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Is shorter always better? The pros and cons of treating Gram-negative bloodstream infections with 7 days of antibiotics

Dafna Yahav [1,2]*, Mical Paul [3,4], Cees Van Nieuwkoop [5] and Angela Huttner[6,7]

[1]*Infectious Diseases Unit, Sheba Medical Center, Ramat-Gan, Israel;* [2]*Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel;* [3]*Infectious Diseases Institute, Rambam Health Care Campus, Haifa, Israel;* [4]*The Ruth and Bruce Rappaport Faculty of Medicine, Technion - Israel Institute of Technology, Haifa, Israel;* [5]*Department of Internal Medicine, Haga Teaching Hospital, The Hague, The Netherlands;* [6]*Division of Infectious Diseases, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland;* [7]*Centre for Clinical Research, Geneva University, Geneva, Switzerland*

*Corresponding author. E-mail: dafna.yahav@gmail.com

Accumulating evidence from randomized controlled trials (RCTs) supports 7 days treatment for uncomplicated Gram-negative bacteraemia. However, some patient populations were not well represented in these RCTs, including critically ill patients, immunocompromised patients and those with MDR bacteria. In this debate document, we discuss the pros and cons for treating patients with Gram-negative bacteraemia with a 7 day antibiotic course. We surmise that the patients who were not well represented in the RCTs are probably those who have most to lose from the drawbacks of prolonged antibiotic courses, including adverse events, superinfections and resistance development. Treatment durations among these patients can be managed individually, with C-reactive protein or procalcitonin guidance or by clinical measures, and with care to discontinue antibiotics as soon as the patient recovers clinically from the infection.

Introduction

Gram-negative bloodstream infections are increasingly frequent in both community and hospital settings, with *Escherichia coli* the leading pathogen in many countries.[1] These infections, more frequent in elderly and comorbid patients, lead to lengthy and repeated antibiotic courses, which in turn select for MDR bacteria.[2] With increasing resistance, more patients require IV treatment for Gram-negative bloodstream infections, requiring hospitalization or home-care arrangements, further exposing patients to infections. In the context of the ongoing antimicrobial resistance (AMR) crisis, determining the minimal treatment duration necessary for clinical cure without later relapse has become an important step in the larger effort to preserve antibiotic efficacy. Historically, patients with Gram-negative bacteraemia were treated for at least 2 weeks, even when clinical recovery was apparent within a few days.[3] Reasons for continuing antibiotics beyond clinical recovery included the treatment of presumed residual infection and prevention of resistance development by completing a treatment course. The practice of prolongation of treatment is not evidence-based, however, and physicians began to prescribe shorter durations.[4] In adults, though shortening of antibiotic treatment to $\leq$7 days is becoming common practice, there is still substantial heterogeneity in treatment duration among infectious diseases providers.[5] Here we explore arguments for and against shorter antibiotic courses in patients with Gram-negative bloodstream infections.

Pros

Routine clinical experience and the current AMR pandemic argue in favour of shortening antibiotic durations for Gram-negative bloodstream infections. In the clinic, we know that most Gram-negative pathogens—certainly those most frequently causing bacteraemia—do not behave like *Staphylococcus aureus*. They do not tend to seed distal anatomical sites and thereby lead to recurrence of bacteraemia, abscess, endocarditis or other complications after initial, successful therapy has been discontinued. If clinical failure occurs, it is more likely to be non-response rather than later relapse after initial resolution. Most antibiotics concentrate in the urine, reaching high bactericidal levels at the site of infection for the most common Gram-negative bacteraemia source.[6] Indeed, clinical failure typically occurs when source control is not achieved, which is less common with a urinary source. In addition, it should be noted that bacteraemia is not a prognostic factor in urinary tract infection (UTI); thus positive blood cultures should not lead to prolongation of therapy.[7]

Shortening antibiotic treatment courses is also an important antibiotic stewardship strategy. Antibiotic consumption is by far the most important driver of antibiotic resistance.[8] Gram-negative bloodstream infections are becoming increasingly frequent as populations age and grow more comorbid and more complex, with prolonged states of immunosuppression and critical illness. They require increasingly broad-spectrum therapy with the rising prevalence of ESBL producers in the community, especially if the IDSA guidance on carbapenem treatment for such infections is adopted.[9,10] These infections drive an increasing share of current antibiotic consumption and are thus a natural—and necessary—target for stewardship interventions. The historical adage that completing the antibiotic treatment course will prevent resistance development is not based on evidence. With any treatment duration, we remain with surviving bacteria in various microbiota that have been exposed to the antibiotic. In a recent study from Sweden, a country with low background ESBL carriage, a 3 to14 day course of a third generation cephalosporin resulted in cephalosporin-resistant Enterobacterales or toxin-producing *Clostridioides difficile* carriage among almost half of 75 treated patients.[11] Longer courses of antibiotics are associated with patients' risk for colonization with MDR microorganisms.[12] Antibiotic therapy has been suggested to increase the risk of UTI by MDR uropathogens in women, following vaginal colonization with these pathogens.[13]

Thus, reducing antibiotic use for such infections is not only in the interest of society as a whole; it is also for the individual patient's direct benefit, to avoid possible subsequent infection with a more difficult-to-treat pathogen.

