013;68(10):2183-2191.

11. Sawyer RG, Claridge JA, Nathens AB, et al. Trial of short-course antimicrobial therapy for intraabdominal infection. *N Engl J Med*. 2015;372(21):1996-2005.

12. El Moussaoui R, Roede BM, Speelman P, Bresser P, Prins JM, Bossuyt PM. Short-course antibiotic treatment in acute exacerbations of chronic bronchitis and COPD: a meta-analysis of double-blind studies. *Thorax*. 2008;63(5):415-422.

13. Falagas ME, Karageorgopoulos DE, Grammatikos AP, Matthaiou DK. Effectiveness and safety of short vs. long duration of antibiotic therapy for acute bacterial sinusitis: a meta-analysis of randomized trials. *Br J Clin Pharmacol*. 2009;67(2):161-171.

14. Hepburn MJ, Dooley DP, Skidmore PJ, Ellis MW, Starnes WF, Hasewinkle WC. Comparison of short-course (5 days) and standard (10 days) treatment for uncomplicated cellulitis. *Arch Intern Med*. 2004;164(15):1669-1674.

15. Bernard L, Dinh A, Ghout I, et al; Duration of Treatment for Spondylodiscitis (DTS) study group. Antibiotic treatment for 6 weeks versus 12 weeks in patients with pyogenic vertebral osteomyelitis: an open-label, non-inferiority, randomised, controlled trial. *Lancet*. 2015;385(9971):875-882.