Open Forum Infectious Diseases

PERSPECTIVES

Can the Future of ID Escape the Inertial Dogma of Its Past? The Exemplars of Shorter Is Better and Oral Is the New IV

Kusha Davar,[1] Devin Clark,[1] Robert M. Centor,[2] Fernando Dominguez,[1] Bassam Ghanem,[3] Rachael Lee,[4] Todd C. Lee,[5] Emily G. McDonald,[6] Matthew C. Phillips,[7,8] Parham Sendi,[9] and Brad Spellberg[1]

[1]Los Angeles County + University of Southern California (LAC+USC) Medical Center, Los Angeles, California, USA, [2]Department of Medicine, Birmingham Veterans Affairs (VA) Medical Center, Birmingham, Alabama, Birmingham, Alabama, USA, [3]King Abdulaziz Medical City, Jeddah, Saudi Arabia, [4]Department of Medicine, Division of Infectious Diseases, University of Alabama at Birmingham, Birmingham, Alabama, USA, [5]Division of Infectious Diseases, Department of Medicine, McGill University, Montreal, Canada, [6]Division of General Internal Medicine, Department of Medicine, McGill University, Montreal, Quebec, Canada, [7]Division of Infectious Diseases, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts, USA, [8]Harvard Medical School, Boston, Massachusetts, USA, and [9]Institute for Infectious Diseases, University of Bern, Bern, Switzerland

Like all fields of medicine, Infectious Diseases is rife with dogma that underpins much clinical practice. In this study, we discuss 2 specific examples of historical practice that have been overturned recently by numerous prospective studies: traditional durations of antimicrobial therapy and the necessity of intravenous (IV)-only therapy for specific infectious syndromes. These dogmas are based on uncontrolled case series from >50 years ago, amplified by the opinions of eminent experts. In contrast, more than 120 modern, randomized controlled trials have established that shorter durations of therapy are equally effective for many infections. Furthermore, 21 concordant randomized controlled trials have demonstrated that oral antibiotic therapy is at least as effective as IV-only therapy for osteomyelitis, bacteremia, and endocarditis. Nevertheless, practitioners in many clinical settings remain refractory to adopting these changes. It is time for Infectious Diseases to move beyond its history of eminent opinion-based medicine and truly into the era of evidenced-based medicine.

Keywords. antibiotic; dogma; evidenced-based medicine; oral antibiotics; shorter is better.

Introduction

The millennia-long annals of medical history are replete with placebos or poisons that doctors administered ad libitum, based on limited or no data, often to the overt detriment of patients [1–3]. Snake oil, mercurous compounds, arsenicals, and purgative bleeding dominated the practice of medicine for centuries. It is a small wonder that Voltaire observed, "The art of medicine consists of amusing the patient while nature cures the disease" [4].

Although all fields of medicine contain elements of practice based on tradition and lore, few are more afflicted than Infectious Diseases. We believe there are 2 primary reasons. First, antimicrobials were among the earliest effective treatments in all of medicine [3]. In contrast to virtually all other modern drugs, the availability of antimicrobial agents predated the use of randomized controlled trials to establish safety and efficacy. Second, antimicrobials were far more effective at reducing death from disease than virtually any other therapy. They were so effective that by the time randomized controlled trials became the means of establishing care standards, therapeutic paradigms for typical bacterial infections were already locked in place, and many were never challenged.

The question now becomes, can the field of infectious diseases overcome the inertia of our past? In an era of modern clinical trials, and cutting-edge analytic techniques, is it finally time for us to demand evidence-based medicine, and no longer rely on eminence-based medicine? To do so will require our field to come together and challenge entrenched therapeutic paradigms. In this study we discuss 2 specific examples of dogmatic practice that have recently been overturned by numerous prospective studies: (1) extended durations of antimicrobial therapy and (2) the absolute necessity of intravenous (IV)-only therapy for specific infectious syndromes.

A BRIEF HISTORICAL PRIMER

Antimicrobials were among the first safe and effective therapies in modern medicine, preceded arguably only by digitalis and relatively impure insulin harvested from the porcine pancreas [3]. The first safe and effective antibacterial agent administered to patients was prontosil rubrum, a synthetic prodrug that is metabolized in vivo to sulfanilamide, designed by Gerhard Domagk and colleagues in 1931 by chemical modification of industrial red dye for clothing [5]. So revolutionary was the effectiveness of prontosil rubrum that word spread out

Received 26 October 2022; editorial decision 27 December 2022; accepted 28 December 2022; published online 29 December 2022

Correspondence: Brad Spellberg, MD, Hospital Administration, 2051 Marengo Street, Los Angeles, CA 90033 (bspellberg@dhs.lacounty.gov).

Open Forum Infectious Diseases®

https://doi.org/10.1093/ofid/ofac706

of the research laboratory and into the surrounding community, and local doctors began treating patients with it, even before the publication of animal model data [5]!

The first person in history whose life was described to be saved from a lethal infection by an antimicrobial agent was a 10-month-old boy with *Staphylococcus aureus* bacteremia treated with prontosil rubrum whose case was reported on May 17, 1933, seven and half years before the first therapeutic administration of purified penicillin [5]. Other miraculous cures followed, generating fame for these new antimicrobial drugs. For example, in November 1936, Franklin Roosevelt Jr., son of the President, was diagnosed with severe streptococcal pharyngitis and was treated with prontosil rubrum; his case generated considerable angst in the public because a decade earlier, President Calvin Coolidge's 16-year-old son had died of a streptococcal infection [6]. Successful resolution of Roosevelt Jr.'s infection on sulfonamide therapy was widely celebrated in the news media, and this led to considerable public interest in antimicrobial agents [6].

Shortly thereafter, Drs. Snodgrass and Anderson [7] established the superiority of sulfanilamide over the previous standard treatment of cellulitis, in one of the earliest prospective, active-controlled clinical trials ever conducted (in 1937). They alternated every other patient to receive sulfanilamide or treatment with ultraviolet lamp therapy, which had been the primary therapy for skin infections before sulfa drugs. In addition, all patients enrolled were given a standard regimen of medical therapy that included the following: administering a liquid diet of Horlick's malted milk, arrowroot, and junket, with eggs and onions explicitly forbidden from their meals (a very specific recipe outlined in the study methods section); and the coup de grâce, all patients received a mandatory, hot, liquid paraffin soap-and-water enema. This combination was state-of-the-art in medicine before the advent of antimicrobials, not far off from the "Oh, you need an ear nail" for the common cold, lampooned in the movie *A Million Ways to Die in the West*.

This transformation of care brought on by sulfonamides was witnessed by Lasker-award winner Dr. Lewis Thomas [8]. He remarked that before sulfa drugs, bourbon was the most frequently prescribed substance for patients in Boston. Bourbon prescriptions were written in Latin script, rendering them impressive to patients and providing reassurance that treatment was being administered. He wrote, "For most of the infectious diseases on the wards of Boston City Hospital in 1937, there was nothing that could be done beyond bed rest and good nursing care. Then came the explosive news of sulfanilamide, and the start of the real revolution in medicine" [8].

Even more profound were the effects of penicillin. On March 14, 1942, Mrs. Ann Sheafe Miller became the first patient in the United States to benefit from life-saving penicillin [9]. Doctors were certain she would die due to postpartum streptococcal sepsis and bacteremia, having failed sulfa therapy. In desperation, her treating physician contacted an old colleague, Dr. Howard Florey, who had led the effort to purify penicillin and graciously arranged for a small amount of penicillin to be shipped. The curative effect was so shocking and miraculous that Dr. Wilder Tileston, one of Mrs. Miller's senor consulting physicians, was overheard muttering to himself during chart review, "Black magic!" [9].

