

The Changing Landscape of Uncomplicated Gram-Negative Bacteremia: A Narrative Review to Guide Inpatient Management

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Gram-negative bacteremia secondary to focal infection such as skin and soft-tissue infection, pneumonia, pyelonephritis, or urinary tract infection is commonly encountered in hospital care. Current practice guidelines lack sufficient detail to inform evidence-based practices. Specifically, antimicrobial duration, criteria to transition from intravenous to oral step-down therapy, choice of oral antimicrobials, and reassessment of follow-up blood cultures are not addressed. The presence of bacteremia is often used as a justification for a prolonged course of antimicrobial therapy regardless of infection source or clinical response. Antimicrobials are lifesaving but not benign. Prolonged antimicrobial exposure is associated with adverse effects, increased rates of *Clostridioides difficile* infection, antimicrobial resistance, and longer hospital length of stay.

Emerging evidence supports shorter overall duration of antimicrobial treatment and earlier transition to oral agents among patients with uncomplicated Enterobacteriaceae bacteremia who have achieved adequate source control and demonstrated clinical stability and improvement. After appropriate initial treatment with an intravenous antimicrobial, transition to highly bioavailable oral agents should be considered for total treatment duration of 7 days. Routine follow-up blood cultures are not cost-effective and may result in unnecessary healthcare resource utilization and inappropriate use of antimicrobials. Clinicians should incorporate these principles into the management of gram-negative bacteremia in the hospital. *Journal of Hospital Medicine* 2020;15:746-753. © 2020 Society of Hospital Medicine

Uncomplicated bacteremia, while not precisely defined in the literature, generally implies bacteremia in the absence of a persistent or difficult-to-eradicate infectious source. Bacteremia secondary to focal infections such as skin and soft-tissue infection, pneumonia, pyelonephritis, or urinary tract infection (UTI) accounts for up to 25% of bloodstream infections (BSIs) and usually resolves with prompt and appropriate antimicrobial therapy.^{1,2} Current practice guidelines do not adequately address key aspects of the optimal management of gram-negative (GN)-BSI commonly encountered in hospital care.³⁻⁷ Notably, antimicrobial duration, criteria to transition from intravenous (IV) to oral step-down therapy, choice of oral antimicrobials, and reassessment of follow-up blood cultures have not been addressed. In the absence of consensus guidelines, clinicians rely on “conventional wisdom” and clinical experience, which may not be supported by scientific rigor. A

growing body of research now challenges some long-standing practices once thought to be standard of care.

In this narrative review, we aim to examine and synthesize emerging information to provide an evidence-based framework in the management of hospitalized patients with GN-BSI. We highlight the unintended consequences and potential harms of excessive antimicrobial exposure and focus on areas in the fundamental approach to duration of therapy, the role of oral antimicrobials, and usefulness of follow-up blood cultures. A comprehensive search of the published literature was performed in PubMed with an emphasis on articles published during 2015-2019 with use of search terms including gram-negative bacteremia, duration, antibiotics, adverse effects, intravascular catheter, and follow-up blood cultures.

ANTIMICROBIAL RISKS: ‘PRIMUM NON NOCERE’

Antimicrobial overuse is common and may be driven by concerns for undertreatment. Clinicians may believe that prolonged antimicrobial therapy maximizes cure rates, with treatment duration often defined arbitrarily by a fixed number of “Constantine-units” (dating back to the ancient Roman emperor’s decree of 7 days in a week).⁸⁻¹⁰ Recent publications refute this notion and point out that the harms of overprescribing outweigh the perceived benefits of longer treatment duration.

