ID CORNER
If The Gut Works… Use It!

Oral Step-down Therapy for Bloodstream Infections

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With an estimated incidence of over 600,000 cases annually, bloodstream infections (BSIs) pose a significant challenge to patients and healthcare providers.[1,2] Even with advances in the diagnosis and management of infectious diseases, BSIs consistently rank among the top ten causes of mortality in the United States with rates nearing 20% depending upon the pathogen and burden of infection.[2] BSIs are also an important cause of community-onset sepsis, metastatic complications, and recurrent infections, leaving little room for error when managing these infections in clinical practice.[2-4]

Recommendations for the early management of BSIs are clear: administer empiric intravenous (IV) antibiotic therapy and identify and eradicate the source of infection. There is a clear survival benefit to the early administration of IV antibiotic therapy in critically ill patients. IV therapy provides rapid and reliable attainment of serum drug levels in patients with a variable volume of distribution or questionable oral absorption.[5] Because BSIs are such a heterogeneous disease state, management often diverges there as determined by the pathogen, suspected or documented source of infection, and patient-specific risk factors.[6-9] Much of the currently available guidance consists of outdated or archived guidelines informed by historical literature, in which IV antibiotic therapy demonstrated superiority over older oral agents in the treatment of invasive infections such as bacteremia, infective endocarditis (IE) and osteomyelitis.[10] However, contemporary literature and landmark trials such as POET and OVIVA have suggested that oral step-down therapy can be utilized on a case-by-case basis in such infections.[11,12] Continued IV therapy requires long-term venous access, which puts patients at risk for thromboembolism, phlebitis, and secondary infection while incurring significant costs to the patient.[13] In an appropriate patient, oral step-down therapy can maintain comparable clinical outcomes to complete IV courses of therapy while reducing healthcare costs, length of hospital stay, and rates of antibiotic-associated adverse drug events (ADEs).[10,13,14]

There are certainly nuances to interpreting the literature and identifying appropriate patients for oral step-down therapy

TABLE 1. Definitions of Uncomplicated BSIs

IDSA Guidelines for the Treatment of MRSA Infections[7]	*Management of Uncomplicated Gram-negative BSIs*[9]
• Rule out recurrent BSI and/or failure of source control • Clearance of bacteremia • Lack of systemic symptoms of infection within 72 hours of initiating active therapy • No IE or metastases • No implanted prostheses	• Source: UTI, IAI, CLABSI, pneumonia, SSTI • Source control • No immunocompromise or risk factors for opportunistic infections • Clinical improvement within 72 hours of effective antibiotic treatment

BSI: bloodstream infection; CLABSI: central-line associated bloodstream infection; IAI: intra-abdominal infection, IDSA: Infectious Diseases Society of America; IE: infective endocarditis; MRSA: methicillin-resistant Staphylococcus aureus; SSTI: skin and soft tissue infection; UTI: urinary tract infection.

in BSIs. A seemingly simple starting point would be to classify a BSI as "complicated" or "uncomplicated," but a clear distinction exists between gram-negative and gram-positive bacteremia. Although gram-negative organisms can cause severe and rapid onset illness, they are typically more readily eradicated than gram-positive organisms as they do not tend to metastasize to prosthetic material or other secondary foci of infection.[3,4] This leads to confusion in defining a "complicated" BSI, but Table 1 delineates some recommended considerations for an uncomplicated BSI in both groups of pathogens.

The early data for oral step-down therapy in BSIs indicated the preferential selection of fluoroquinolones and trimethoprim-sulfamethoxazole (TMP-SMX) over β-lactams largely because of their high bioavailability. In observational studies, patients receiving β-lactams experienced a non-significant trend toward increased rates of recurrent infection. There is, however, a lack of clear evidence demonstrating the superiority of fluoroquinolones and overall rates of recurrence were very low.[16-19] The use of fluoroquinolones raises concerns for drug resistance and serious ADEs when compared to the tolerability profile of β-lactams.[14] The use of TMP-SMX may also be limited by a lack of well-defined dosing targets. β-lactams are often dismissed because of a generalized perception of poor absorption and disadvantage of frequent administration. They are not without ADEs and resistance concerns but may be an effective and safe option for step-down therapy for BSIs in select patient cases, though the data do suggest significant opportunity to dose optimize these agents.[17-19]

Gram-negative Bloodstream Infections

Gram-negative BSIs, especially those caused by *Enterobacterales*, are most widely represented in the literature for oral step-down therapy. When compared with IV-only therapy, patients experienced similar rates of mortality and recurrent bacteremia, and length of hospital stay was significantly decreased.[16] Although *Enterobacterales* can cause a wide range of illnesses, most patients received oral step-down treatment for BSIs secondary to a