Thereafter, antibiotics transformed medicine from a field of diagnostic acumen and prognostication to an interventional profession, where the new expectation was therapeutic cure. As another infectious diseases expert who experienced this transformation wrote, "It is not too much to state that the introduction of [antibiotics] has represented a force for change in the 20th century of the same general kind as James Watt's modification of the steam engine did in the 18th. The crossing of the historic watershed could be felt at the time. One day we could not save lives, or hardly any lives; on the very next day we could do so across a wide spectrum of diseases. This was an awesome acquisition of power" [10].

It is a small wonder that a fervent belief in the awesome power (black magic!) of antimicrobial agents rapidly spread across the globe, establishing therapeutic paradigms that would remain unchallenged for decades, despite the absence of high-quality, prospective studies.

The Historical Dogma of Antimicrobial Durations of Therapy

We and others have previously summarized the historical literature that established traditional durations of antimicrobial therapy [11–19]. Ironically, original durations of penicillin therapy in uncontrolled case series from the early to mid-1940s were short (often 4–5 days), underdosed compared to modern regimens, and with parenteral often referring to intramuscular administration, yet still showing favorable outcomes [16, 17]. However, over time, a belief grew that longer courses were necessary to prevent relapse of infection, which in turn would prevent the emergence of antimicrobial resistance resulting from partial or incomplete treatment [16, 20]. Nevertheless, as Dr. Rice [16] pointed out in 2008, no data support the notion that longer courses of therapy reduce the emergence of antimicrobial resistance, or that relapses lead to resistance. Indeed, longer courses expose microbes to more antimicrobial selective pressure and perversely increase the likelihood of emergent resistance [14, 21–24].

Over time, 2 predominant schools of thought evolved to define antimicrobial durations of therapy. The first was based on the historical fact that in 321 C.E., Constantine the Great decreed that there would be 7 days in a week [12, 14, 15]. That is the actual historical basis for

therapeutic durations as multiples of 7 days. We have described these durations as "Constantine Units" to underscore the absurdity of using the decree of an ancient Roman Emperor as an evidentiary basis for modern therapy [14, 15]. The second line of evidence was based on the number of metacarpal bones that evolved in the hominid hand, which has resulted in 5- to 10-day durations. This latter line of evidence has led 1 or more of us to speculate that the world might be a better place, with diminished antimicrobial resistance, if we had instead evolved as 3-toed sloths [14].

The unfortunate reality is that until the advent of modern-day clinical trials, it was lore, the number of days in a week, or the number of fingers on hominid hands, and not evidence, that drove therapeutic durations for many infections. When considered from this perspective, one would think that a relatively small number of modern, high-quality, randomized controlled trials might be sufficient to change practitioner behavior away from historical norms and toward evidenced-based, optimal durations of antimicrobial therapy.

The Historical Dogma of Intravenous Therapy for Osteomyelitis and Endocarditis

No prospective study ever established IV antimicrobial therapy as more effective than oral therapy for the treatment of osteomyelitis or endocarditis. So, from where did the nearly universal, fervently held belief that IV-only therapy must be used to treat these diseases originate?

The first is osteomyelitis: we traced the dogma for IV-only therapy back to an uncontrolled case series published in 1970 by Dr. Waldvogel et al [25]. The patients described received IV penicillin or aminoglycosides in the 1950s and 1960s—oral agents were not attempted. The authors concluded in their discussion, "In our experience…osteomyelitis is rarely controlled without the combination of careful, complete surgical debridement and prolonged (4 to 6 weeks) parenteral antibiotic therapy at high dosage." Subsequent literature that insists on IV-only therapy often traces back to this original citation [26].

The second is endocarditis: once again, the dogma of IV-only derives from case series, this time from the 1940s to early 1950s, which demonstrated that oral sulfanilamide, erythromycin, or tetracycline resulted in cure rates of <30%, substantially lower than the >75% cure rate observed with parenteral penicillin [27–30]. As a result, Dr. Max Finland [31], one of the giants of infectious diseases, published a review article in 1954 in which he wrote, "Presumably, the oral route is at times successful…it is more likely, however, that such usage is responsible for many therapeutic failures.…However, little of this type of experience is recorded, and therefore this assumption cannot be authenticated". This opinion established a dogma that has lasted for almost 70 years.

Unfortunately, the pharmacological properties of sulfanilamide, erythromycin, and tetracycline are such that they would not be hypothesized to be adequate for treating high-grade bloodstream infections. These old antibiotics do not achieve peak levels in blood that exceed the target minimum inhibitory concentrations (MICs) of bacterial pathogens, and, thus, these drugs would be predicted not to be able to reliably inhibit microbial growth during high-grade bacteremia [30]. In contrast, multiple modern oral antibiotics do achieve levels in blood adequate to exceed target MICs [30]. Thus, uncontrolled case series of these original oral antibiotics from the 1930s to 1940s are of unclear relevance to modern practice.

The Bottom Line of Historical Dogma

All-in-all, when considering antimicrobial durations and oral therapy data, practitioners need to appreciate that much of modern practice simply stems from the comfortable habit of historical practice. Furthermore, that comfortable, historical practice was not based on high-quality data, but rather eminent opinions from prominent figures in healthcare and academia that were in turn based on little to no data.

Given the minimal database upon which historical practice rests, a moderate amount of equipoise ought to be accepted in the design, conduct, and interpretation of modern clinical trials with respect to durations of treatment and selection of the antimicrobial route. In short, modern data do not confront previously established therapeutic paradigms based on high-quality data—they confront previously established therapeutic paradigms based on little to no data.

MODERN DATA FOR SHORTER IS BETTER AND ORAL THERAPY

Shorter Is Better

More than 120 modern, randomized controlled trials have established that short-course antimicrobial regimens are at least as effective as longer regimens for numerous infections (Table 1). The use of shorter courses of therapy also reduces the risk of harm of antimicrobials, including adverse events, superinfections, and selection for resistance, and indeed such harm avoidance was found in many of the randomized controlled trials. The evidence base is so robust that the American College of Physicians has released a position paper endorsing short-course therapy as standard of care for many infections [18]. Specifically, the American College of Physicians Scientific Medical Policy Committee commissioned a position paper on short-course therapy for 4 common infections: bronchitis in patients with chronic obstructive pulmonary disease, community-acquired pneumonia, pyelonephritis, and cellulitis. These 4 infections account for a high proportion of care across a wide spectrum of encounter settings (outpatient, inpatient, and urgent care/emergency department). Thus, the Committee believed that these infections were the most appropriate to perform an intense review of the randomized

