Guidance for Duration of Antimicrobial Therapy in Uncomplicated Bloodstream Infections

Sections covered

What new data is available for guiding duration of therapy in uncomplicated bacteremia?

Despite evidence from observational studies and clinical trials supporting the use of shorter durations for bloodstream infections (BSI) in select patient populations with specific characteristics of infection, there has been widespread hesitation of adoption of this approach into clinical practice.[1-2] This hesitation is likely due to the data being limited to retrospective or small prospective trials. Until recently, there was no data from a large, randomized trial supporting the use for 7-day treatment durations in uncomplicated BSI.

The BALANCE study was a large, multicenter, randomized, non-inferiority trial assessing 7 days of antibiotic treatment compared with 14 days in patients hospitalized with bloodstream infections.[3] This study was designed with the intention of including broader patient populations compared to historic data by enrolling patients with any pathogenic bacteria.[3] Patients were excluded if they had an immunocompromising condition (i.e. ANC < 500 or immunosuppressive therapy for solid organ transplant or bone marrow transplant), prosthetic cardiac material, documented infection requiring prolonged duration of therapy (DOT), BSI from *Staphylococcus aureus* or *Staphylococcus lugdunensis*, or positive culture with a known contaminant.[3] Over 50% of patients enrolled were in the intensive care unit, with 20% of patients requiring mechanical ventilation and overall median SOFA score was 4 at baseline.[3] Despite the goal to include a wider variety of pathogens, 70% of infections were due to Enterobacterales, with 5% (n=170) due to *Pseudomonas aeruginosa*, and gram-positive organisms made up the remaining 25%.[3] The primary outcome of 90-day all-cause mortality occurred in 261 patients (14.5%) in the 7-day DOT group versus 286 patients (16.1%) in the 14-day DOT group. In the primary analysis, 7 days of therapy was non-inferior to 14-days of therapy (difference, −1.6 percentage points [95.7% confidence interval {CI}, −4.0 to 0.8].[3] There was no observed difference in death in the ICU, death in the hospital, or bacteremia relapse among 7 versus 14 days of therapy groups.[3] This study instills confidence that in a variety of patients presenting with bloodstream infections, shorter durations of therapy are a viable and safe option.

Large randomized-control trials are not without limitations. Although there was no difference overall between the two cohorts, it is difficult to extrapolate to organisms other than Enterobacterales due to the limited number included in the study. When assessing the outcomes within pre-specified subgroups, it is evident that gram negative bacteremia may have been driving these outcomes due to the low ratio of included patients with gram positive bacteremia. Despite most pathogens being Enterobacterales, this study did include a heterogenous sample of patients, including those admitted to intensive care units requiring mechanical ventilation. To enable appropriate application of these results, the remainder of this review will focus on appropriate patient selection to optimize DOT, and provide historical context of pathogen-specific trials published prior to the BALANCE study.

How is uncomplicated bacteremia defined?

Thirteen infectious disease specialists (7 physicians and 6 pharmacists) from across the United States participated in a four round Delphi process through responding to- and modifying 11 statements concerning the management of gram negative blood stream infections (GN-BSI).[4] Considerations in determining if a GN-BSI was uncomplicated included host immune status, response to initial antibiotic therapy, organism identified, source of GN-BSI, and source control measures.[4] The consensus

definition for uncomplicated GN-BSI is highlighted in Table 1 below, notably, 10 panelists strongly agreed with these conditions and 3 panelists agreed upon final review using a 5-point Likert scale.[4] Panelists recommend all four criteria are met for the diagnosis of uncomplicated GN-BSI.[4]

Table 1: Consensus for Defining Uncomplicated GN-BSI

Characteristic	Description
Source of Infection	Bloodstream infection confirmed to be secondary to one of the following: • Urinary tract infection • Intra-abdominal or biliary tract infection • Catheter-related BSI • Pneumonia (without structural lung disease, empyema/abscess, cystic fibrosis) • Skin and soft tissue infection
Source Control	Yes (i.e. removal of infected hardware, catheters, or devices and near complete drainage of infected fluid collections, as well as imaging assurance [as needed] of no residual or metastatic sites of infection)
Patient Characteristics	Without immunocompromise and risk for opportunistic infections (i.e. recent solid organ transplant recipients; expected prolonged neutropenia with ANC < 500 cells/mL; chronic corticosteroids and/or immunomodulator therapy)
Response to Therapy	Clinical improvement within 72 hours of effective antibiotic treatment • At minimum includes defervescence and hemodynamic stability