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Antimicrobials are lifesaving but not benign; adverse effects are common and costly to our patients and healthcare system. Among 1,488 hospitalized adults who received at least 24 hours of systemic antimicrobials, 20% had an antimicrobial-associated adverse event, mostly gastrointestinal, renal, or hematologic in nature.¹¹ Prolonged duration of antimicrobials is further associated with adverse effects such as antimicrobial-associated diarrhea, increased rates of *Clostridioides difficile* infection (CDI), emergence of antimicrobial resistance, and longer hospital length of stay (LOS).¹¹⁻¹⁵ Vaughn and colleagues conducted the largest observational study to date, evaluating antimicrobial prescriptions for the treatment of nearly 6,500 adults with community-acquired pneumonia in a 43-hospital consortium in Michigan.¹⁴ More than two-thirds of patients received antimicrobial courses (median 8 days) that exceeded guideline-recommended duration. Patients who received longer antimicrobial courses did not have reduced mortality, readmission, or emergency department visits. More importantly, each excess day of treatment was associated with a relative 5% increase in the odds of antimicrobial-associated adverse effects reported by patients. This is further supported by national and state hospital data that antimicrobial-associated adverse events are an independent predictor of longer LOS.¹²

CDI is commonly linked to destructive changes to the indigenous microbiota of the intestinal flora caused by antimicrobial administration. Stevens and colleagues identified 7,792 hospitalized patients who received at least 2 consecutive days of antimicrobial therapy¹³; comparing 241 cases of CDI with the control group, they observed a dose-dependent risk of CDI associated with increasing cumulative dose, number of antimicrobials, and days of antimicrobial exposure. Compared with patients who received fewer than 4 days of antimicrobials, the adjusted hazard ratios (aHR) for those who received 4-7 days or 8-18 days of therapy were 1.4 (95% CI, 0.8-2.4) and 3.0 (95% CI, 1.9-5.0), respectively. This correlates to a threefold increase in CDI risk for patients who received more than 7 days of antimicrobials. More specifically, the empiric use of antipseudomonal β -lactams (APBL) for more than 48 hours was also found to be an independent risk factor for CDI among 808 patients with Enterobacteriaceae BSI.¹⁶ The risk of CDI within 90 days of BSI was higher among those who received >48 hours of APBL than it was among those who received \leq 48 hours (HR, 3.6; 95% CI, 1.5-9.9).

While *C difficile* may be the most well-known pathogen implicated in antimicrobial usage, the incidence of multidrug-resistant (MDR) organisms, either as infectious or colonizing pathogens, is also tied to antimicrobial exposure. Among patients receiving systemic antimicrobials, 6% developed an MDR infection within 90 days.¹¹ Over a 5-year period, Teshome and colleagues evaluated 7,118 critically ill patients and demonstrated that prolonged exposures to APBLs increased the risk of new antimicrobial resistance within 60 days.¹⁵ This resistance pattern was not an institutional or environmental finding but a patient-level finding. For each additional day of cefepime or piperacillin/tazobactam received, the risk of new antimicrobial resistance was increased by 8%. The authors concluded that defining a piperacillin/tazobactam course as 10 vs 7 days would re-

sult in a 24% higher relative risk of resistance per patient related to those 3 additional days of antimicrobial exposure.

Catheter complications including thrombophlebitis, infiltration, and infection are serious and frequent problems associated with IV medication administration.¹⁷ Even with short-term use, peripherally inserted central catheters (PICCs) carry a substantial risk of venous thrombosis (superficial and deep veins). The incidence of deep vein thrombosis (DVT) for PICCs is estimated between 5% and 15% for hospitalized patients and 2% and 5% for ambulatory patients.¹⁸ A recent randomized controlled trial (RCT) of oral vs IV antimicrobials for bone and joint infections reported that, compared with patients randomized to oral antimicrobials, those randomized to IV antimicrobials were more likely to have catheter complications (9.4% vs 1.0%; $P < .001$) and to discontinue therapy earlier (18.9% vs 12.8%; $P = .006$).¹⁹ Median hospital stay was also significantly longer in the IV group (14 days vs 11 days; $P < .001$).