Table 1. Summary of Shorter Is Better Randomized Controlled Trials

Diagnosis	Short (d)	Long (d)	Result	No. of RCTs	Refs.
Community-acquired pneumonia	3–5	5–14	Equal	14	[32–45]
Atypical community-acquired pneumonia	1	3	Equal	1	[46]
Possible pneumonia in ICU	3	14–21	Equal	1	[47]
Ventilator-associated pneumonia	8	15	Equal	2	[48, 49]
Complicated UTI/pyelonephritis	5 or 7	10 or 14	Equal	9	[50–58]
Complicated intra-abdominal infection	4–8	10–15	Equal	2	[59, 60]
Gram-negative bacillus bacteremia	7	14	Equal	3	[61–63]
Cellulitis/wound/abscess	5–6	10	Equal	4	[64–67]
Osteomyelitis	42	84	Equal	2	[68, 69]
Osteomyelitis s/*P* implant removal	28	42	Equal	1	[70]
Diabetic osteomyelitis s/*P* Debridement	10–21	42–90	Equal	2	[71, 72]
Septic arthritis	14	28	Equal	1	[73]
Acute exacerbations of bronchitis and sinusitis	≤5	≥7	Equal	>25	[74–81]
Neutropenic fever	AFx72 h/3d	ANC > 500/9d	Equal	2	[82, 83]
Perioperative prophylaxis	0–1	1–5	Equal	56	[84–88]
Plasmodium vivax malaria	7	14	Equal	1	[89]
Erythema migrans (Lyme disease)	7	14	Equal	1	[90]

Abbreviations: ANC, absolute neutrophil count; d, day; h, hour; ICU, intensive care unit; RCT, randomized controlled trial; Refs., references; UTI, urinary tract infection.

controlled trials. Since that particular publication, more studies have been published focusing on a variety of infection types that are well designed, and they consistently show shorter treatment duration is similarly effective and with fewer adverse events. Hence, shorter is better.

Thorough reviews of short-course, randomized controlled trials have been published [13–15, 18, 19], and it is not our intent to repeat these in detail. Rather, we wish to emphasize that substantial cognitive dissonance persists in the selection of longer treatment durations. Although dozens of randomized controlled trials have confirmed the safety and efficacy of shorter course regimens, uptake remains generally poor in many clinical settings [13, 15, 91–96].

There are, of course, exceptions to Shorter Is Better. For example, shorter course regimens are not equally effective for prosthetic joint infections with retention of the device [97], nor for otitis media in children under 2 years of age [98], nor for treatment of chronic pulmonary aspergillosis [99]. Thus, we cannot and do not presume to know the optimal duration of therapy for all infections, neither based on the historical past, nor from transposition of modern trials to other diseases. For unstudied infectious diseases, trials are still needed to delineate the optimal duration of therapy [19, 100].

Oral Antimicrobial Therapy for Osteomyelitis, Bacteremia, and Endocarditis

We have also recently summarized the literature on oral therapy for the treatment of osteomyelitis, bacteremia, and endocarditis [30, 101, 102]. The overwhelming concordance of data have demonstrated that oral therapy is effective for these infections, contrary to fixed, firm beliefs otherwise. There are more than 40 published observational studies demonstrating that oral therapy is effective for osteomyelitis [26, 102] and more than 15 such studies demonstrating efficacy for endocarditis [30]. More importantly, there are 21 randomized controlled trials demonstrating that oral therapy is at least as effective as IV-only therapy for these diseases, including 9 trials of osteomyelitis, 10 trials of bacteremia, and 3 trials of endocarditis (1 trial included separate cohorts of osteomyelitis and bacteremia) (Table 2) [101, 103]. There are no trials to the contrary.

Furthermore, for osteomyelitis, another 17 randomized controlled trials (8 in children and 9 in adults) and 1 quasi-experimental study (in children) compared predominantly oral therapy in both arms, either different antimicrobial regimens or different durations of therapy [68–72, 97, 102, 124–135]. These studies encompassed virtually every conceivable manifestation of osteomyelitis, including vertebral, diabetic foot infection, prosthetic joint, etc, treated with a variety of different antimicrobial regimens, and found similarly high cure rates in all cases. Indeed, pediatricians have treated osteomyelitis with oral antibiotics

Table 2. Summary of Randomized Controlled Trials of Oral vs IV-Only Therapy

Diagnosis	No. of RCTs Demonstrating IV > Oral	No. of RCTs Demonstrating Oral ≥ IV	References
Osteomyelitis	0	9 (all equal)	[103–111]
Bacteremia	0	10 (8 equal, 2 superior cure for oral)	[109, 112–120]
Endocarditis	0	3 (2 equal, 1 superior mortality for oral)	[121–123]

Abbreviations: IV, intravenous; RCT, randomized controlled trial.

for decades based on these randomized controlled trials.

Not only have none of these trials ever demonstrated the superiority of IV-only therapy, but in several of the bacteremia trials and the largest randomized control trial of bacterial endocarditis, oral therapy significantly improved outcomes (including mortality!) compared to IV-only therapy [30, 101]. Furthermore, by using oral therapy, the significant harms caused by persistence of a plastic catheter in central veins for weeks at a time can be avoided. Yet, prescriber uptake of oral therapy for these diseases remains low, particularly for endovascular infections [93, 136].

Conclusions From Modern Data

For many infections, no reasonable data have ever established that longer courses of therapy are more effective, nor that IV-only therapy is superior to oral-transitional therapy. In contrast, an incredibly robust, concordant set of modern studies, including numerous randomized controlled trials, have established the opposite: that many short-course regimens are as effective as long course, and that oral transitional therapy is at least as effective, and safer, than IV-only therapy for most cases of osteomyelitis, bacteremia, and endocarditis.

These studies do not, of course, indicate that all patients should receive a specific short duration of therapy, nor do they indicate that every patient is appropriate for an oral regimen, or that any oral regimen is effective for any disease. Healthcare practitioners must customize therapy to the unique circumstances of their patient. In addition, practitioners might be encouraged to seek pharmacists' input regarding the appropriateness of giving an oral antimicrobial for a particular pathogen or syndrome; indeed, pharmacists have long been instrumental in antimicrobial stewardship. What these trials do establish is that the average duration of therapy for specific, studied infectious syndromes should be shortened from the historical norm, and that oral therapy is a reasonable consideration for osteomyelitis, bacteremia, and endocarditis in patients who meet specific clinical criteria.

We have suggested that such clinical criteria may include [30, 101, 102] the following: (1) the patient is clinically and hemodynamically stable; (2) procedural source control has been achieved when appropriate, ideally with clearance of bacteremia; (3) the patient's gut is functioning and likely to absorb oral medications; (4) a published regimen is available for the target pathogen(s); and (5) there are no patient-level, psychosocial, or economic factors that would cause IV therapy to be favored.

WE MUST DO BETTER

So where do we go from here? We believe it is time for the field of infectious diseases to adopt evidenced-based over eminence-based medicine [1, 2]. Where high-quality data exist, we urge our community to embrace a change in practice in accordance with the evidence. To do so in no way undermines or diminishes our appreciation and respect for the giants who came before us and the work they did. Indeed, it acknowledges them. Osler himself purportedly once said, "Fifty percent of everything I'm teaching you is wrong. The only problem is, I don't know which 50%" [137].

A common, contrarian refrain points to the flaws and limitations of the available randomized controlled trials, maintaining that we cannot adopt them into practice until edge cases have been addressed. The fallacy of this argument is that it presumes existing practice is based on unflawed data, whereas it is instead based on either no data or low-quality data far below that of randomized controlled trials, amped up by historical opinions of eminent experts. Thus, even for patients who may not have explicitly been enrolled in many of the trials, what we are left with is equipoise, not certainty of a longer duration of therapy or an IV-only approach. Indeed, the data most proximate to edge cases would indicate consideration of short-course or oral regimens is reasonable, and no data are available to indicate that such consideration is unreasonable.

Arguably, it is to the detriment of patient care that the findings of numerous, concordant, randomized controlled trials are not adopted into practice due to existing limitations, particularly in circumstances in which actual practice is based on no evidence at all. Delay in changing practice after new data are published is not unique infectious diseases. The entire field of medicine faces this challenge. Indeed, in numerous studies, researchers have found that it typically takes 15–20 years for practitioners to change their practice after high-quality studies are published [138]. Nevertheless, all trials have some flaws or limitations, and concordant conclusions from high-quality trials must, after rational consideration, start to outweigh the burden of historical inertia.

