

Short-course Antibiotic Therapy—Replacing Constantine Units With “Shorter Is Better”

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(See the Major article by Fernandez-Lazaro et al on pages 1467–75.)

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Ten years ago, Dr Lou Rice gave a keynote address at the annual meeting of the Infectious Diseases Society of America [1]. In his address, Dr Rice pointed out that treating bacterial infections for only as long as necessary was probably the safest and most achievable means to reduce unnecessary antibiotic use [1]. He also pointed out that many traditional antibiotic courses are unnecessarily long. Indeed, durations of antibiotic therapy for most bacterial infections are based on the fact that the week has 7 days in it, resulting in traditional 7- to 14-day antibiotic courses [2]. And the modern week has 7 days in it because the Roman Emperor Constantine the Great said so in 321 CE [2]. Had Constantine chosen a 4-day week, providers would likely routinely prescribe 4- to 8-day courses of therapy.

Fortunately, in the last 25 years, clinical investigators have clarified necessary antibiotic durations by conducting over 40 randomized controlled trials (RCT) comparing short course vs traditional courses of antibiotics for a variety of bacterial infections (Table 1). Interestingly,

in many cases, the short-course regimens were not based on “Constantine units” of duration. In every RCT thus far published for the diseases shown in Table 1, short-course therapy was just as effective as longer courses and often with better point estimates of clinical success, fewer adverse events, and/or diminished emergence of resistance at the site of infection [2–5].

Based on such a potent tour de force of data, one might expect short-course therapy to have become the standard of care in the decade since Dr Rice’s keynote address. Alas, however, a recent study found that only 1 in 3 Infectious Diseases specialists recommend short-course regimens across many countries [32]. The rate is likely lower among providers of other specialties, who prescribe by far the majority of antibiotics.

In this issue of *Clinical Infectious Diseases*, Fernandez-Lazaro et al add to our knowledge of who is, or is not, prescribing short-course antibiotic regimens [33]. They conducted an exhaustive retrospective study of 5.6 million outpatient antibiotic courses prescribed by 10 616 Family Medicine specialists in Ontario, Canada, from March 2016 to February 2017. Unfortunately, the authors found that the median duration of antibiotic regimens was 7–8 days (38%), less than 25% of prescriptions were shorter than 7 days, and substantially more than 30% were for longer than 8 days. Such long durations

of therapy are unlikely warranted for most routine bacterial infections treated with outpatient oral antibiotics.

The authors deemed courses longer than 8 days to be “prolonged” and sought to determine factors associated with prescribing prolonged courses of therapy. An important limitation of the study was the inability to link individual prescriptions to clinical diagnoses. For most infections treated with oral outpatient therapy, it is likely that even 7–8 days of therapy were excessive (Table 1). Thus, the results are a conservative estimate of the overprescription of antibiotics.

In a sign of hope for the future, by multivariate analysis, the authors found that early career physicians (<11 years since graduation from medical school) were significantly less likely to prescribe prolonged courses than mid- or late-career physicians. Late-career physicians (≥25 years since medical school) did the worst. Other factors associated with prolonged courses included practice in a rural setting, patients with more comorbidities, and patients who cared for proportionately more children. One might speculate that practicing in rural areas (where follow-up and continuity might be more limited), or caring for patients with more comorbidities, and/or more children, imparts a greater sense of risk and fear to the provider, resulting in a more conservative approach to antibiotic prescriptions (eg, longer courses

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Table 1. Diseases for Which Short-course Antibiotic Therapy Has Been Found to Be Equally Effective to Longer Traditional Courses of Therapy (With References)

Diagnosis	Short (d)	Long (d)	Result
Community-acquired pneumonia [6–14]	3 or 5	7, 8, or 10	Equal
Hospital-acquired/ventilator-associated pneumonia [15, 16]	7–8	14–15	Equal
Complicated urinary tract infections/pyelonephritis [17–22]	5 or 7	10 or 14	Equal
Complicated/postoperative intraabdominal infections [23, 24]	4 or 8	10 or 15	Equal
Gram-negative bacteremia [25]	7	14	Equal
Acute exacerbation of chronic bronchitis/chronic obstructive pulmonary disease (meta-analysis of 21 trials [26])	≤5	≥7	Equal
Acute bacterial skin and skin structure infections (cellulitis/major abscess) [27–29]	5–6	10	Equal
Chronic osteomyelitis [30]	42	84	Equal
Empiric neutropenic fever [31]	Afebrile and stable × 72 h	Afebrile and stable × 72 h and with absolute neutrophil count > 500 cells/μL	Equal

of therapy). The fact that physicians with more years of practice tended to prescribe longer courses may reflect training in the previous era of tremendous hubris regarding the invincibility of antibiotics [34, 35] and prior to any notions or systematic implementation of antimicrobial stewardship.

The improved prescribing practices of younger physicians offer the hope that as older physicians who have not adapted to changes in evidenced-based medicine retire, overall prescribing practices will improve. However, younger physicians should beware of their own hubris, because they still more often than not prescribed unnecessarily long courses of antibiotics. Furthermore, as mentioned, the expert who first publicly called out providers for prescribing excessive courses of antibiotics was a highly experienced provider [1], as are many of the leading experts in the field of antimicrobial stewardship [36–38]. Thus, when it comes to years of practice, perhaps it may be most accurately concluded that we all perform similarly poorly, with some more poorly than others.

In seeking to improve provider prescribing behaviors for the future, as Lazaro-Fernando et al point out, we need to close significant antimicrobial stewardship knowledge gaps among medical students [39], pharmacy students [40], and postgraduate house staff [41]. Perhaps more discouraging, these training and knowledge gaps are even mirrored by

deficiencies in antimicrobial stewardship curricula of Infectious Disease fellows, the present and future champions of this movement [42]. Educational programs targeting students and early learners need to be implemented as part of core curricula.

Although education is a cornerstone of antibiotic stewardship efforts, it must also be bolstered by other efforts. By itself, education fails time and again to overcome deeply ingrained inappropriate prescribing decisions driven by fear [43]. Countering the fear that underlies poor antibiotic prescribing habits is necessary. Recent efforts have demonstrated that interventions geared toward countering fear with other forms of psychological pressure, including the gentle nudge of public commitment, peer comparison by audit and feedback, accountable justification, and so forth, can improve antibiotic prescribing behaviors [44–46].

A recently described, new psychological approach is the use of the expected practice [47]. Expected practices are care standards developed by broad coalitions of primary and specialty care providers and approved by medical staff committees and institutional leadership. They set stronger standards than guidelines, standards that are expected to be complied with unless specific clinical circumstances dictate otherwise, in which case providers are expected to document why in the medical record. The use

of expected practices shifts the sense of medical-legal responsibility from a provider to the institution and can provide psychological reassurance around changing care standards. A recent application of an expected practice around duration of antibiotic therapy resulted in a substantial decrease in antibiotic usage at a large, public hospital, where historically medical-legal fears were commonly verbalized as a reason to not prescribe short-course therapy [48]. Thus, increasingly we are learning that psychological tools can help drive behavioral change among providers, including in the field of antibiotic stewardship.

The practice of medicine is constantly evolving as the results of new research become available, and as secular trends change over time (eg, fluctuations in antibiotic resistance and new antibiotic development). Infectious Diseases practitioners carry the burden of stewarding the life-saving, societal trust that is effective antibiotic therapy in the face of these changes. Irrespective of years spent in training, practice setting, or patient comorbidities, it is time to retire Constantine unit-based antibiotic durations and, for diseases which have been studied, adopt the mantra, “Shorter Is Better.”

Notes

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