TABLE 2. Summary of Select Pieces of Literature Supporting Oral Step-Down Therapy for Gram-Negative BSIs

Association of 30-Day Mortality with Oral Step-Down vs Continued Intravenous Therapy in Patients Hospitalized with *Enterobacteriaceae* Bacteremia[16]		
Design	Retrospective cohort study	
Inclusion Criteria	• Adults hospitalized with monomicrobial *Enterobacterales* bacteremia • Source control measures as applicable • Appropriate clinical response	
Exclusion Criteria	• Patients transitioned to oral antibiotics after day five of IV therapy • <7 OR >16 days of total antibiotic therapy	
Treatment	• Median total duration of antibiotic therapy: 14 days • Median duration of IV therapy prior to oral step-down: 3 days	
	Antibiotic Regimen	***Patients, No. (%)***
	Amoxicillin-clavulanate 500-1000 mg q8-12h	38 (5.1)
	Cefdinir 300 mg q12h	30 (4.1)
	Cephalexin 500 mg q6h	16 (2.2)
	Ciprofloxacin 500-750 mg q12h	337 (45.6)
	Levofloxacin 500-750 mg q24h	171 (23.1)
	TMP-SMX 160-320 mg q6-12h	99 (13.4)
Patient Population Oral step-down vs IV	Propensity score-matched cohort (N=1478) • Source: urinary tract (40%), GI tract (20%), CLABSI (18%), biliary (14%) • *Escherichia coli* (43%), *Klebsiella pneumoniae* (34%), *Enterobacter spp* (12%)	
Results Oral step-down vs IV	• 30-day mortality: 13.1% vs 13.4%, NS • 30-day recurrent bacteremia: 0.8% vs 0.5%, NS • Time from day 1 bacteremia to hospital discharge: 5 days vs 7 days **(P < 0.001)**	
Conclusions	Early oral step-down therapy may be effective for patients with *Enterobacterales* BSIs who have achieved source control and demonstrated an appropriate clinical response. Early oral step-down therapy may also be associated with a decrease in the duration of hospital stay.	
Oral β-Lactam Antibiotics vs Fluoroquinolones or Trimethoprim-Sulfamethoxazole for Definitive Treatment of *Enterobacterales* Bacteremia from a Urine Source[17]		
Design	Retrospective cohort study	
Inclusion Criteria	Hospitalized adult patients with matching blood and urine cultures positive for *Escherichia coli*, *Klebsiella spp*, or *Proteus spp*	
Exclusion Criteria	• Polymicrobial bacteremia • Urologic abscess or chronic prostatitis • *Escherichia coli, Klebsiella spp,* or *Proteus spp* bacteremia in the prior 365 days	
Treatment	• Median duration of total therapy: 14 days • Median duration of oral therapy: 10 days	
	Antibiotic Regimen	***Patients, No.***
	Amoxicillin-clavulanate 500-875 mg BID	251
	Cephalexin 500mg BID-QID	245
	Ciprofloxacin 250-750 mg BID	2447
	TMP-SMX 800/160mg daily-BID	259

genitourinary source or an uncomplicated intra-abdominal source, such as cholecystitis or appendicitis where adequate source control was achieved.[16-18] It is important to note that patients with complicated infections and/or structural abnormalities (indwelling devices, obstructions, abscesses, etc.) were often excluded in aforementioned studies or were observed in subgroup analyses to have higher rates of treatment failure. The duration of IV therapy prior to oral step-down ranged from 3 to 5 days, with a total duration of 10-14 days. More recent data have demonstrated even shorter total durations of 7 days to be adequate for uncomplicated *Enterobacterales* BSIs.[9] Table 2 provides a detailed summary of select literature supporting oral step-down therapy in gram-negative BSIs. Of note, *Pseudomonas aeruginosa* and other non-fermenters are almost entirely unrepresented in the literature. These organisms also have very few (if any) oral options available for step-down therapy. Contemporary guidance does suggest that oral step-down therapy can be considered if a suitable agent is available, and the patient is immunocompetent and has achieved an appropriate clinical response and adequate source control.[9,19]

TABLE 2. Summary of Select Pieces of Literature Supporting Oral Step-Down Therapy for Gram-Negative BSIs Cont.