SHORTEST EFFECTIVE DURATION: LESS MAY BE MORE

Optimization of antimicrobial duration has long been recognized as one of the key strategies in reducing unnecessary antimicrobial exposure, yet high-quality evidence on comparative effectiveness of duration in the setting of bacteremia has been limited until recently.²⁰ The presence of bacteremia is often used as a justification for prolonged courses of antimicrobial regardless of infection source or clinical response. The Infectious Diseases Society of America guidelines suggest 7 to 14 days of treatment for intravascular catheter-associated gram-negative bacteremia, but the optimal duration for non-catheter-related gram-negative bacteremia is not addressed.²¹ This lack of clear guidance and the historical scarcity of robust data make it difficult to inform best practices, which leads to wide variability in clinical practice and 14 days being the most prescribed duration.^{22,23}

Pooled clinical trials' data from subsets of patients with bacteremia and those from observational studies have been the best available evidence for the treatment duration of GN-BSI until recently (Table 1).²⁴⁻³² Two meta-analyses evaluating RCTs of adult and pediatric patients with pyelonephritis, UTI, peritonitis, and pneumonia found no differences in clinical failure, microbiologic cure, or survival between short and long courses of therapy in the subset of patient with associated bacteremia.^{24,25} Six heterogeneous RCTs of short vs long courses of therapy for complicated UTI or pyelonephritis reported no differences in clinical cure rates in the subset of patients with associated GN-BSI.² The observational studies outlined in Table 1 are also consistent with RCT results supporting noninferiority in clinical cure and mortality outcomes between short and long courses of therapy.²⁶⁻³² These findings may also be extrapolated to immunocompromised hosts given a considerable representation of 10% to 47% of the study population with immunosuppressive conditions.

Nelson and colleagues conducted the only retrospective study to date reporting conflicting results of higher risk of treatment failure (defined as composite endpoint of mortality

TABLE 1. Evidence Summary of Studies Evaluating Duration of Therapy

Author	Study design	Participants (median duration in days)	Immuno-compromised hosts (%)	Source of BSI and microbiology	Outcomes	Risk (95% CI)
Daneman 2016 ²⁶	Multicenter, retrospective, propensity score–matched cohort study	S=222 (7) L=222 (15)	S=95 (39) L=73 (30)	Urinary, respiratory, abdominal, hepato-biliary, CVC, SSTI Gram-negative bacilli (40%)	In-hospital mortality S=27.5% L=29.3%	RR, 0.94 (0.70-1.26)
Nelson 2017 ²⁷	Multicenter, retrospective cohort study	S=117 (8.5) L=294 (13)	S=15 (13) L=30 (10)	Urinary source (69%) Enterobacteriaceae (90%)	Composite of either 90-day mortality or recurrent infection S=13.2% L=8.5%	aHR, 2.60 (1.20-5.53)
Chotiprasitsakul 2018 ²⁸	Multicenter, retrospective, propensity score–matched cohort study	S=385 (8) L=385 (15)	S=127 (33) L=134 (35)	Urinary (36%), respiratory, gastrointestinal, biliary, CVC, SSTI Monomicrobial: Enterobacteriaceae (100%)	30-day mortality S=9.6% L=10.1%	aHR, 1.00 (0.62-1.63)
Doi 2018 ²⁹	Single-center, retrospective cohort study	S=85 (6) L=176 (12)	S=35 (41) L=83 (47)	Cholangitis (>96% with source control) Gram-negative bacilli (88%)	30-day mortality S=4.7% L=5.7%	aOR, 1.07 (0.25-4.52)
Giannella 2018 ³⁰	Single-center, retrospective cohort study	S=426 (8) L=430 (15)	S=87 (20) L=85 (20)	Urinary (51%), biliary, intra-abdominal, primary bacteremia, respiratory, catheter related, SSTI Monomicrobial: <i>E coli</i> (100%)	90-day mortality S=4.9% L=6.0%	aHR, 1.15 (0.60-2.18)
Sousa 2019 ³¹	Single-center, prospective, observational cohort study	S=163 (10) L=232 (14)	S=30 (18) L=55 (24)	Urinary (51%), biliary, respiratory, catheter related, abdominal Gram-negative bacilli: <i>E coli</i> (56%), <i>Klebsiella</i> spp. (15%)	30-day mortality S=14.1% L=9.9%	aHR, 0.75 (0.43-3.44)
Fabre 2019 ³²	Multicenter, retrospective, propensity-weighted cohort study	S=69 (9) L=180 (16)	S=45 (65) L=116 (64)	Urinary (30%), biliary, respiratory, catheter related, abdominal, SSTI <i>Pseudomonas aeruginosa</i> (100%) with >94% source control	Composite of either 30-day mortality or recurrent <i>P aeruginosa</i> infection S=14.5% L=13.3%	OR, 1.06 (0.42-2.68)
Yahav 2019 ³³	Open-label, randomized, controlled trial	S=306 (7) L=298 (14)	S=69 (23) L=81 (27)	Urinary (69%), abdominal, primary bacteremia, respiratory, catheter related, SSTI Gram-negative bacilli: <i>E coli</i> (63%), <i>Klebsiella</i> spp. (13%)	Composite of either all-cause mortality or clinical failure S=45.8% L=48.3%	RD, -2.6% (-10.5 to 5.3)