The role of bacterial pathogen and resistance phenotype in defining uncomplicated GN-BSI was controversial amongst panelists.[4] The overwhelming majority of available data for shorter duration of therapy in GN-BSI is specific to the Enterobacterales family, and there is limited data evaluating outcomes with other gram-negative organisms. One available cohort study of 249 patients with uncomplicated *Pseudomonas aeruginosa* BSI demonstrated patients receiving a median 9 day course of appropriate antibiotics had similar odds of recurrent infection or death compared to those receiving a median 16 day course.[5] Ultimately, panelists opted to forego a pathogen-specific definition for uncomplicated GN-BSI, however, agreed that patients with Enterobacterales BSI are more likely to meet the criteria described in Table 1 compared to patients with BSI from nonfermenting organisms.[4]

Data prior to BALANCE to guide duration of therapy in uncomplicated GN-BSI:

Observational studies have yielded conflicting results.[6-7] Nelson and colleagues conducted a retrospective review at two centers examining risk of treatment failure in patients hospitalized with uncomplicated GN-BSI receiving 7-10 days of treatment compared with > 10 days.[6] This excluded patients with in-hospital mortality, prolonged hospitalization, and deep-seated infections (i.e. liver abscesses, septic arthritis, osteomyelitis).[6] Approximately 90% of included patients had GN-BSI caused by Enterobacterales, and 70% due to urinary source of infection.[6] Risk of treatment failure was higher in patients who received shorter courses of antimicrobial therapy.[6]. A second retrospective study was conducted at three medical centers evaluating outcomes of short vs long courses of antibiotics for Enterobacteriaceae bacteremia.[7] Patients with polymicrobial BSI and history of stem cell transplantation

or solid organ transplantation were excluded.[7] After propensity score matching there were 385 patients in each cohort, and the most common sources of infection were urinary (40%) and gastrointestinal (20%).[7] Short durations of antibiotic therapy were not associated with an increased risk of mortality.[7] Limitations of these studies include the nature of observational studies and selection bias, the small sample size in the short course cohort, and the liberal definition of uncomplicated GN-BSI compared to standard practice.[6-7]

A recent up-tick in RCT data has provided more reassurance for the potential of shorter courses in uncomplicated GN-BSI.[8-10] Please refer to Table 2 below for a summary of RCT's evaluating outcomes of short antibiotic courses in the management of uncomplicated GN-BSI.

Table 2. RCT's Evaluating Long vs Short DOT in Uncomplicated GN-BSI

Characteristic	Yahav et. Al (2019)[8]	Von Dach et. Al (2020)[9]	Molina et. Al (2021)[10]
Number Included	• N = 604	• N = 504	• N = 248
Inclusion Criteria	• GN-BSI • Hemodynamically stable, afebrile for 48 hours	• GN-BSI	• Enterobacterales BSI
Exclusion Criteria	• Source of infection requiring prolonged duration • Uncontrolled source • Immunosuppression	• Fever or hemodynamic instability • Severe immunosuppression • Bacteremia with nonfermenting bacilli or polymicrobial • Recurrent bacteremia • Complicated infections (i.e. abscess, endocarditis)	• Non-controlled source • Chemotherapy with expected ANC < 500 for > 7 days • Infections requiring prolonged treatment • Carbapenemase producing Enterobacterales • Polymicrobial BSI
Interventions	• 7-day duration • 14-day duration	• CRP – guided duration of therapy • 7-day duration • 14-day duration	• 7-day duration • 14-day duration
Population	• 26% malignancy • 25% receiving immunosuppressive therapy • 68% urinary source • 10% Non-fermenting *bacilli* • 18% multi-drug resistant BSI	• 66% urinary source • No non-fermenting *bacilli* included • 8% multi-drug resistant BSI	• 26% malignancy • 12.5% receiving immunosuppressive therapy • 55% urinary source
Primary Outcome	Composite at 90 days: • Mortality • Relapse	Composite at 30 days: • Mortality • Relapse	Number of days of antibiotic treatment required at end of follow up

	• Complications at re-admission • Extended hospitalization	• Distal complications • Restarted antibiotics for suspected relapse	
Results	• Primary outcome occurred in 45.8% of patients in 7-day cohort versus 49.3% of patients in 14-day cohort • No significant difference in safety or efficacy	• Primary outcome 2.4% CRP guided, 6.6% 7-day, and 5.5% 14-day durations • CRP guided DOT and 7-day DOT non-inferior to 14-day DOT for primary outcome	• No significant difference in relapse, mortality, or drug related adverse events