Yet randomized controlled trials (RCTs) are needed to define and confirm best practices, especially when considering halving the treatment duration for an infection. Recently, three trials were conducted demonstrating non-inferiority of 7 day to 14 day courses for Gram-negative bacteraemia. These trials addressed uncomplicated bacteraemia at time of antibiotic discontinuation, meaning patients that were haemodynamically stable, afebrile and source controlled. Yahav *et al.*[14] randomized 604 patients with any Gram-negative bacteraemia to 7 or 14 antibiotic days, demonstrating non-inferiority of the short treatment arm for the composite outcome at 90 days of mortality, relapse, complications, and readmission or extended hospitalization. von Dach *et al.*[15] randomized 504 patients with non-pseudomonal, Gram-negative bacteraemia to fixed durations of 7 or 14 days or to a C-reactive protein (CRP)-guided duration. Of note, patients randomized to CRP-guided durations could receive as few as 5 days of antibiotics. Ultimately the median duration in this arm was 7 days. Non-inferiority of the 7 day and CRP-guided durations was demonstrated for the composite outcome at 30 days of mortality, relapse, distal complications and the re-starting of antibiotics for suspected relapse by the initially infecting organism. Molina *et al.*[16] randomized 248 patients with Enterobacterales bacteraemia to either 7 or 14 day durations, demonstrating non-inferiority of the short treatment arm in terms of mortality, clinical cure and relapse at 28 days after end of treatment. In the Molina trial, relapse of bacteraemia was rare (roughly 5%) and occurred equally among patients receiving 7 or 14 days of antibiotics. While non-response ('absence of cure') was more frequent, it occurred at roughly the same frequency in both groups (7.3% versus 9.8%, respectively). Recurrent bacteraemia in the von Dach trial was even more infrequent, with only 1/166 (0.6%) and 2/163 (1.2%) episodes in the 7 day and 14 day arms, respectively. The Yahav trial's results are remarkably consistent, with recurrent bacteraemia occurring in only 2.6% and 2.7% of patients receiving 7 and 14 days of

Table 1. Summary of inclusion/exclusion criteria influencing generalizability of results

	Molina *et al.*[16]	von Dach *et al.*[15]	Yahav *et al.*[14]
Patient characteristics			
Immunocompromised patients	Excluded only prolonged neutropenia	Excluded severe immunosuppression[a]	Excluded less broadly[b]
Pregnancy	Excluded	Not excluded	Not excluded
Infection characteristics			
Non-fermenting bacilli	Excluded	Excluded	Not excluded
Recurrent bacteraemia (previous 60 days)	Not excluded	Excluded	Not excluded
Complicated bacteraemia[c]	Excluded	Excluded	Excluded
Polymicrobial growth	Excluded	Excluded	Excluded
Clinical instability or fever 24–48 h prior to randomization	Not excluded	Excluded	Excluded
MDR bacteria	Excluded carbapenem-resistant enterobacteria	Not excluded	Not excluded

[a]The following were excluded: HIV infection with CD4 cell count ≤500 cells/mm^3, haematopoietic stem-cell transplantation in the first month after transplantation and at any time before engraftment, neutropenia in the 48 h prior to randomization, receipt of high-dose steroids (>40 mg prednisone or its equivalent) daily for >2 weeks, in the 2 weeks prior to randomization.

[b]Similar exclusion criteria, but patients on high-dose steroids were included.

[c]Including endovascular infections without a removable focus, osteomyelitis and septic arthritis, necrotizing fasciitis, prostatitis, undrainable abscess/source, central nervous system infection, empyema.

antibiotic therapy, respectively. Importantly, mortality at end of follow-up was not affected by shortening the treatment duration in all three trials. Subgroup analyses for urinary tract/non-urinary tract infections; UTIs in men; wide- versus narrow-spectrum empirical antibiotic treatment; and MDR versus susceptible Gram-negative bacteria revealed no significant differences between short and long treatment arms with respect to the primary composite outcome.[14,17]

Cons

The principal counterargument to short treatment duration for Gram-negative bacteraemia is that certain patient populations were excluded from the existing randomized trials, as were some common pathogens. Though all three trials were pragmatic, investigator-initiated trials, entry criteria and consent requirements still separated, to some extent, the trials' population from 'real-life' populations treated for Gram-negative bacteraemia.

