

Opinion-Based Recommendations: Beware the Tyranny of Experts

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Numerous randomized controlled trials (RCTs) have established that 4–8 days of antibiotic therapy is as effective as longer courses for patients with various infections caused by gram-negative bacilli [1–14]. These infections include complicated urinary tract infections (cUTIs) [1–8], complicated intra-abdominal infections (cIAIs) [9, 10], ventilator-associated pneumonia [11, 12], and gram-negative bacteremia irrespective of source [13, 14]. Similarly, RCTs have demonstrated that oral antibiotics are as effective as intravenous therapy for the same infections, including cUTIs [15–18], cIAIs [19–23], and gram-negative bacteremia irrespective of source [24–26]. Of course, no group of RCTs can possibly encompass every patient variation, which always leaves questions regarding how well the data extrapolate to some patients in real-world settings.

In this context, Heil et al invited a panel of primarily academic infectious

diseases physicians and pharmacists to discuss a series of questions about their opinions regarding treatment of gram-negative bacteremia [27]. Based on interactive dialogue, the experts achieved consensus on how to define the term “uncomplicated gram-negative bacteremia,” which was intended to guide treatment decisions, such as duration of therapy, use of oral agents, and need for repeat blood cultures.

A strength of the approach is the acknowledgment of controversy where it existed, for example regarding what type of immunocompromise or which species of bacteria, if any, should make a case of bacteremia complicated rather than uncomplicated. Another strength is their resulting consensus that 7 days of antibiotic therapy and oral therapy are generally appropriate for gram-negative bacteremia, which is concordant with the multiple RCTs cited above that have addressed these questions.

Yet, there are also concerns with the approach. For example, the extensive body of RCTs demonstrating that short-course therapy and oral antibiotics are effective for gram-negative bacteremia had specific enrollment criteria, which already define the populations studied. Thus, it is not clear why the term “uncomplicated bacteremia” needs to be separately defined per se, or how it would be useful to determine how to treat patients with gram-negative bacteremia. Indeed, 3 RCTs and a quasi-experimental study have demonstrated that oral antibiotic

therapy is at least as effective as intravenous therapy for bacterial endocarditis, which is the most complicated of all forms of bacteremia [28]. So, why should the term “uncomplicated bacteremia” be needed to define treatment parameters? Rather than creating a consensus definition of this term, elucidating for practitioners the nature of the patients enrolled in the relevant RCTs, and thoughtfully discussing the pros and cons of extrapolating therapeutic concepts beyond those limits, might be a helpful process.

Another limitation of the approach was the lack of inclusion of a more diverse panel [29], to include experts of other specialties, and perhaps more importantly, primary physicians (eg, hospitalists, critical care physicians), who provide the majority of care in health systems. It is common for experts of different specialties to have differing views on optimal care. This is particularly true for primary physicians, who are responsible for making care decisions for the benefit of the entire patient (rather than just the one problem that a subspecialist consults on), and integrate recommendations from across multiple consulting services, which sometimes conflict. Furthermore, many physicians, allied health professionals, and other health care providers work in environments very different than highly resourced, quaternary care, academic medical centers. Optimal health care decision-making may differ across care environments in ways not accounted

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for when limited, academic expert panels are established by invitation due to their social connectedness in specialty societies. Our experience in the Los Angeles County Department of Health Services is that treatment paradigms are best optimized when both primary and specialty physicians work together to establish care pathways, or “expected practices” [30].

Despite controversy on several topics as delineated above, the group was able to continue rounds of questioning until “consensus” was achieved, which is often a goal of guidelines and guidances. Achieving consensus provides a sense of comfort about conclusions drawn. Yet, the cost of this comfort is that the consensus may be somewhat artificial and may mask important and legitimate divergences in opinions on unsettled matters, which can in turn create an artificial sense of standard of care where no standard of care should exist. Former UK Prime Minister Margaret Thatcher summarized the risks of consensus approaches when she observed that “consensus seems to be the process of abandoning all beliefs, principles, values and policies. It is something in which no one believes and to which no one objects” [31].