The amount of new data required to change previous practice depends on the totality of the evidence. What is the level of evidence that established the prior practice in the first place? What level of new evidence has resulted in the potential change in practice? How precise are the estimates of relative efficacy and harm (particularly relevant for noninferiority studies)? Is the proposed change in practice based on change in efficacy, change in safety, change in cost, change in patient satisfaction, or other? Is efficacy defined by a surrogate endpoint, or a hard clinical endpoint (resolution of signs/symptoms of disease, or mortality)? Is the efficacy dissociated from safety—for example, clinical cure increases but harm events also increase? Proposed changes indeed require complex considerations where incremental advances are achieved, possibly via surrogate endpoints, but accompanied by considerably increased cost, patient inconvenience, or adverse effects. However, in circumstances where prior evidence that established historical practice is weak, new, practice-changing evidence is based on multiple, concordant, randomized controlled trials,

the outcomes are hard clinical endpoints, and safety, patient satisfaction, and cost are all improved, the considerations are more straightforward. In this review, we hope to have illustrated 2 common examples in which this is exactly the case.

We continue to encounter many dogmas in everyday practice. Some have already been successfully debunked based on reproducible, high-quality studies, such as the fallacy of static versus cidal antibiotics [139], combination therapy or double coverage in the treatment of *Pseudomonas* and/or sepsis [140–144], the recommendation for continuation of antibiotics for neutropenic fever until the resolution of neutropenia [82, 145], the use of aminoglycoside or rifampin for synergistic treatment in staphylococcal endocarditis or sepsis [142, 146–148], the inability to shorten antimicrobial therapy in patients with immune dysfunction [11], and the need for routine antibiotic therapy for uncomplicated diverticulitis [149]. Other long-standing dogmas are now being rightfully questioned, with studies poised to commence that may well overturn them, such as high-dose trimethoprim-sulfamethoxazole for pneumocystis pneumonia [100], the preference of pyrimethamine-containing regimens over trimethoprim-sulfamethoxazole for the treatment of toxoplasma encephalitis [150], the advantage of antistaphylococcal penicillin over cefazolin for the treatment of *S aureus* bacteremia [151], the routine fundoscopic examination in candidemia [152], and additional anaerobic coverage for aspiration pneumonia [153].

Conversely, other long-standing dogmas may ultimately be proven correct, when eventually subjected to rigorous clinical investigation. All outcomes are welcome, so long as they are based on actual evidence. Indeed, in the absence of contrary high-quality data, historical practice may be reasonable.

CONCLUSIONS

Fundamentally, however, where robust data exists or emerges (or enrollment in a clinical trial is feasible), we must not cling to historical practice simply because "that's the way it's always been." If we can overcome our own resistances, both intrinsic and extrinsic, the specialty of infectious diseases is ideally positioned to model evidence-based antimicrobial prescribing for trainees, for each other, and for our colleagues in other specialties. With the shared goal of bettering patient care, we believe it is our collective responsibility to lead the way. We owe it to our patients to do so.

Acknowledgments

Potential conflict of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

References

1. Spellberg B, Shorr AF. Opinion-based recommendations: beware the tyranny of experts. Open Forum Infect Dis **2021**; 8:ofab490.
2. Spellberg B, Wright WF, Shaneyfelt TM, Centor RM. The future of medical guidelines—standardizing clinical care with the humility of uncertainty. Ann Intern Med **2021**; 174:1740–42.
3. Spellberg B. Rising Plague: The Global Threat from Deadly Bacteria and Our Dwindling Arsenal to Fight Them. New York: Prometheus Press, **2009**.
4. Swainson B. Encarta Book of Quotations. Bellevue, Washington: Encarta, **2000**.
5. Northey EH. The Sulfonamides and Allied Compounds. New York: Reinhold Publishing, Inc., **1948**.
6. YOUNG ROOSEVELT SAVED BY NEW DRUG; Doctor Used Prontylin in Fight on Streptococcus Infection of the Throat. CONDITION ONCE SERIOUS But Youth, in Boston Hospital, Gains Steadily – Fiancee, Reassured, Leaves Bedside. YOUNG ROOSEVELT SAVED BY NEW DRUG. *New York Times*, December 17, 1936.
7. Snodgrass WR, Anderson T. Sulphanilamide in the treatment of erysipelas. Br Med J **1937**; 2: 1156–9.
8. Thomas L. The Youngest Science. Notes of a Medicine-Watcher. New York: The Viking Press, **1983**.
9. Grossman CM. The first use of penicillin in the United States. Ann Intern Med **2008**; 149:135–6.
10. McDermott W, Rogers DE. Social ramifications of control of microbial disease. Johns Hopkins Med J **1982**; 151:302–12.
11. Imlay H, Laundy N, Forrest G, Slavin M. Shorter antibiotic courses in the immunocompromised: the impossible dream? Clin Microbiol Infect **2022**.
12. Spellberg B. The new antibiotic mantra-"shorter is better". JAMA Intern Med **2016**; 176:1254–5.
13. Spellberg B, Rice LB. Duration of antibiotic therapy: shorter is better. Ann Intern Med **2019**; 171: 210–1.
14. Spellberg B, Rice LB. The shorter is better movement: past, present, future. Clin Microbiol Infect **2022**.
15. Wald-Dickler N, Spellberg B. Short course antibiotic therapy-replacing Constantine units with "shorter is better". Clin Infect Dis **2019**; 69: 1476–9.
16. 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.
17. Dominguez F, Davar K, Wald-Dickler N, et al. How to change the course: practical aspects of implementing shorter is better. Clin Microbiol Infect **2022**.
18. Lee RA, Centor RM, Humphrey LL, et al. Appropriate use of short-course antibiotics in common infections: best practice advice from the American college of physicians. Ann Intern Med **2021**; 174:822–7.
19. Lee R, Stripling JT, Spellberg B, Centor RM. Short course antibiotics for common infections: what do we know and where do we go from here? Clin Microbiol Infect **2022**.
20. Fleming A. Penicillin: Nobel Lecture. 1945 Stockholm, Sweden, December 10, 1945.
21. Curran J, Lo J, Leung V, et al. Estimating daily antibiotic harms: an umbrella review with individual study meta-analysis. Clin Microbiol Infect **2022**; 28:479–90.
22. Teshome BF, Vouri SM, Hampton N, Kollef MH, Micek ST. Duration of exposure to antipseudomonal beta-lactam antibiotics in the critically ill and development of new resistance. Pharmacotherapy **2019**; 39:261–70.
23. Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. BMJ **2010**; 340:c2096.
24. Llewelyn MJ, Fitzpatrick JM, Darwin E, et al. The antibiotic course has had its day. BMJ **2017**; 358: j3418.
25. Waldvogel FA, Medoff G, Swartz MN. Osteomyelitis: a review of clinical features, therapeutic considerations and unusual aspects. N Engl J Med **1970**; 282:198–206.
26. Spellberg B, Lipsky BA. Systemic antibiotic therapy for chronic osteomyelitis in adults. Clin Infect Dis **2012**; 54:393–407.
27. Lichtman SS. Treatment of subacute bacterial endocarditis: current results. Ann Intern Med **1943**; 19:787–04.
28. Smith C, Sauls HC, Stone CF. Subacute bacterial endocarditis due to Streptococcus viridans: survey of present status of previously reported cures and clinical study of fifteen treated cases, including another cure. JAMA **1942**; 119:478–82.
29. Kelson SR. Observations on the treatment of subacute bacterial (streptococcal) endocarditis since 1939. Ann Intern Med **1945**; 22:75–96.
30. Spellberg B, Chambers HF, Musher DM, Walsh TL, Bayer AS. Evaluation of a paradigm shift from intravenous antibiotics to oral step-down therapy for the treatment of infective endocarditis: a narrative review. JAMA Intern Med **2020**; 180:769.
31. Finland M. Treatment of bacterial endocarditis. N Engl J Med **1954**; 250:372–83.
32. Dunbar LM, Khashab MM, Kahn JB, Zadeikis N, Xiang JX, Tennenberg AM. Efficacy of 750-mg, 5-day levofloxacin in the treatment of community-acquired pneumonia caused by atypical pathogens. Curr Med Res Opin **2004**; 20:555–63.
33. Zhao X, Wu JF, Xiu QY, et al. A randomized controlled clinical trial of levofloxacin 750 mg versus 500 mg intravenous infusion in the treatment of