Entry criteria for specific patient and infection characteristics in the existing RCTs are provided in Table 1. The trials mostly excluded patients with severe immunosuppression, non-fermenting pathogens (e.g. *Pseudomonas aeruginosa* and *Acinetobacter baumannii*) or complicated infection (suspicion of endocarditis, etc.). Actual representation of populations and bacteria are presented in Table 2. UTIs were the dominant infection source in 55%–69% of patients in the three RCTs (55% Molina *et al.*,[16] 68% Yahav *et al.*,[14] 69% von Dach *et al.*[15]), leaving other infection sources less well represented. Bacteraemia with MDR Gram-negative organisms was not well-represented. Subgroup analyses for these patient populations in the Yahav trial were not powered to prove non-inferiority. Critically ill patients in ICUs were mostly not included in these RCTs.

Table 2. Actual representation of specific populations in the three randomized controlled trials

	Molina *et al.*,[16] *n/N* (%)	von Dach *et al.*,[15] *n/N* (%)	Yahav *et al.*,[14] *n/N* (%)
Patient characteristics			
Immunocompromised patients			
Malignancy	64/248 (26)	NR	159/604 (26)
Immunosuppressive drugs	31/248 (12.5)	None	150/604 (25)
Solid-organ transplant	11/248 (4.5)	None	51/604 (8.5)
Stem-cell transplant	NR	None	5/604 (0.8)
Pregnancy	None	NR	NR
Infection characteristics			
Non-fermenting bacilli	None	None	6/604 (10)
Recurrent bacteraemia (previous 60 days)	NR	None	NR
Complicated bacteraemia	NR	NR	NR
Polymicrobial growth	NR	NR	NR
Clinical instability or fever 24–48 h prior to randomization	NR	NR	NR
MDR bacteria	41/248 (16.5)	40/504 (8)	109/604 (18)

NR, not reported.

Formal evaluation of two of the trials revealed moderate to poor external validity. In the von Dach *et al.* trial, patients excluded by ineligibility or inability or refusal to grant informed consent were found to have higher Charlson scores and were more likely to have healthcare-associated bacteraemia. The clinical success rate was significantly lower among excluded compared with included patients.[18] Similarly, 613 patients excluded from the Yahav *et al.* study were more likely to have functional or cognitive decline and acquire their infection in the hospital. The primary composite outcome occurred significantly more commonly among excluded patients in this study as well (D. Yahav and M. Paul, unpublished data).

It should also be stated that none of these RCTs demonstrated significantly lower rates of adverse events, resistance emergence or superinfections with shorter therapy. Duration of hospital stay was not significantly shorter either. In a metagenomic study nested within the von Dach trial, shorter antibiotic durations did not lead to significantly fewer antibiotic-resistance genes in the intestinal microbiome at 1, 2 and 3 months post-inclusion.[19] Additional data are needed to prove the assumed benefits of shorter antibiotic duration for all patient populations. Meta-analyses compiling current data may shed light on specific patient subgroups. In the meantime, duration of therapy should be individually tailored.

Additional RCTs, and possibly individual patient-level meta-analyses of existing RCTs, may shed more light on patient subgroups. The ongoing BALANCE trial, recruiting intensive-care patients with bacteraemia to receive either 7 or 14 days of antibiotic therapy, will provide evidence for critically ill patients.[20] In order to represent real-world bacteraemia patients in RCTs, ethics committees should acknowledge the growing population of patients unable to consent, even more so during acute infection, and provide strategies for surrogate consent processes.[21] In addition, studies are needed to evaluate personalized duration of therapy, using CRP or procalcitonin guidance in addition to clinical measures.[22]

Summary

Current evidence supports treatment of 7 days for patients who achieve clinical resolution of infection by that time or so-called 'uncomplicated' Gram-negative bacteraemia. Although not all patient populations were represented in these RCTs, there is no evidence that short treatment durations will harm them. Critically ill patients and those with MDR Gram-negative bacteraemia have the most to lose from further resistance development. Treatment durations among patients under-represented in the current trials can be managed individually, with CRP or procalcitonin guidance or by clinical measures, and with care to discontinue antibiotics as soon as the patient recovers clinically from the infection.

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Transparency declarations

None to declare.