It is uncomfortable for clinicians to admit when equipoise remains because it leaves practitioners uncertain what course to take. There may also be an ego risk to the expert, who may be confronted by the fact that despite their expertise, they are not the sole possessor of truth, and other qualified experts may not concur. Yet, acknowledging this uncertainty is critical to avoiding mistakes of the past in medicine, where the tyranny of experts has resulted in harmful care becoming standard.

Indeed, expert opinion can be much more dangerous than the opinion of nonexperts, because harmful practices may and have propagated for generations due to the eminence of their expert advocates. Examples from the annals of medical history include centuries of use of poisonous mercury and bleeding patients to release harmful humors. Even

in the modern era, expert opinion has led to society-wide adoption of practices that subsequent controlled investigations found were incredibly harmful or wasteful (eg, hormone replacement therapy for postmenopausal women, various aspects of sepsis care, perioperative β -blockade, hemoglobin targets for transfusion or erythropoietin, vancomycin target dosing) [32, 33].

Thus, no matter how strongly beliefs are held, or how august the experts’ academic statuses are, opinions absent high-quality, prospective, controlled data should never be used to set standards of care. Opinions are just that: a description of what people think in the absence of appropriate data. It is absolutely reasonable that such opinions inform clinical thinking by nonexperts. But those opinions, absent high-quality confirmatory data, should not create standards of care that constrain, bind, or coerce providers to do what the experts say should be done based on the “because we said so” level of evidence. And it is all the more important when expert opinions diverge to describe the nature of the divergence (eg, how many or what proportion of experts disagreed, and what was the nature of the disagreement?).

In the case of gram-negative bacteremia, irrespective of whatever opinions exist, and irrespective of expert consensus, numerous RCTs have unanimously demonstrated that short-course and oral antibiotic regimens are as effective as longer and intravenous courses of therapy (including for cUTIs, cIAs, and other sources). Thus, the role of the expert is really to educate and remind the primary physicians of the data establishing these 2 demonstrated standards of care, and about the limits of those data, whatever they may be.

Experts should always be very careful to distinguish what is known to be established from reproducibly concordant, carefully controlled, prospective investigations, versus what is not and is solely based on their opinions [33]. And when based solely on opinions, irrespective

of consensus, a safer, humbler approach than making explicit recommendations is to discuss the pros and cons of care options so that primary physicians can make better informed choices for their patients [33].

Notes

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References

1. 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.
2. 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.
3. Talan DA, Stamm WE, Hooton TM, et al. Comparison of ciprofloxacin (7 days) and trimethoprim-sulfamethoxazole (14 days) for acute uncomplicated pyelonephritis in women: a randomized trial. *JAMA* **2000**; 283:1583–90.
4. 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.
5. Peterson J, Kaul S, Khashab M, et al. 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.
6. 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.
7. 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.
8. Drekonja DM, Trautner B, Amundson C, et al. 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.
9. Sawyer RG, Claridge JA, Nathens AB, et al; STOP-IT Trial Investigators. Trial of short-course antimicrobial therapy for intraabdominal infection. *N Engl J Med* **2015**; 372:1996–2005.