Abbreviations: aHR, adjusted hazard ratio; aOR, adjusted odds ratio; BSI, bloodstream infection; CI, confidence interval; CVC, central venous catheters; *E coli*, *Escherichia coli*; HR, hazard ratio; L, long duration; OR, odds ratio; RD, risk difference; RR, relative risk; S, short duration; SSTI, skin and soft-tissue infection.

or recurrent infection within 90 days of index BSI) in patients receiving a short course of therapy.²⁷ However, the difference was driven by 90-day mortality (8.2% vs 3.3%; *P* = .04) not recurrent infection (6.7% vs 6.5%; *P* = 0.93). Giannella and colleagues also evaluated 90-day mortality as a primary endpoint in a much larger cohort of over 850 patients in Italy and found no difference in mortality rates between short and long courses of antimicrobials.³⁰

Yahav and colleagues conducted the first well-designed open-label RCT comparing short and long courses of antimicrobials in uncomplicated GN-BSI.³³ This noninferiority study randomized more than 600 hospitalized patients with adequate source control who were afebrile and hemodynamically stable for ≥48 hours to receive either 7 days or 14 days of therapy. The source of infections was predominantly urinary (68%), and the causative pathogens were 90% Enterobacteriaceae, including 20% MDR strains. The primary outcome was a composite of 90-day all-cause mortality or clinical failure defined as either relapse of bacteremia, local or distant complications, readmission, or extended hospital stay >14 days. The authors reported

no statistically significant differences in the primary outcome between short (45.8%) and long (48.3%) courses of treatment. In the prespecified post hoc analysis designed to evaluate infection-related outcomes at an earlier time frame, there were no observed differences in complications, relapses, or mortality between study groups at 14 and 28 days. Further subgroup analysis demonstrated similar results among patients with MDR pathogens, primarily extended-spectrum β-lactamases (ESBL). Interestingly, there was a more rapid return to baseline activity and functional capacity among patients randomized to a short course of therapy. The authors acknowledged that the patients' perception of illness while taking antimicrobials may have influenced self-reported well-being and functional performance. In exploratory analysis, prolonged hospitalization and readmission were excluded from the primary study endpoint to mirror outcomes assessed by Nelson and colleagues. There were no statistically significant differences in death, relapses, or complications between groups randomized to short (18.6%) or long (15.1%) courses of therapy, with a risk difference of 3.5% (95% CI, -2.5% to 9.5%) in this study population.

TABLE 2. Evidence Summary of Studies Evaluating Continued Intravenous Therapy vs Conversion of Intravenous to Oral Antimicrobials