References

1 Kern WV, Rieg S. Burden of bacterial bloodstream infection-a brief update on epidemiology and significance of multidrug-resistant pathogens. *Clin Microbiol Infect* 2020; **26**: 151–7.

2 Palin V, Welfare W, Ashcroft DM *et al*. 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.

3 Chotiprasitsakul D, Han JH, Cosgrove SE *et al*. Comparing the outcomes of adults with Enterobacteriaceae bacteremia receiving short-course versus prolonged-course antibiotic therapy in a multicenter, propensity score-matched cohort. *Clin Infect Dis* 2018; **66**: 172–7.

4 Park SH, Milstone AM, Diener-West M *et al*. Short versus prolonged courses of antibiotic therapy for children with uncomplicated Gram-negative bacteraemia. *J Antimicrob Chemother* 2014; **69**: 779–85.

5 Thaden JT, Tamma PD, Pan Q *et al*. 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.

6 Frimodt-Møller N. Correlation between pharmacokinetic/pharmacodynamic parameters and efficacy for antibiotics in the treatment of urinary tract infection. *Int J Antimicrob Agents* 2002; **19**: 546–53.

7 van Nieuwkoop C, Bonten TN, Wout JWV *et al*. Risk factors for bacteremia with uropathogen not cultured from urine in adults with febrile urinary tract infection. *Clin Infect Dis* 2010; **50**: e69–72.

8 Huttner A, Harbarth S, Carlet J *et al*. Antimicrobial resistance: a global view from the 2013 World Healthcare-Associated Infections Forum. *Antimicrob Resist Infect Control* 2013; **2**: 31.

9 Tamma PD, Aitken SL, Bonomo RA *et al*. Infectious Diseases Society of America guidance on the treatment of extended-spectrum β-lactamase producing Enterobacterales (ESBL-E), carbapenem-resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with difficult-to-treat resistance (DTR-*P. aeruginosa*). *Clin Infect Dis* 2021; **72**: e169–83.

10 Harris PNA, Tambyah PA, Lye DC *et al*. Effect of piperacillin-tazobactam vs meropenem on 30-day mortality for patients with E coli or *Klebsiella pneumoniae* bloodstream infection and ceftriaxone resistance: a randomized clinical trial. *JAMA* 2018; **320**: 984–94.

11 Edlund C, Ternhag A, Ståhlgren GS *et al*. The clinical and microbiological efficacy of temocillin versus cefotaxime in adults with febrile urinary tract infection, and its effects on the intestinal microbiota: a randomised multicentre clinical trial in Sweden. *Lancet Infect Dis* 2022; **22**: 390–400.

12 Wang J, Foxman B, Mody L *et al*. Network of microbial and antibiotic interactions drive colonization and infection with multidrug-resistant organisms. *Proc Natl Acad Sci U S A* 2017; **114**: 10467–72.

13 Smith HS, Hughes JP, Hooton TM *et al*. Antecedent antimicrobial use increases the risk of uncomplicated cystitis in young women. *Clin Infect Dis* 1997; **25**: 63–8.

14 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.

15 von Dach E, Albrich WC, Brunel A-S *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.

16 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.

17 Yahav D, Mussini C, Leibovici L *et al*. Reply to De Greef *et al*. *Clin Infect Dis* 2020; **70**: 351–3.

18 Rossel A, Zandberg KPM, Albrich WC *et al*. How representative is a point-of-care randomized trial? Clinical outcomes of patients excluded from a point-of-care randomized controlled trial evaluating antibiotic duration for Gram-negative bacteraemia: a multicentre prospective observational cohort study. *Clin Microbiol Infect* 2022; **28**: 297.e1–6.

19 Leo S, Lazarevic V, von Dach E *et al*. Effects of antibiotic duration on the intestinal microbiota and resistome: the PIRATE RESISTANCE project, a cohort study nested within a randomized trial. *EBioMedicine* 2021; **71**: 103566.

20 Daneman N, Rishu AH, Pinto RL *et al*. Bacteremia antibiotic length actually needed for clinical effectiveness (BALANCE) randomised clinical trial: study protocol. *BMJ Open* 2020; **10**: e038300.

21 Holden TR, Keller S, Kim A *et al*. Procedural framework to facilitate hospital-based informed consent for dementia research. *J Am Geriatr Soc* 2018; **66**: 2243–8.

22 Meier MA, Branche A, Neeser OL *et al*. Procalcitonin-guided antibiotic treatment in patients with positive blood cultures: a patient-level meta-analysis of randomized trials. *Clin Infect Dis* 2019; **69**: 388–96.