Based on the RCT data described above, 7-day DOT provides similar microbiological cure rates and clinical response as 14-day DOT in select patient populations.[8-9] A majority of patients included presented with Enterobacteriaceae from a urinary source, achieved adequate source control, and responded well to initial therapy.[8-10] Current evidence, compounded by the fact that unnecessary antibiotics pose significant healthcare risks - such as *Clostridoides difficile* infection and antimicrobial resistance – supports the use of 7-day DOT in patients with uncomplicated BSI secondary to Enterobacterales bacteria.[11-12]

Data prior to BALANCE to guide duration of therapy in gram-positive BSI:

Similar to GN-BSI, evidence supporting short DOT in gram-positive (GP) BSI is pathogen specific, and patient selection is crucial. For ease of clinical application, the remainder of this section will be divided into pathogen specific considerations for DOT in aerobic GP-BSI.

Enterococcus species

Enterococcal BSI are often complicated by infective endocarditis (IE) or antimicrobial resistance (AMR), with *Enterococcus faecalis* causing over 90% of Enterococcal IE cases and *Enterococcus faecium* displaying unreliable sensitivity to first line therapy options.[13] International guidelines provide recommendations for 7 to 14 days DOT in uncomplicated Enterococcal BSI, however, this is focused primarily on catheter-related BSI.[14] This recommendation is based on a retrospective study of Enterococcal central line – associated BSI that demonstrated safety and efficacy of a 7-day course versus DOT > 7 days.[15] Rosselli Del Turco and colleagues proposed using imaging alongside other diagnostic tools for ruling out complicated processes (i.e. IE, uncontrolled source) to help guide DOT with ultimate recommendations spanning 1-6 weeks.[16] Overall, there is limited data strictly evaluating adequate DOT for Enterococcal BSI, however, a study currently underway is aiming to target this pathogen specifically.[17] The INTENSE study protocol defined uncomplicated Enterococcal bacteremia as BSI secondary to low risk sources, including urinary tract, biliary tract, catheter related, abdominal infection (with source control within 72 hours) and primary bacteremia; without endovascular complications or low risk of developing them, and without septic metastases.[17] Results of this study are not yet published, though may further guide evaluation and management principles of Enterococcal

BSI. Clinicians are advised to exercise caution in vancomycin-resistant Enterococcus (VRE) BSI, as published DOT varies from 12-16 days.[18] Outside of uncomplicated central-line associated Enterococcal BSI, there is a significant lack of data to support short (7-day) DOT. Patients with Enterococcal BSI should be thoroughly assessed to identify source of infection and rule out complications prior to definitive DOT decisions.

Streptococcus species

There is currently a lack of guidelines and data alike evaluating appropriate duration of therapy in Streptococcal BSI. The IDSA community acquired pneumonia (CAP) guidelines provide recommendations for management of *Streptococcus pneumoniae* pneumonia, but do not expand to describe appropriate duration in secondary bacteremia.[19] A total of four retrospective studies have evaluated short (≤ 10 days) DOT in uncomplicated Streptococcal bacteremia to date.[20-23] One trial evaluated *Streptococcus pyogenes* BSI[20], one trial evaluated *Streptococcus pneumoniae* BSI[21], and two trials evaluated all Streptococcal BSI.[22-23] Crotty and colleagues evaluated 162 episodes of *S. pneumoniae* BSI where patients achieved clinical stability by day 10 after positive blood culture and did not have invasive infections.[21] They concluded shorter DOT (median 7 days) may be appropriate in patients with *S. pneumoniae* BSI secondary to community acquired pneumonia as rates of clinical failure were similar to patients receiving longer DOT (median 14 days).[21] Nguyen and colleagues evaluated 286 episodes of *S. pyogenes* BSI excluding patients with polymicrobial or recurrent BSI.[20] Shorter courses of antibiotics (< 10 days) were not associated with higher rates of 90-day mortality compared to longer courses.[20] A retrospective study in Switzerland compared 5-10 day DOT with 11-18 day DOT in patients with uncomplicated Streptococcal BSI, including 1,152 episodes.[22] The most common focus of infections were skin and soft tissue, pneumonia, and intra-abdominal, with Viridans Group *Streptococcus* (VGS) accounting for a majority of cases.[22] There was no difference in clinical failure rates between groups, however, median DOT in the short course cohort was 10 days.[22] Lastly, a retrospective cohort study out of Northern California hospitals included patients with non-invasive Streptococcal infections comparing 5-10 days versus 11-15 days of therapy.[23] *S. pneumoniae* was the most common organism followed closely by VGS and bacteremia was secondary to pneumonia and skin and soft tissue sources in a majority of cases.[23] The overall incidence of all-cause mortality and clinical failure at 90-days was similar between groups, noting median DOT in the short course cohort was 9 days.[23] Acknowledging inconsistencies in defining uncomplicated BSI, organisms included, and selection bias associated with retrospective studies – there is a lack of data to support 5-7-day DOT in Streptococcal BSI.