Author	Study design	Participants and antimicrobial	Median days to PO	Source of BSI and microbiology	Outcome	Risk (95% CI)	Length of stay (days)
Amodio-Groton 1996 ³⁹	Single-center RCT	IV = 26 PO = 24 Ciprofloxacin	3	Urinary (66%) Gram-negative bacilli: <i>E coli</i> (64%) <i>K pneumoniae</i> (14%)	Clinical resolution and improvement IV = 92.3% PO = 95.8%	RD, 3.5% (<i>P</i> = NS)	IV = 15.7 PO = 9.8 <i>P</i> < .05
Park 2014 ⁴⁰	Multicenter RCT	IV = 30 PO = 29 Ciprofloxacin	6	Cholangitis (100%) Gram-negative bacilli: <i>E coli</i> (76%) <i>K pneumoniae</i> (14%)	30-day microbiologic eradication IV = 93.3% PO = 93.1%	RD, -0.2% (-0.13 to 0.14)	IV = 12.3 PO = 10.8 <i>P</i> = .02
Reiger 2017 ⁴¹	Single-center, retrospective cohort study	IV = 106 PO = 135 FQ: 65% BL: 19% T/S: 9%	4	Urinary (100%) Enterobacteriaceae: <i>E coli</i> (57%) <i>K pneumoniae</i> (23%)	Treatment failure IV = 3.8% PO = 8.2% <i>P</i> = 0.19	NA	IV = 7.1 PO = 4.6 <i>P</i> < .001
Thurber 2019 ⁴²	Single-center, retrospective cohort study	IV = 82 PO = 264 FQ: 87% BL: 5% T/S: 8%	3	Urinary (100%) Gram-negative bacilli: <i>E coli</i> (66%) <i>Klebsiella</i> spp (14%)	Treatment failure IV = 2.4% PO = 1.5%	HR, 0.62 (0.11-3.39)	IV = 6 PO = 4 <i>P</i> < .001
Tamma 2019 ⁴³	Multicenter, propensity score-matched, retrospective cohort study	IV = 739 PO = 739 FQ (High bio): 70% BL (Low bio): 17% T/S (High bio): 13%	3	Urinary (40%), GI, catheter, biliary, respiratory, SSTI Enterobacteriaceae: <i>E coli</i> (44%) <i>K pneumoniae</i> (34%)	30-day mortality IV = 13.4% PO = 13.1% 30-day recurrent bacteremia IV = 0.5% PO = 0.8%	30-day mortality HR = 1.03 (0.82-1.30) 30-day recurrent bacteremia HR, 0.82 (0.33-2.01)	IV = 7 PO = 5 <i>P</i> < .001

Abbreviations: bio, bioavailability; BL, β -lactam; BSI, bloodstream infection; CI, confidence interval; *E coli*, *Escherichia coli*; FQ, fluoroquinolones; GI, gastrointestinal; HR, hazard ratio; IV, intravenous; *K pneumoniae*, *Klebsiella pneumoniae*; NS, not significant; PO, oral; RCT, randomized controlled trial; RD, risk difference; SSTI, skin and soft-tissue infection; T/S, trimethoprim/sulfamethoxazole.

Patients with *Pseudomonas aeruginosa* BSI often have more chronic medical comorbidities, immunocompromised conditions, higher severity of illness, and more indwelling catheters than do patients with Enterobacteriaceae BSI.³² It is uncertain whether shorter duration of therapy is generalizable to this population, given that *Pseudomonas* accounted for a relatively low number (8%) of infections in the published RCT.³³ Fabre and colleagues included high-risk patients with >65% of the cohort with severe immunocompromised conditions consisting of stem cell transplantation, recent chemotherapy, or neutropenia, and they reported no difference in 30-day mortality or recurrent infections among patients with pseudomonal BSI regardless of duration of therapy.³²

ORAL TREATMENT: CHALLENGING TRADITIONAL DOGMA

It is a well-accepted standard of practice that BSI are treated with upfront IV antimicrobials that can rapidly achieve therapeutic serum concentration. Whether IV administration is warranted for the entire duration of therapy, though, remains controversial. Even in an era of highly bioavailable oral antimicrobials, clinicians often assume that IV antimicrobials are more potent and efficacious than oral antimicrobials.^{8,9} This belief has contributed to the dogma that IV therapy is necessary irrespective of the associated risks and costs. Oral antimicrobials are often over-

looked as alternatives despite established benefits in avoiding complications associated with IV catheters, decreasing hospital LOS, and improving quality of life.³⁴ There are promising clinical data in support of the efficacy and safety of transitioning from sequential-IV to highly bioavailable oral agents for the treatment of uncomplicated bacteremia caused by both gram-positive and gram-negative pathogens.^{2,35} Highly bioavailable oral antimicrobials are also increasingly integrated as sequential therapy for deep-seated infections in bone and joint infections, such as vertebral osteomyelitis.^{19,36} These findings have been confirmed in a recent RCT demonstrating noninferiority of oral antimicrobial combinations after satisfactory clinical responses to at least 10 days of IV therapy, compared with continued IV regimens, in left-sided infective endocarditis.³⁶ While not a prespecified endpoint, hospital LOS was shorter among patients randomized to oral antimicrobials.