10. Montravers P, Tubach F, Lescot T, et al; DURAPOP Trial Group. 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.
11. Chastre J, Wolff M, Fagon JY, et al; PneumaA Trial Group. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. *JAMA* **2003**; 290:2588–98.
12. 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.
13. Yahav D, Franceschini E, Koppel F, et al; Bacteremia Duration Study Group. Seven versus 14 days of antibiotic therapy for uncomplicated gram-negative bacteremia: a noninferiority randomized controlled trial. *Clin Infect Dis* **2019**; 69:1091–8.
14. 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.
15. Cherubin C, Stilwell S. Norfloxacin versus parenteral therapy in the treatment of complicated urinary tract infections and resistant organisms. *Scand J Infect Dis Suppl* **1986**; 48:32–7.
16. Fass RJ, Plouffe JF, Russell JA. Intravenous/oral ciprofloxacin versus ceftazidime in the treatment of serious infections. *Am J Med* **1989**; 87:164S–8S.
17. Fang GD, Brennen C, Wagener M, et al. Use of ciprofloxacin versus use of aminoglycosides for therapy of complicated urinary tract infection: prospective, randomized clinical and pharmacokinetic study. *Antimicrob Agents Chemother* **1991**; 35:1849–55.
18. Mombelli G, Pezzoli R, Pinoja-Lutz G, et al. Oral vs intravenous ciprofloxacin in the initial empirical management of severe pyelonephritis or complicated urinary tract infections: a prospective randomized clinical trial. *Arch Intern Med* **1999**; 159:53–8.
19. Solomkin JS, Reinhart HH, Dellinger EP, et al. Results of a randomized trial comparing sequential intravenous/oral treatment with ciprofloxacin plus metronidazole to imipenem/cilastatin for intra-abdominal infections. the intra-abdominal infection study group. *Ann Surg* **1996**; 223:303–15.
20. Cohn SM, Lipsett PA, Buchman TG, et al. Comparison of intravenous/oral ciprofloxacin plus metronidazole versus piperacillin/tazobactam in the treatment of complicated intraabdominal infections. *Ann Surg* **2000**; 232:254–62.
21. Wacha H, Warren B, Bassaris H, Nikolaidis P; Intra-Abdominal Infections Study Group. Comparison of sequential intravenous/oral ciprofloxacin plus metronidazole with intravenous ceftriaxone plus metronidazole for treatment of complicated intra-abdominal infections. *Surg Infect (Larchmt)* **2006**; 7:341–54.
22. Fraser JD, Aguayo P, Leys CM, et al. A complete course of intravenous antibiotics vs a combination of intravenous and oral antibiotics for perforated appendicitis in children: a prospective, randomized trial. *J Pediatr Surg* **2010**; 45:1198–202.
23. Arnold MR, Wormer BA, Kao AM, et al. Home intravenous versus oral antibiotics following appendectomy for perforated appendicitis in children: a randomized controlled trial. *Pediatr Surg Int* **2018**; 34:1257–68.
24. Amodio-Groton M, Madu A, Madu CN, et al. Sequential parenteral and oral ciprofloxacin regimen versus parenteral therapy for bacteremia: a pharmaco-economic analysis. *Ann Pharmacother* **1996**; 30:596–602.
25. Monmaturapoj T, Montakantikul P, Mootsikapun P, Tragulpiankit P. A prospective, randomized, double dummy, placebo-controlled trial of oral cefditoren pivoxil 400mg once daily as switch therapy after intravenous ceftriaxone in the treatment of acute pyelonephritis. *Int J Infect Dis* **2012**; 16:e843–9.
26. Park TY, Choi JS, Song TJ, et al. Early oral antibiotic switch compared with conventional intravenous antibiotic therapy for acute cholangitis with bacteremia. *Dig Dis Sci* **2014**; 59:2790–6.
27. Heil EL, Bork JT, Abbo LM, et al. Optimizing the management of uncomplicated gram-negative bloodstream infections: consensus guidance using a modified Delphi process. *Open Forum Infect Dis* **2021**; XX:XXX–XX.
28. 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**; 180:769–77.
29. Guallar E, Laine C. Controversy over clinical guidelines: listen to the evidence, not the noise. *Ann Intern Med* **2014**; 160:361–2.
30. Soni SM, Giboney P, Yee HF Jr. Development and implementation of expected practices to reduce inappropriate variations in clinical practice. *JAMA* **2016**; 315:2163–4.
31. Margaret Thatcher Foundation. Margaret Thatcher Speech at Monash University (1981 Sir Robert Menzies Lecture). **1981**. <https://www.margaretthatcher.org/document/104712>. Accessed 28 September 2021.
32. Wright WF, Jorgensen SCJ, Spellberg B. Heaping the pelion of vancomycin on the ossa of methicillin-resistant *Staphylococcus aureus*: back to basics in clinical care and guidelines. *Clin Infect Dis* **2021**; 72:e682–4.
33. Spellberg B, Wright WF, Shaneyfelt T, Centor RM. The future of medical guidelines—standardizing clinical care with the humility of uncertainty. *Ann Int Med* **2021**. In Press.