community-acquired pneumonia. Diagn Microbiol Infect Dis **2014**; 80:141–7.
34. Pakistan Multicentre Amoxycillin Short Course Therapy Pneumonia Study Group. Clinical efficacy of 3 days versus 5 days of oral amoxicillin for treatment of childhood pneumonia: a multicentre double-blind trial. Lancet **2002**; 360:835–41.
35. Greenberg D, Givon-Lavi N, Sadaka Y, Ben-Shimol S, Bar-Ziv J, Dagan R. Short-course antibiotic treatment for community-acquired alveolar pneumonia in ambulatory children: a double-blind, randomized, placebo-controlled trial. Pediatr Infect Dis J **2014**; 33:136–42.
36. 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**; 332:1355.
37. Uranga A, Espana PP, Bilbao A, et al. Duration of antibiotic treatment in community-acquired pneumonia: a multicenter randomized clinical trial. JAMA Intern Med **2016**; 176:1257–65.
38. Dinh A, Davido B, Bouchand F, Duran C, Ropers J, Cremieux AC. Honey, I shrunk the antibiotic therapy. Clin Infect Dis **2018**; 66:1981–2.
39. Harris JA, Kolokathis A, Campbell M, Cassell GH, Hammerschlag MR. Safety and efficacy of azithromycin in the treatment of community-acquired pneumonia in children. Pediatr Infect Dis J **1998**; 17:865–71.
40. Ginsburg AS, Mvalo T, Nkwopara E, et al. Amoxicillin for 3 or 5 days for chest-indrawing pneumonia in Malawian children. N Engl J Med **2020**; 383:13–23.
41. Pernica JM, Harman S, Kam AJ, et al. Short-course antimicrobial therapy for pediatric community-acquired pneumonia: the SAFER randomized clinical trial. JAMA Pediatr **2021**; 175:475–82.
42. Dinh A, Ropers J, Duran C, et al. Discontinuing beta-lactam treatment after 3 days for patients with community-acquired pneumonia in non-critical care wards (PTC): a double-blind, randomised, placebo-controlled, non-inferiority trial. Lancet **2021**; 397:1195–203.
43. Bielicki JA, Stohr W, Barratt S, et al. Effect of amoxicillin dose and treatment duration on the need for antibiotic re-treatment in children with community-acquired pneumonia: the CAP-IT randomized clinical trial. JAMA **2021**; 326: 1713–24.
44. Williams DJ, Creech CB, Walter EB, et al. Short- vs standard-course outpatient antibiotic therapy for community-acquired pneumonia in children: the SCOUT-CAP randomized clinical trial. JAMA Pediatr **2022**; 176:253–61.
45. McCallum GB, Fong SM, Grimwood K, et al. Extended versus standard antibiotic course duration in children <5 years of age hospitalized with community-acquired pneumonia in high-risk settings: four-week outcomes of a multicenter, double-blind, parallel, superiority randomized controlled trial. Pediatr Infect Dis J **2022**; 41: 549–55.
46. Schonwald S, Kuzman I, Oreskovic K, et al. Azithromycin: single 1.5 g dose in the treatment of patients with atypical pneumonia syndrome–a randomized study. Infection **1999**; 27:198–202.
47. 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**; 162:505–11.
48. Chastre J, Wolff M, Fagon JY, et al. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. JAMA **2003**; 290:2588–98.
49. Capellier G, Mockly H, Charpentier C, et al. Early-onset ventilator-associated pneumonia in adults randomized clinical trial: comparison of 8 versus 15 days of antibiotic treatment. PLoS One **2012**; 7:e41290.
50. Jernelius H, Zbornik J, Bauer CA. One or three weeks' treatment of acute pyelonephritis? A double-blind comparison, using a fixed combination of pivampicillin plus pivmecillinam. Acta Med Scand **1988**; 223:469–77.
51. de Gier R, Karperien A, Bouter K, et al. A sequential study of intravenous and oral fleroxacin for 7 or 14 days in the treatment of complicated urinary tract infections. Int J Antimicrob Agents **1995**; 6: 27–30.
52. Talan DA, Stamm WE, Hooton TM, et al. Comparison of ciprofloxacin (7 days) and trimethoprim-sulfamethoxazole (14 days) for acute uncomplicated pyelonephritis pyelonephritis in women: a randomized trial. JAMA **2000**; 283:1583–90.
53. Sandberg T, Skoog G, Hermansson AB, et al. Ciprofloxacin for 7 days versus 14 days in women with acute pyelonephritis: a randomised, open-label and double-blind, placebo-controlled, non-inferiority trial. Lancet **2012**; 380:484–90.
54. Peterson J, Kaul S, Khashab M, Fisher AC, Kahn JB. A double-blind, randomized comparison of levofloxacin 750 mg once-daily for five days with ciprofloxacin 400/500 mg twice-daily for 10 days for the treatment of complicated urinary tract infections and acute pyelonephritis. Urology **2008**; 71:17–22.
55. Klausner HA, Brown P, Peterson J, et al. A trial of levofloxacin 750 mg once daily for 5 days versus ciprofloxacin 400 mg and/or 500 mg twice daily for 10 days in the treatment of acute pyelonephritis. Curr Med Res Opin **2007**; 23:2637–45.
56. Dinh A, Davido B, Etienne M, et al. Is 5 days of oral fluoroquinolone enough for acute uncomplicated pyelonephritis? The DTP randomized trial. Eur J Clin Microbiol Infect Dis **2017**; 36:1443–8.
57. van Nieuwkoop C, van der Starre WE, Stalenhoef JE, et al. Treatment duration of febrile urinary tract infection: a pragmatic randomized, double-blind, placebo-controlled non-inferiority trial in men and women. BMC Med **2017**; 15:70.
58. Drekonja DM, Trautner B, Amundson C, Kuskowski M, Johnson JR. Effect of 7 vs 14 days of antibiotic therapy on resolution of symptoms among afebrile men with urinary tract infection: a randomized clinical trial. JAMA **2021**; 326:324–31.
59. Sawyer RG, Claridge JA, Nathens AB, et al. Trial of short-course antimicrobial therapy for intraabdominal infection. N Engl J Med **2015**; 372: 1996–2005.
60. Montravers P, Tubach F, Lescot T, et al. Short-course antibiotic therapy for critically ill patients treated for postoperative intra-abdominal infection: the DURAPOP randomised clinical trial. Intensive Care Med **2018**; 44:300–10.
61. Yahav D, Franceschini E, Koppel F, et al. Seven versus 14 days of antibiotic therapy for uncomplicated gram-negative bacteremia: a noninferiority randomized controlled trial. Clin Infect Dis **2019**; 69:1091–8.
62. von Dach E, Albrich WC, Brunel AS, et al. Effect of C-reactive protein-guided antibiotic treatment duration, 7-day treatment, or 14-day treatment on 30-day clinical failure rate in patients with uncomplicated gram-negative bacteremia: a randomized clinical trial. JAMA **2020**; 323:2160–9.
63. Molina J, Montero-Mateos E, Praena-Segovia J, et al. Seven-versus 14-day course of antibiotics for the treatment of bloodstream infections by enterobacterales: a randomized, controlled trial. Clin Microbiol Infect **2022**; 28:550–7.
64. 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**; 164:1669–74.
65. Prokocimer P, De Anda C, Fang E, Mehra P, Das A. Tedizolid phosphate vs linezolid for treatment of acute bacterial skin and skin structure infections: the ESTABLISH-1 randomized trial. JAMA **2013**; 309:559–69.
66. Moran GJ, Fang E, Corey GR, Das AF, De Anda C, Prokocimer P. Tedizolid for 6 days versus linezolid for 10 days for acute bacterial skin and skin-structure infections (ESTABLISH-2): a randomised, double-blind, phase 3, non-inferiority trial. Lancet Infect Dis **2014**; 14:696–705.
67. Cranendonk DR, Opmeer BC, van Agtmael MA, et al. Antibiotic treatment for 6 days versus 12 days in patients with severe cellulitis: a multicentre randomised, double-blind, placebo-controlled, non-inferiority trial. Clin Microbiol Infect **2020**; 26:606–612.
68. 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 **2015**; 38:302–7.
69. Bernard L, Dinh A, Ghout I, et al. Antibiotic treatment for 6 weeks versus 12 weeks in patients with pyogenic vertebral osteomyelitis: an open-label, non-inferiority, randomised, controlled trial. Lancet **2015**; 385:875–82.
70. Benkabouche M, Racloz G, Spechbach H, Lipsky BA, Gaspoz JM, Uckay I. Four versus six weeks of antibiotic therapy for osteoarticular infections after implant removal: a randomized trial. J Antimicrob Chemother **2019**; 74:2394–9.
71. Lazaro-Martinez JL, Aragon-Sanchez J, Garcia-Morales E. Antibiotics versus conservative surgery for treating diabetic foot osteomyelitis: a randomized comparative trial. Diabetes Care **2014**; 37:789–95.
72. Gariani K, Pham TT, Kressmann B, et al. Three versus six weeks of antibiotic therapy for diabetic foot osteomyelitis: a prospective, randomized, non-inferiority pilot trial. Clin Infect Dis **2021**; 73:e1539–e1545.
73. 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**; 78:1114–21.
74. Moussaoui R E, 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**; 63:415–22.
75. Messous S, Trabelsi I, Bel Haj Ali K, et al. Two-day versus seven-day course of levofloxacin in acute COPD exacerbation: a randomized controlled trial. Ther Adv Respir Dis **2022**; 16: 175346662210997.
76. Henry DC, Riffer E, Sokol WN, Chaudry NI, Swanson RN. Randomized double-blind study comparing 3- and 6-day regimens of azithromycin with a 10-day amoxicillin-clavulanate regimen for