Although there are no large-scale RCTs sufficiently powered to address the role of oral antimicrobials in the treatment of uncomplicated GN-BSI, some insights can be gleaned from the existing literature (Table 2). In the RCT establishing noninferiority of short vs long courses of antimicrobials for uncomplicated GN-BSI, the majority of patients randomized to 7 days vs 14 days of therapy, 64% and 81%, respectively, were de-escalated to oral antimicrobials, with fluoroquinolones (FQs) being the predominant (>70%) oral regimen, followed by trimethoprim/

TABLE 3. Evidence Summary of Studies Comparing Various Oral Regimens for Definitive Therapy

Author	Study design	Participants	Median days to PO	Source of BSI and microbiology	Outcome	Risk (95% CI)
Kutob 2016 ⁴⁵	Multicenter, retrospective cohort study	High bio = 106 Mid bio = 179 Low bio = 77	Mean, 4.7	Urinary source (67%) Gram-negative bacilli: <i>E coli</i> (67%) <i>K pneumoniae</i> (14%)	Composite of either 90-day mortality or recurrence High bio = 2% Mid bio = 12% Low bio = 14% P = .02	High-bio = REF Mid-bio aHR, 5.9 (1.6-38.5) Low-bio aHR, 7.7 (1.9-51.5)
Mercurio 2018 ⁴⁴	Single-center, retrospective cohort study	BL = 84 FQ = 140	3	Urinary (71%), intra-abdominal, SSTI, respiratory, catheter Enterobacteriaceae: <i>E coli</i> (71%) <i>K pneumoniae</i> (17%)	Clinical success BL = 86.9% FQ = 87.1%	RD, 0.2% (97.5% CI, -10.3 to 10.7)
Tamma 2019 ⁴³	Multicenter, propensity score-matched, retrospective cohort study	High bio = 617 Low bio = 122	3	Urinary (40%), GI, catheter, biliary, respiratory, SSTI Enterobacteriaceae: <i>E coli</i> (46%) <i>K pneumoniae</i> (32%)	30-day mortality High bio = 11.0% Low bio = 12.3%	HR, 1.05 (0.67-1.66)
Punjabi 2019 ⁴⁶	Systematic review and meta-analysis	FQ = 1,489 BL = 623 T/S = 177	3-5	Urinary (40%-100%) Gram-negative bacilli (100%)	All-cause mortality FQ or T/S = 5.1% BL = 3.5% Recurrence FQ or T/S = 2.0% BL = 5.5%	All-cause mortality OR, 1.13 (0.69-1.87) Recurrence OR, 2.06 (1.18-3.61)

Abbreviations: aHR, adjusted hazard ratio; bio, bioavailability; BL, β-lactam; CI, confidence intervals; *E coli*, *Escherichia coli*; FQ, fluoroquinolones; GI, gastrointestinal; HR, hazard ratio; *K pneumoniae*, *Klebsiella pneumoniae*; OR, odds ratio; PO, oral; RD, risk difference; REF, reference; SSTI, skin and soft-tissue infection; T/S, trimethoprim/sulfamethoxazole.

sulfamethoxazole (T/S) and oral β-lactams.³³

Despite the Food and Drug Administration warnings of the potentially permanent adverse effects involving tendons, muscles, joints, nerves, and most recently, aortic aneurysms and ruptures,³⁷ FQs remain a unique class of drugs with favorable pharmacodynamic and pharmacokinetic properties that achieve approximately equivalent serum and tissue concentration when administered either intravenously or orally. This advantage was recognized early on as a potential IV-sparing therapeutic option. A prospective RCT that evaluated oral vs IV ciprofloxacin as initial empiric therapy among 141 patients with pyelonephritis or complicated UTI (38% with secondary BSI) reported no significant differences in microbiological failure or clinical response between the two treatment groups.³⁸ Two small RCTs have also demonstrated the safety and effectiveness of sequential-IV antimicrobial to oral FQs in the setting of GN-BSI secondary to urinary source and cholangitis.^{39,40} Oral β-lactams, however, achieve substantially lower serum concentration than do their IV counterparts and, accordingly, may be less reliably effective.²