Staphylococcus species

There is evidence to support the use of algorithm-based management of Staphylococcal BSI.[24] An algorithm-based approach standardizes clinical classification and duration of therapy of BSI, while increasing success rates by 46.9% versus standard practice.[24] Duration of therapy recommendations in coagulase-negative Staphylococcus (CoNS) BSI are vastly different from recommendations in *Staphylococcus aureus* BSI. Notably, guidelines recommend shorter DOT (2 weeks) in *S. aureus* BSI (SAB) in select patient populations, however, this was not validated with RCT data prior to the study referred to above by Holland and colleagues.[14,24-25] Most RCT data published excludes patients with

Staphylococcal BSI. Please refer to the table below for classifications and DOT recommendations of CoNS and *Staphylococcus aureus* BSI from an algorithm-based approach validated by Holland and colleagues in a RCT.[24] Notably, it is uncommon for patients to be diagnosed with uncomplicated SAB, and a majority of patients will require at minimum 4 weeks DOT.

Table 3. Clinical Classification and DOT Recommendations in Staphylococcal BS

Definition	Duration of Therapy (d)
Coagulase-Negative Staphylococcal BSI	
Simple BSI • Single blood culture positive • Negative follow-up blood culture • No signs or symptoms of local infection at a catheter site • No signs or symptoms of metastatic infection • No indwelling intravascular prosthetic devices	0-3*
Uncomplicated BSI • ≥ 2 blood cultures positive ≤ 24 hours apart OR • Single blood culture positive PLUS signs or symptoms of infection at catheter site	5-7
Complicated BSI • ≥ 2 blood cultures positive > 24 hours apart OR • Echocardiography with evidence of endocarditis OR • Signs or symptoms of metastatic infection	7-28**
***Staphylococcus aureus* BSI**	
Uncomplicated BSI • Intravascular catheter source of infection (if present) removed within 5 days • Negative follow up blood culture 24-72 hours after initial positive culture • Defervescence within 72 hours of initial positive culture • Echocardiogram without evidence of endocarditis • No signs or symptoms of metastatic infection • No indwelling intravascular prosthetic devices	14
Complicated BSI • Positive follow up blood culture for *S. aureus* OR • Persistent fever OR • Echocardiography with evidence of endocarditis OR • Signs or symptoms of metastatic infection	28-42**

** For patients with simple CoNS BSI where clinicians suspect the positive culture result is attributable to contamination, antibiotic therapy may not be warranted*

*** Upper ends of DOT recommendations account for possible diagnosis of IE or other potential complications of staphylococcal BSI*

Practical Implications:

Bloodstream infections pose significant mortality risks, contributing to over 90,000 deaths annually. Excess antibiotic exposure poses risks to patients, including increased rates of *Clostridoides difficile* infections and increased risk of antimicrobial resistance.[11-12] Although there is clear benefit associated with reduction in antibiotic use, it is vital to understand suitable clinical scenarios for stewardship intervention, such as implementing shorter durations of therapy.

Where historical data is limited due to being observational or retrospective, lacking heterogeneity, and including small sample sizes, the BALANCE trial adds to the available literature overcoming these common limitations. The BALANCE trial was a large RCT including 3,608 patients with BSI's from various pathogens and underlying infectious syndromes.[3] The BALANCE trial results extends available evidence for 7-day DOT to critically ill patients presenting with sepsis in intensive care units and those requiring mechanical ventilation.[3] Although a majority of patients enrolled presented with Enterobacterales BSI, other GN and GP organisms were not excluded from randomization or analysis.[3] The BALANCE study was a pragmatic trial design, including a heterogenous sample of patients, sources of infection, and organisms, instilling further confidence in the use of short DOT for uncomplicated bacteremia.[3] When considering institutional implementation of shorter DOTs – it is important to consider the patients, organisms, and underlying infectious syndromes included in available data. The BALANCE study enrolled patients on a large scale, and should instill clinicians with further confidence in the management of uncomplicated BSI and targeting shorter durations in suitable clinical scenarios. With appropriate patient selection based on host and organism factors, the pathway to shorter DOT continues to be paved for uncomplicated BSI's.

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