Patient Population FQs, TMP-SMX vs β-lactams	N=4089 • Median CrCl: 60mL/min • Urinary retention, obstruction, other structural abnormality: 23.1% vs 30.2%
Results FQs, TMP-SMX vs β-lactams	• 30-day mortality and recurrent bacteremia: 3.0% vs 4.4%, NS • 90-day mortality and recurrent bacteremia: 7.6% vs 10.1%, NS • 30-day re-hospitalization with UTI: 0.7% vs 1.5%, NS
Conclusion	Oral β-lactam antibiotics are a reasonable oral step-down option on an individual patient basis, primarily when alternative options are limited by resistance or ADEs.
Oral Beta-Lactams, Fluoroquinolones, or Trimethoprim-Sulfamethoxazole for Definitive Treatment of Uncomplicated *Escherichia coli* or *Klebsiella* species Bacteremia from a Urinary Source[18]	
Design	Multicenter observational cohort study
Inclusion Criteria	Adult patients with matching blood and urine cultures positive for *Escherichia coli* or *Klebsiella spp*
Exclusion Criteria	• Polymicrobial BSI • Complicated UTI • Concomitant non-urinary infections
Treatment	• Median duration of total therapy: 11 days (IQR 10-14) • Median duration of oral therapy: 10 days (IQR 7-10)
	Antibiotic Class — ***Patients, No.***
	FQs (ciprofloxacin or levofloxacin) — 248
	TMP-SMX — 99
	High-bioavailability β-lactam — 201
	Low-bioavailability β-lactam — 100
Patient Population	N=648 • Chronic Kidney Disease: 24% • Received recommended dosing: 32%
Results	60-day recurrence (UTI only) • Fluoroquinolones: 4.8% (4.4%) • TMP/SMX: 8.1% (5.1%) • High-bioavailability β-lactams: 8.0% (6.0%) • Low-bioavailability β-lactams: 9.0% (7.0%)
Conclusions	Fluoroquinolones and TMP-SMX had similar effectiveness in this real-world dataset. High bioavailability β-lactams were associated with higher recurrence rates, but suboptimal dosing may have contributed. Further studies are needed to define optimal β-lactam dosing and duration to mitigate treatment failures.

ADE: adverse drug event; BSI: bloodstream infection; CLABSI: central-line associated bloodstream infection; FQ: fluoroquinolone; GI: gastrointestinal; IQR: interquartile range; IV: intravenous; NS: not statistically significant; TMP-SMX: trimethoprim/sulfamethoxazole; UTI: urinary tract infection

Gram-positive Bloodstream Infections

The data to support oral step-down therapy in gram-positive BSIs indicate high clinical success rates in *Streptococcus* and *Enterococcus spp* infections of uncomplicated sources, including skin and soft tissue, pulmonary, and genitourinary.[19] Table 3 summarizes select literature supporting oral step-down therapy in gram-positive BSIs. In the SABATO trial, Kaasch et al. noted similar rates of infection-related complications when using oral step-down therapy in *Staphylococcus aureus* bacteremia (SAB), with key limitations. SAB is associated with a high incidence of metastatic complications and mortality. Prolonged durations of therapy are typically recommended to clear infection and reduce the risk of complications.[7,20] Although we have highly bioavailable agents that have activity against *S. aureus*, including methicillin-resistant *S. aureus* (MRSA), the practice of oral step-down is rarely considered. Streptococcus and *Enterococcus spp* are also associated with metastatic complications, albeit to a lesser extent, which makes oral step-down a more viable option in uncomplicated infections. A crucial element in managing gram-positive BSIs is the exclusion of metastases and the documented clearance with negative repeat blood cultures. The observed duration of IV therapy prior to oral step-down in gram-positive BSIs was 5-7 days with a minimum total duration of 14 days.[19,21] MRSA is incredibly underrepresented (~10%) in the literature. Although most infections were caused by methicillin-susceptible isolates virtually no patients received oral step-down therapy with oral β-lactams.[21,22] This, along with the small sample size and incredibly low-risk SAB patients, limits the generalizability of these data and highlights

the scarcity of truly "uncomplicated" cases of SAB.

Optimizing Oral Antimicrobial Therapy

Choosing an antibiotic regimen for any infection requires consideration of the organism minimal inhibitory concentration (MIC) and drug exposure target relative to the MIC to determine whether an agent can be adequately dosed to meet the pharmacokinetic and pharmacodynamic targets at the source of infection.[23] For example, β-lactams exert their microbiological effect in a time-dependent manner, with a general target of 40-70% of time above the MIC. Although bioavailability often factors heavily in these conversations, it is only part of the equation. Considering drug properties, such as serum concentration, tissue distribution and protein binding, as well as patient specific factors, such as organ function, age and weight, will help to determine the probability of target attainment.[23] Heil, et al. provide dosing recommendations of select oral antibiotics with a high probability of target attainment when used for step-down therapy in BSIs.[9] It is, of course, important to consider whether aggressive doses and/or longer durations of antibiotic therapy will be tolerated by patients.