Five retrospective cohort studies have more directly investigated the role of oral antimicrobials in the setting of GN-BSI secondary to common focal infections (Table 2 and Table 3).⁴¹⁻⁴⁵ Two observational studies reported no difference of treatment failure among patients who received IV-only therapy vs those who were switched to oral therapy in bacteremia secondary to UTIs.^{41,42} Catheter-associated complications were higher in the IV cohort (6.1% vs 0.4%; P = .03).⁴² In the largest multicenter cohort study to date, which included 1,478 patients with Enterobacteriaceae bacteremia, there was no difference in 30-day mortality or recurrent bacteremia between patients converted

to oral step-down therapy and patients who received the full course of IV antimicrobials.⁴³ Furthermore, the median hospital LOS was shorter (5 days vs 7 days; P < .001) among patients who were transitioned to oral therapy, a finding that is consistent with other studies.^{39,42} In their analysis, the oral antimicrobials were categorized as low-bioavailability (β-lactams) or high-bioavailability (FQ and T/S), and there was no difference in outcomes when results were stratified by bioavailability. Mercurio and colleagues reported similar clinical success among patients who received oral β-lactams and those who received FQs as step-down therapy.⁴⁴ Notably, patients were more likely to tolerate β-lactams without experiencing adverse effects than were those who received FQs (91.7% vs 82.1%; P = .049). In contrast, Kutob and colleagues compared step-down oral antimicrobials categorized as low bioavailability (β-lactams), moderate bioavailability (ciprofloxacin and T/S), and high bioavailability (levofloxacin). They reported that treatment failures were significantly higher among patients who received low-bioavailability (14%) and moderate-bioavailability (12%) antimicrobials, compared with those who received the high-bioavailability agent (2%; P = .02).⁴⁵ Interestingly, the bioavailability of ciprofloxacin reaches 85% and T/S approaches 90%, and they are often categorized as highly bioavailable agents in other studies.^{43,46} If they were reclassified as highly bioavailable agents, the study conclusions might differ. Nevertheless, the reported success with oral step-down therapy exceeded 85% in all five studies.⁴¹⁻⁴⁵

It is important to acknowledge the possibility of unmeasured confounders in these retrospective, observational studies despite statistical adjustments and that they are likely underpowered to determine the clinical significance of oral bioavailability

TABLE 4. Summary of Management Recommendations for Gram-Negative Bloodstream Infection

Management	Comments	Recommendations
Follow-up blood cultures	Documentation of follow-up blood culture clearance is not associated with improved clinical care.	Avoid routine use of follow-up blood cultures.
Oral antimicrobials	Oral antimicrobials are safe and effective. Consider oral antimicrobials with high bioavailability as step-down therapy.	Transition to oral antimicrobials with clinical improvement.*
Duration of antimicrobials	Longer courses of antimicrobials are associated with adverse effects, including <i>Clostridioides difficile</i> infections, emergence of antimicrobial resistance, catheter-related complications, and longer hospital length of stay.	Prescribe a total 7 days of therapy (intravenous and oral).

*Once patients demonstrate clinical improvement (are afebrile, have improved white blood cell count, are hemodynamically stable, achieve adequate source control)

of antimicrobials. In a meta-analysis of published studies and abstracts that included 2,289 patients with Enterobacteriaceae bacteremia, all-cause mortality was similar between patients de-escalated to an oral FQ, T/S, or β -lactam.⁴⁶ Overall recurrence of infection (bacteremia or primary site) occurred more frequently in patients transitioned to oral β -lactams than FQs, but relapse of bacteremia was not statistically different between comparator groups. Bioavailability of the oral agents may not be the sole determinant of higher recurrence; adherence may be poor because of the more frequent dosing required for oral β -lactams to achieve targeted pharmacokinetics. Additionally, suboptimal dosing of oral β -lactams noted in the studies may have also contributed to the increased recurrences.

