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Duration of Antibiotic Therapy: Shorter Is Better

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Society continues to face a crisis of antibiotic resistance, caused largely by the unabated overuse of antibiotics. The emergence of antibiotic resistance is the result of natural selection: Prescribing more antibiotics causes more selective pressure, which drives greater resistance. Thus, to decrease resistance, we need to prescribe fewer antibiotics.

In 2008, one of us (L.B.R.) posited that of the different ways the medical community could reduce the amount of antibiotic treatment prescribed, the one that seemed safest and most achievable was to treat infections only for as long as necessary to achieve optimal cure rates (1). It is difficult and potentially dangerous for providers not to prescribe antibiotics at all, but it should be easier to convince them not to prescribe antibiotics for so long.

The evidentiary basis of traditional durations of antibiotic therapy is that a week is 7 days (2), which is why tried-and-true antibiotic regimens are 7 to 14 days long. The definition of a week was decreed by Roman Emperor Constantine the Great nearly 2000 years ago (2). This seems an unsatisfactory evidentiary basis for modern medical practice.

Fortunately, in recent years, more than 45 randomized controlled trials (RCTs) have compared the efficacy of short-course versus traditional, longer courses of antibiotic therapy for the treatment of community-acquired and nosocomial pneumonia, acute exacerbation of chronic bronchitis and sinusitis, complicated urinary and intra-abdominal infections, Gram-negative bacteremia, acute bacterial skin infections, osteomyelitis and septic arthritis, and even neutropenic fever (3, 4). All RCTs for these diseases and 2 meta-analyses of these RCTs (5, 6) found no difference in efficacy between shorter and traditional courses of antibiotic therapy. Of note, the short-course regimens that were studied were typically not based on Constantine's 7-day week.

For pneumonia specifically, 8 RCTs have shown that 3- to 5-day courses of antibiotic therapy are at least as effective as 7- to 14-day courses for community-acquired pneumonia, and 2 RCTs demonstrated that 8 days is as effective as 15 days for nosocomial ventilator-

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associated pneumonia (3). A post hoc analysis of another RCT found that a single dose of ceftriaxone cured a large proportion of patients with community-acquired pneumonia who subsequently received ineffective therapy (7), underscoring how severely we overtreat. In the several RCTs that evaluated the effect on resistance, shorter courses decreased emergence of antibiotic resistance in respiratory secretions.

In this context, the large observational study conducted by Vaughn and colleagues adds valuable insight (8). They took advantage of a 43-hospital quality improvement consortium in Michigan to evaluate antibiotic prescriptions for the treatment of nearly 6500 adults with community-acquired pneumonia from 2017 to 2018. Strengths of the analysis include the size of the database and that the investigators required clinical and radiographic evidence of pneumonia in addition to the discharge diagnostic code, which increased the accuracy of case identification. Patients in the intensive care unit and those who had immunocompromise, unusual organisms (such as fungi), or septic complications (such as bacteremia or empyema) were excluded. Nevertheless, more than half of the evaluated patients had pneumonia severity indices of IV or V, indicating severe disease.

Not surprisingly, more than two thirds of patients received antibiotic courses that exceeded necessary durations, with a median of 8 days. Most of the excess was caused by overly long courses of oral stepdown therapy at discharge from the hospital in addition to the parenteral therapy that had already been received. Of great importance, and consistent with previous RCTs, patients who received longer courses of antibiotic treatment did not have increased survival or reduced readmission or repeated emergency department visits. Thus, longer was not better. Furthermore, patients who received longer courses had significantly more adverse effects, showing that longer was in fact worse. Indeed, the risk for an adverse effect increased by an alarming 5% for each additional day of antibiotic therapy.

Vaughn and colleagues' findings add to the considerable body of evidence supporting the antibiotic mantra "shorter is better" (2, 3, 9). The cumulative evidence indicates that each day of antibiotic therapy beyond the first confers a decreasing additional benefit to clinical cure while increasing the burden of harm in the form of adverse effects, superinfections, and selection of antibiotic resistance. The question is, where do those 2 competing trends cross, such that continuing tilts the balance to harm over benefit? For community-acquired pneumonia, the data indicate net harm somewhere around 3 to 5 days of therapy for most patients.

Unfortunately, short-course antibiotic therapy remains underused by clinicians (3, 10). Agencies governing health care in the United States, Europe, and elsewhere do not include short-course therapy in hospital regulations on antibiotic stewardship. The U.S. Food and Drug Administration continues to require companies to compare new antibiotics with traditional durations rather than short-course therapy in the comparator groups of pivotal trials. Payers covering antibiotic prescriptions cover the full duration of therapy even when evidence indicates that shorter treatment would be just as effective, with fewer adverse effects and less selective pressure. And, national societal guidelines continue to recommend traditional treatment durations for many types of infections. It is time for regulatory

agencies, payers, and professional societies to align themselves with the overwhelming data and assist in converting practice patterns to short-course therapy.

Change is scary, and medicine is a conservative profession. The core ethos of our profession is based on an oath that is 3 millennia old. Nevertheless, to live up to the expectations that our patients have for us and that we have for one another, we must overcome inertia and tradition and change practice when compelling evidence becomes available. After dozens of RCTs and more than a decade since the initial clarion call to move to short-course therapy, it is time to adapt clinical practice for diseases that have been studied and adopt the mantra "shorter is better."

References

1. 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;46:491–6. doi: 10.1086/526535 [PubMed: 18194098]
2. Spellberg B The new antibiotic mantra–"shorter is better". JAMA Intern Med. 2016;176:1254–5. doi:10.1001/jamainternmed.2016.3646 [PubMed: 27455385]
3. Wald-Dickler N, Spellberg B. Short course antibiotic therapy–replacing Constantine units with "shorter is better". Clin Infect Dis. 2019. doi:10.1093/cid/ciy1134
4. Gjika E, Beaulieu JY, Vakalopoulos K, et al. Two weeks versus four weeks of antibiotic therapy after surgical drainage for native joint bacterial arthritis: a prospective, randomised, non-inferiority trial. Ann Rheum Dis. 2019. doi:10.1136/annrheumdis-2019-215116
5. Royer S, DeMerle KM, Dickson RP, et al. Shorter versus longer courses of antibiotics for infection in hospitalized patients: a systematic review and meta-analysis. J Hosp Med. 2018;13:336–42. doi: 10.12788/jhm.2905 [PubMed: 29370318]
6. Hanretty AM, Gallagher JC. Shortened courses of antibiotics for bacterial infections: a systematic review of randomized controlled trials. Pharmacotherapy. 2018;38:674–87. doi:10.1002/phar.2118 [PubMed: 29679383]
7. Pertel PE, Bernardo P, Fogarty C, et al. Effects of prior effective therapy on the efficacy of daptomycin and ceftriaxone for the treatment of community-acquired pneumonia. Clin Infect Dis. 2008;46: 1142–51. doi:10.1086/533441 [PubMed: 18444848]
8. Vaughn VM, Flanders SA, Snyder A, et al. Excess antibiotic treatment duration and adverse events in patients hospitalized with pneumonia. A multihospital cohort study. Ann Intern Med. 2019 [Epub ahead of print]. doi:10.7326/M18-3640
9. Spellberg B The maturing antibiotic mantra: "shorter is still better". J Hosp Med. 2018;13:361.362. doi:10.12788/jhm.2904 [PubMed: 29370317]
10. Fernandez-Lazaro CI, Brown KA, Langford BJ, et al. Late-career physicians prescribe longer courses of antibiotics. Clin Infect Dis. 2019. doi:10.1093/cid/ciy1130