treatment of acute bacterial sinusitis. Antimicrob Agents Chemother **2003**; 47:2770–4.
77. Ferguson BJ, Anon J, Poole MD, et al. Short treatment durations for acute bacterial rhinosinusitis: five days of gemifloxacin versus 7 days of gemifloxacin. Otolaryngol Head Neck Surg **2002**; 127:1–6.
78. Sher LD, McAdoo MA, Bettis RB, Turner MA, Li NF, Pierce PF. A multicenter, randomized, investigator-blinded study of 5- and 10-day gatifloxacin versus 10-day amoxicillin/clavulanate in patients with acute bacterial sinusitis. Clin Ther **2002**; 24:269–81.
79. Roos K, Brunswig-Pitschner C, Kostrica R, et al. Efficacy and tolerability of once-daily therapy with telithromycin for 5 or 10 days for the treatment of acute maxillary sinusitis. Chemotherapy **2002**; 48:100–8.
80. Williams JW Jr, Holleman DR Jr, Samsa GP, Simel DL. Randomized controlled trial of 3 vs 10 days of trimethoprim/sulfamethoxazole for acute maxillary sinusitis. JAMA **1995**; 273:1015–21.
81. Klapan I, Culig J, Oreskovic K, Matrapazovski M, Radosevic S. Azithromycin versus amoxicillin/clavulanate in the treatment of acute sinusitis. Am J Otolaryngol **1999**; 20:7–11.
82. Aguilar-Guisado M, Espigado I, Martin-Pena A, et al. Optimisation of empirical antimicrobial therapy in patients with haematological malignancies and febrile neutropenia (how long study): an open-label, randomised, controlled phase 4 trial. Lancet Haematol **2017**; 4:e573–83.
83. de Jonge NA, Sikkens JJ, Zweegman S, et al. Short versus extended treatment with a carbapenem in patients with high-risk fever of unknown origin during neutropenia: a non-inferiority, open-label, multicentre, randomised trial. Lancet Haematol **2022**; 9:e563–72.
84. de Jonge SW, Boldingh QJJ, Solomkin JS, et al. Effect of postoperative continuation of antibiotic prophylaxis on the incidence of surgical site infection: a systematic review and meta-analysis. Lancet Infect Dis **2020**; 20:1182–92.
85. Berry PS, Rosenberger LH, Guidry CA, Agarwal A, Pelletier S, Sawyer RG. Intraoperative versus extended antibiotic prophylaxis in liver transplant surgery: a randomized controlled pilot trial. Liver Transpl **2019**; 25:1043–53.
86. Prophylactic Antibiotic Regimens in Tumor Surgery (PARITY) Investigators; Ghert M, Schneider P, et al. Comparison of prophylactic intravenous antibiotic regimens after endoprosthetic reconstruction for lower extremity bone tumors: a randomized clinical trial. JAMA Oncol **2022**; 8: 345–53.
87. Nagata K, Yamada K, Shinozaki T, et al. Effect of antimicrobial prophylaxis duration on health care-associated infections after clean orthopedic surgery: a cluster randomized trial. JAMA Netw Open **2022**; 5:e226095.
88. Gahm J, Ljung Konstantinidou A, Lagergren J, et al. Effectiveness of single vs multiple doses of prophylactic intravenous antibiotics in implant-based breast reconstruction: a randomized clinical trial. JAMA Netw Open **2022**; 5:e2231583.
89. Taylor WRJ, Thriemer K, von Seidlein L, et al. Short-course primaquine for the radical cure of plasmodium vivax malaria: a multicentre, randomised, placebo-controlled non-inferiority trial. Lancet **2019**; 394:929–38.
90. Stupica D, Collinet-Adler S, Blagus R, et al. Treatment of erythema migrans with doxycycline for 7 days versus 14 days in Slovenia: a randomised open-label non-inferiority trial. Lancet Infect Dis **2022**.
91. Macheda G, Dyar OJ, Luc A, et al. Are infection specialists recommending short antibiotic treatment durations? An ESCMID international cross-sectional survey. J Antimicrob Chemother **2018**; 73:1084–90.
92. Palin V, Welfare W, Ashcroft DM, van Staa TP. Shorter and longer courses of antibiotics for common infections and the association with reductions of infection-related complications including hospital admissions. Clin Infect Dis **2021**; 73: 1805–12.
93. Buis DTP, Prins JM, Betica-Radic L, et al. Current clinical practice in antibiotic treatment of Staphylococcus aureus bacteraemia: results from a survey in five European countries. J Antimicrob Chemother **2022**; 77:2827–34.
94. Thaden JT, Tamma PD, Pan Q, Doi Y, Daneman N. Survey of infectious diseases providers reveals variability in duration of antibiotic therapy for the treatment of gram-negative bloodstream infections. JAC Antimicrob Resist **2022**; 4:dlac005.
95. Vaughn VM, Flanders SA, Snyder A, et al. Excess antibiotic duration and adverse-1 events in patients hospitalized with pneumonia: a multihospital cohort study. Ann Intern Med **2019**; 171:153–63.
96. Fernandez-Lazaro CI, Brown KA, Langford BJ, Daneman N, Garber G, Schwartz KL. Late-career physicians prescribe longer courses of antibiotics. Clin Infect Dis **2020**; 70:1795–6.
97. Bernard L, Arvieux C, Brunschweiler B, et al. Antibiotic therapy for 6 or 12 weeks for prosthetic joint infection. N Engl J Med **2021**; 384: 1991–2001.
98. Hoberman A, Paradise JL, Rockette HE, et al. Shortened antimicrobial treatment for acute otitis media in young children. N Engl J Med **2016**; 375: 2446–56.