After source control has been achieved and bacterial inoculum burden is sufficiently reduced with appropriate upfront IV therapy, the bioavailability of oral antimicrobials may become less important. However, existing observational data indicate clinical experience is most established with highly bioavailable oral agents, particularly FQs, though the risks vs benefits require careful consideration. For now, the preferred oral agent remains uncertain and selections should be individualized based on susceptibility, patient factors, and other clinical considerations. More importantly, if there are no contraindications or concerns of malabsorption, oral step-down therapy should be initiated as soon as source control and good clinical responses have been achieved.

TEST OF CURE: RECONSIDERING FOLLOW-UP BLOOD CULTURES

Routine follow-up blood cultures (FUBCs) are strongly recommended in *Staphylococcus aureus* bacteremia because of the propensity for endovascular and metastatic infection, which dictates clinical decision-making regarding duration of therapy. In contrast, GN-BSI secondary to focal infections is usually transient, and the need for confirmation of blood culture clearance is less clear. The low yield of FUBC in many clinical settings suggests that it may not be helpful.⁴⁷⁻⁵⁰ Despite the questionable impact on the clinical management of GN-BSI, FUBCs are routinely ordered in the hospital.^{1,47} Although there is no high-quality evidence addressing the utility of FUBC, several observational studies suggest clinicians should reconsider routinely ordering FUBC.

Canzoneri and colleagues retrospectively evaluated 383 episodes of bacteremia with at least one FUBC drawn after the ini-

tial blood culture.⁴⁸ On average, 2.32 FUBC were performed per patient for GN-BSI episode, and only 8 patients (5.7%) had persistent bacteremia. Specifically, only 3% had documented positive FUBC among patients with urinary tract source of infection. It was estimated that 17 FUBCs are needed to yield one positive result for GN-BSI. This finding is consistent with results from another study that examined 1,801 episodes of bacteremia, 901 of which were gram-negative organisms, predominantly (67%) *Escherichia coli* and *Klebsiella* spp.⁴⁹ Among GN-BSI episodes, FUBCs were performed in 247 cases, with 27 (10.9%) cases demonstrating persistent bacteremia. A nested case-control analysis between patients with cleared or persistent bacteremia found a lower yield in FUBC with gram-negative organisms and a genitourinary source of infection. Moreover, persistent bacteremia did not influence a change in antimicrobial regimen. Kang and colleagues investigated 1,068 episodes of *Klebsiella pneumoniae* bacteremia, with FUBCs performed in 862 (80.7%) cases despite only a 7.2% incidence of persistent bacteremia.⁵⁰ The independent risk factors associated with persistent bacteremia were intra-abdominal infection, solid organ transplantation, high Charlson comorbidity index score, and unfavorable treatment responses, which suggests the need for FUBC may be individualized rather than routine.

In the setting of GN-BSI in which the probability of persistent bacteremia is relatively low, especially in genitourinary sources of infection, FUBCs are not warranted. It is uncomfortable for patients and exposes them to harms of false-positive results, leading to antimicrobial administration with possible adverse effects, which can be further compounded by unnecessary testing, potentially missed alternative diagnosis, and increasing hospital LOS.^{1,51} Given the low yield of FUBC in GN-BSI, and the lack of association of persistent bacteremia with change in antimicrobial therapy or clinical outcomes, we recommend avoiding FUBC as a test of cure. Documentation of gram-negative blood culture clearance should be reserved for situations in which there is concern for deeper or otherwise uncontrolled source of infection.

CONCLUSION

The optimal management of gram-negative bacteremia in hospitalized patients is evolving. There is a growing body of evidence supporting shorter duration for a total of 7 days with oral step-down therapy as safe and effective for patients with uncomplicated Enterobacteriaceae bacteremia who have

achieved adequate source control and demonstrated clinical stability and improvement. Although comparative data regarding the optimal duration of therapy in the setting of MDR strains such as ESBL Enterobacteriaceae and pseudomonal BSI are limited, available data appear promising in favor of shorter treatment duration with oral step-down therapy. Routine follow-up blood culture is not cost-effective and may result in unnecessary healthcare resource utilization and inap-

propriate use of antimicrobials. Table 4 provides a framework for the clinical management of GN-BSI in the hospital. Taken together, these steps will facilitate antimicrobial stewardship, limit unnecessary antimicrobial exposure, and improve quality of patient care.

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