Pharmacists in a variety of healthcare settings play a vital role in antimicrobial stewardship by optimizing antibiotic agents, dosing and durations of therapy, to name a few important interventions.[24] As the roles and responsibilities of pharmacists evolve to meet the increasing demands of healthcare services, we are well poised to collaborate with other members of the healthcare team to optimize the treatment of patients with BSIs. This can involve recommending initial empiric treatment, monitoring the patient's clinical response, and designing a regimen for oral step-down. Pharmacists can also thereby facilitate transitions of care by ensuring the completion of safe and effective therapy.[25]

Current literature has demonstrated that oral step-down therapy for BSIs can maintain efficacy while decreasing costs, reducing adverse events, and providing ease of administration for patients. This is typically best applied to an immunocompetent patient who

TABLE 3. Summary of Select Pieces of Literature Supporting Oral Step-Down Therapy for Gram-Positive BSIs

Fluoroquinolone versus β-Lactam Oral Step-Down Therapy for Uncomplicated Streptococcal Bloodstream Infections[19]		
Design	Multicenter retrospective cohort study	
Inclusion Criteria	Adult hospitalized patients with ≥1 positive blood culture for *Streptococcus spp*	
Exclusion Criteria	• Polymicrobial bacteremia • Infective endocarditis or central nervous system infection	
Treatment	• Median time to oral step-down 5.3 (FQ) vs 5.8 (β-lactam) days • Median durational of total therapy: 14 days • High vs low dose therapy	
	Antibiotic Class	***Patients, No.***
	Fluoroquinolones	87
	β-lactams	133
Patient Population FQs vs β-lactams	N=220 • >95% community-acquired infections • Source of infection: SSTI (21.8% vs 45.1%), respiratory (62.1% vs 24.1%), urinary, intra-abdominal, surgical site	
Results FQs vs β-lactams	• Clinical success: 92% vs 93.2% Multivariate analysis – risk factors for treatment failure • Oral step-down at <3 days (OR=5.18; **95% CI, 1.21 to 22.16**) • Low-dose oral step-down therapy (OR=2.74; NS)	
Conclusions	Oral step-down therapy may be reasonable for patients with uncomplicated Streptococcal BSIs. A β-lactam may be noninferior to a fluoroquinolone.	
Efficacy and Safety of an Early Oral Switch in Low-risk *Staphylococcus aureus* Bloodstream Infection (SABATO): An International, Open-label, Parallel-group, Randomised, Controlled, Non-inferiority Trial[21]		
Design	International, open label, randomized, controlled, non-inferiority trial	
Inclusion Criteria	Adult patients with low-risk *S. aureus* BSIs	
Exclusion Criteria	• Signs/symptoms of complicated BSI • Non-removable foreign device • Severe comorbidity	
Treatment	• Median duration of total therapy: 14 days • Median duration of step-down therapy: 8 days	
	Antibiotic agent	***Patients, No. (%)***
	Cotrimoxazole	63 (58%)
	Clindamycin	35 (32%)
	Linezolid	9 (8%)
Patient Population Oral vs IV	N=213 • Source: peripheral venous catheter (44% vs 44%), central venous catheter (22% vs 24%), SSTI (24% vs 21%) • Methicillin-resistance: 6% vs 10%	
Results Oral vs IV	• SAB-related complication within 90 days: 13% vs 12% • 90-day survival: 83.6% vs 89.0%, NS	
Conclusion	Oral step-down therapy was non-inferior to standard IV therapy in patients with low-risk *S. aureus* bacteremia. However, patients must be carefully assessed for signs and symptoms of complicated BSIs before considering early oral step-down.	

BSI: bloodstream infection; FQ: fluoroquinolone; IV: intravenous; NS: not statistically significant; SSTI: skin and soft tissue infection

has achieved adequate source control, responded to initial treatment and is able to tolerate oral therapy. Certain gaps do remain in the literature as to the optimal timing for oral step-down and the most effective antimicrobial agent(s) and dose, but the current body of evidence provides a solid framework upon which to build this practice. Observational data continue to emerge in light of recent literature and the resource constraints of long-term IV therapy.[26] Future studies and practice experience will no doubt elucidate the place of oral step-down therapy in the treatment of BSIs and other invasive infections as we continue the challenge the dogma of IV-only therapy for all.

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