99. Sehgal IS, Dhooria S, Muthu V, et al. Efficacy of 12-months oral itraconazole versus 6-months oral itraconazole to prevent relapses of chronic pulmonary aspergillosis: an open-label, randomised controlled trial in India. Lancet Infect Dis **2022**; 22:1052–61.
100. Sohani ZN, Butler-Laporte G, Aw A, et al. Low-dose trimethoprim-sulfamethoxazole for the treatment of pneumocystis jirovecii pneumonia (LOW-TMP): protocol for a phase III randomised, placebo-controlled, dose-comparison trial. BMJ Open **2022**; 12:e053039.
101. Wald-Dickler N, Holtom P, Phillips MC, et al. Oral is the new IV–challenging decades of blood and bone infection dogma: a systematic review. Am J Med **2021**; 135:369–379.
102. Spellberg B, Aggrey G, Brennan MB, et al. Use of novel strategies to develop guidelines for management of pyogenic osteomyelitis in adults: a WikiGuidelines group consensus statement. JAMA Netw Open **2022**; 5:e2211321.
103. Manning L, Metcalf S, Dymock M, et al. Short-versus standard-course intravenous antibiotics for peri-prosthetic joint infections managed with debridement and implant retention: a randomised pilot trial using a desirability of outcome ranking (DOOR) endpoint. Int J Antimicrob Agents **2022**; 60:106598.
104. Greenberg RN, Tice AD, Marsh PK, et al. Randomized trial of ciprofloxacin compared with other antimicrobial therapy in the treatment of osteomyelitis. Am J Med **1987**; 82:266–9.
105. Mader JT, Cantrell JS, Calhoun J. Oral ciprofloxacin compared with standard parenteral antibiotic therapy for chronic osteomyelitis in adults. J Bone Joint Surg Am **1990**; 72:104–10.
106. Gentry LO, Rodriguez GG. Oral ciprofloxacin compared with parenteral antibiotics in the treatment of osteomyelitis. Antimicrob Agents Chemother **1990**; 34:40–3.
107. Gentry LO, Rodriguez-Gomez G. Ofloxacin versus parenteral therapy for chronic osteomyelitis. Antimicrob Agents Chemother **1991**; 35:538–41.
108. Gomis M, Barberan J, Sanchez B, Khorrami S, Borja J, Garcia-Barbal J. Oral ofloxacin versus parenteral imipenem-cilastatin in the treatment of osteomyelitis. Rev Esp Quimioter **1999**; 12:244–9.
109. Schrenzel J, Harbarth S, Schockmel G, et al. A randomized clinical trial to compare fleroxacin-rifampicin with flucloxacillin or vancomycin for the treatment of staphylococcal infection. Clin Infect Dis **2004**; 39:1285–92.
110. Euba G, Murillo O, Fernandez-Sabe N, et al. Long-term follow-up trial of oral rifampin-cotrimoxazole combination versus intravenous cloxacillin in treatment of chronic staphylococcal osteomyelitis. Antimicrob Agents Chemother **2009**; 53:2672–6.
111. Li HK, Rombach I, Zambellas R, et al. Oral versus intravenous antibiotics for bone and joint infection. N Engl J Med **2019**; 380:425–36.
112. Pedro GS S, Cammarata SK, Oliphant TH, Todisco T. Linezolid community-acquired pneumonia study G. Linezolid versus ceftriaxone/cefpodoxime in patients hospitalized for the treatment of Streptococcus pneumoniae pneumonia. Scand J Infect Dis **2002**; 34:720–8.
113. Deville JG, Adler S, Azimi PH, et al. Linezolid versus vancomycin in the treatment of known or suspected resistant Gram-positive infections in neonates. Pediatr Infect Dis J **2003**; 22(9 Suppl): S158–63.
114. Jantausch BA, Deville J, Adler S, et al. Linezolid for the treatment of children with bacteremia or nosocomial pneumonia caused by resistant Gram-positive bacterial pathogens. Pediatr Infect Dis J **2003**; 22(9 Suppl):S164–71.
115. Kaplan SL, Deville JG, Yogev R, et al. Linezolid versus vancomycin for treatment of resistant Gram-positive infections in children. Pediatr Infect Dis J **2003**; 22:677–86.
116. Wilcox M, Nathwani D, Dryden M. Linezolid compared with teicoplanin for the treatment of suspected or proven Gram-positive infections. J Antimicrob Chemother **2004**; 53:335–44.
117. Wilcox MH, Tack KJ, Bouza E, et al. Complicated skin and skin-structure infections and catheter-related bloodstream infections: noninferiority of linezolid in a phase 3 study. Clin Infect Dis **2009**; 48:203–12.
118. Amodio-Groton M, Madu A, Madu CN, et al. Sequential parenteral and oral ciprofloxacin regimen versus parenteral therapy for bacteremia: a pharmacoeconomic analysis. Ann Pharmacother **1996**; 30:596–602.
119. Monmaturapoj T, Montakantikul P, Mootsikapun P, Tragulpiankit P. A prospective, randomized, double dummy, placebo-controlled trial of oral cefditoren pivoxil 400 mg once daily as switch therapy after intravenous ceftriaxone in the treatment of acute pyelonephritis. Int J Infect Dis **2012**; 16:e843–9.
120. Park TY, Choi JS, Song TJ, Do JH, Choi SH, Oh HC. Early oral antibiotic switch compared with conventional intravenous antibiotic therapy for acute cholangitis with bacteremia. Dig Dis Sci **2014**; 59:2790–6.
121. Stamboulian D, Bonvehi P, Arevalo C, et al. Antibiotic management of outpatients with

endocarditis due to penicillin-susceptible streptococci. Rev Infect Dis **1991**; 13(Suppl 2):S160–3.
122. Heldman AW, Hartert TV, Ray SC, et al. Oral antibiotic treatment of right-sided staphylococcal endocarditis in injection drug users: prospective randomized comparison with parenteral therapy. Am J Med **1996**; 101:68–76.
123. Bundgaard H, Ihlemann N, Gill SU, et al. Long-term outcomes of partial oral treatment of endocarditis. N Engl J Med **2019**; 380:1373–4.
124. Lipsky BA, Baker PD, Landon GC, Fernau R. Antibiotic therapy for diabetic foot infections: comparison of two parenteral-to-oral regimens. Clin Infect Dis **1997**; 24:643–8.
125. Lipsky BA, Itani K, Norden C. Treating foot infections in diabetic patients: a randomized, multicenter, open-label trial of linezolid versus ampicillin-sulbactam/amoxicillin-clavulanate. Clin Infect Dis **2004**; 38:17–24.
126. Lora-Tamayo J, Euba G, Cobo J, et al. Short- versus long-duration levofloxacin plus rifampicin for acute staphylococcal prosthetic joint infection managed with implant retention: a randomised clinical trial. Int J Antimicrob Agents **2016**; 48: 310–6.
127. Peltola H, Paakkonen M, Kallio P, Kallio MJ, Group O-SS. Clindamycin vs. first-generation cephalosporins for acute osteoarticular infections of childhood–a prospective quasi-randomized controlled trial. Clin Microbiol Infect **2012**; 18: 582–9.
128. Peltola H, Roine I, Fernandez J, et al. Adjuvant glycerol and/or dexamethasone to improve the outcomes of childhood bacterial meningitis: a prospective, randomized, double-blind, placebo-controlled trial. Clin Infect Dis **2007**; 45:1277–86.
129. Peltola H, Unkila-Kallio L, Kallio MJ. Simplified treatment of acute staphylococcal osteomyelitis of childhood. The Finnish study group. Pediatrics **1997**; 99:846–50.
130. Peltola H, Vuori-Holopainen E, Kallio MJ, Group S-TS. Successful shortening from seven to four days of parenteral beta-lactam treatment for common childhood infections: a prospective and randomized study. Int J Infect Dis **2001**; 5:3–8.
131. Jaberi FM, Shahcheraghi GH, Ahadzadeh M. Short-term intravenous antibiotic treatment of acute hematogenous bone and joint infection in children: a prospective randomized trial. J Pediatr Orthop **2002**; 22:317–20.
132. Oosterheert JJ, Bonten MJ, Schneider MM, et al. Effectiveness of early switch from intravenous to oral antibiotics in severe community acquired pneumonia: multicentre randomised trial. BMJ **2006**; 333:1193.
133. Alcobendas R, Remesal A, Murias S, Nunez E, Calvo C. Outpatients with acute osteoarticular infections had favourable outcomes when they received just oral antibiotics without intravenous antibiotics. Acta Paediatr **2018**; 107:1792–7.
134. Bradley JS, Arrieta AC, Digtyar VA, et al. Daptomycin for pediatric Gram-positive acute hematogenous osteomyelitis. Pediatr Infect Dis J **2020**; 39:814–23.
135. Peltola H, Paakkonen M, Kallio P, Kallio MJ; Osteomyelitis-Septic Arthritis Study Group. Short- versus long-term antimicrobial treatment for acute hematogenous osteomyelitis of childhood: prospective, randomized trial on 131 culture-positive cases. Pediatr Infect Dis J **2010**; 29:1123–8.
136. Hospenthal DR, Waters CD, Beekmann SE, Polgreen PM. Practice patterns of infectious diseases physicians in transitioning from intravenous to oral therapy in patients with bacteremia. Open Forum Infect Dis **2020**; 7:ofz386.
137. Shryock RH. The medical reputation of Benjamin Rush: contrasts over two centuries. Bull Hist Med **1971**; 45:507–52.
138. Morris ZS, Wooding S, Grant J. The answer is 17 years, what is the question: understanding time lags in translational research. J R Soc Med **2011**; 104:510–20.
139. Wald-Dickler N, Holtom PD, Spellberg B. Busting the myth of "static vs. cidal": a systemic literature review. Clin Infect Dis **2018**; 66:1470–4.
140. Tang SY, Zhang SW, Wu JD, et al. Comparison of mono- and combination antibiotic therapy for the treatment of Pseudomonas aeruginosa bacteraemia: a cumulative meta-analysis of cohort studies. Exp Ther Med **2018**; 15:2418–28.
141. Hu Y, Li L, Li W, et al. Combination antibiotic therapy versus monotherapy for Pseudomonas aeruginosa bacteraemia: a meta-analysis of retrospective and prospective studies. Int J Antimicrob Agents **2013**; 42:492–6.
142. Paul M, Lador A, Grozinsky-Glasberg S, Leibovici L. Beta lactam antibiotic monotherapy versus beta lactam-aminoglycoside antibiotic combination therapy for sepsis. Cochrane Database Syst Rev **2014**; 2014:CD003344.
143. Brunkhorst FM, Oppert M, Marx G, et al. Effect of empirical treatment with moxifloxacin and meropenem vs meropenem on sepsis-related organ dysfunction in patients with severe sepsis: a randomized trial. JAMA **2012**; 307:2390–9.
144. Vardakas KZ, Tansarli GS, Bliziotis IA, Falagas ME. beta-lactam plus aminoglycoside or fluoroquinolone combination versus beta-lactam monotherapy for Pseudomonas aeruginosa infections: a meta-analysis. Int J Antimicrob Agents **2013**; 41: 301–10.
145. Verlinden A, Jansens H, Goossens H, et al. Safety and efficacy of antibiotic de-escalation and discontinuation in high-risk hematological patients with febrile neutropenia: a single-center experience. Open Forum Infect Dis **2022**; 9:ofab624.
146. Falagas ME, Matthaiou DK, Bliziotis IA. The role of aminoglycosides in combination with a beta-lactam for the treatment of bacterial endocarditis: a meta-analysis of comparative trials. J Antimicrob Chemother **2006**; 57:639–47.
147. Thwaites GE, Scarborough M, Szubert A, et al. Adjunctive rifampicin for Staphylococcus aureus bacteraemia (ARREST): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet **2018**; 391:668–78.
148. Ryder JH, Tong SYC, Gallagher JC, et al. Deconstructing the dogma: systematic literature review and meta-analysis of adjunctive gentamicin and rifampin in staphylococcal prosthetic valve endocarditis. Open Forum Infect Dis **2022**; 9: ofac583.
149. Desai M, Fathallah J, Nutalapati V, Saligram S. Antibiotics versus no antibiotics for acute uncomplicated diverticulitis: a systematic review and meta-analysis. Dis Colon Rectum **2019**; 62: 1005–12.
150. Prosty C, Hanula R, Levin Y, Bogoch II, McDonald EG, Lee TC. Revisiting the evidence base for modern day practice of the treatment of toxoplasmic encephalitis: a systematic review and meta-analysis. Clin Infect Dis **2022**.
151. Weis S, Kesselmeier M, Davis JS, et al. Cefazolin versus anti-staphylococcal penicillins for the treatment of patients with Staphylococcus aureus bacteremia: a systematic review and meta-analysis. Clin Microbiol Infect **2019**; 25:818–27.
152. Breazzano MP, Day HR Jr, Bloch KC, et al. Utility of ophthalmologic screening for patients with Candida bloodstream infections: a systematic review. JAMA Ophthalmol **2019**; 137:698–710.
153. Bowerman TJ, Zhang J, Waite LM. Antibacterial treatment of aspiration pneumonia in older people: a systematic review. Clin Interv Aging **2018**; 13:2201–13.