Characterization of Prescribing Practices for Uncomplicated Streptococcal and Enterococcal Bacteremias: The NARRATE Study

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ABSTRACT

Background: Bloodstream infections (BSIs) rank among the top causes of death in North America. Despite the prevalence of these infections, there remain significant practice variations in the prescribing of antibiotics.

Objective: To investigate current prescribing practices for management of uncomplicated streptococcal and enterococcal BSIs.

Methods: A retrospective cohort study was conducted using charts for patients admitted to an acute care centre in British Columbia between November 16, 2019, and October 20, 2020. Adult patients (≥ 18 years of age) with a diagnosis of uncomplicated streptococcal or enterococcal BSI were included. Patients were excluded if they had polymicrobial bacteremia or deep-seated infection or had been admitted for no more than 48 hours. The primary outcomes were duration of antibiotic therapy (IV and oral) and time to appropriate oral therapy for treatment of BSI. The secondary outcomes were observed rates of re-initiation of antibiotics and readmission with recurrent BSI. Descriptive statistics were calculated and regression analysis was performed for the primary and secondary outcomes.

Results: A total of 96 patients met the inclusion criteria. The median total duration of therapy for uncomplicated streptococcal and enterococcal BSI was about 2 weeks. *Streptococcus pneumoniae* BSIs were associated with a significantly shorter duration of IV therapy and were more likely to be associated with transition to oral antibiotics. No recurrent BSIs were observed in patients for whom therapy was transitioned to oral antibiotics.

Conclusions: Further study is warranted to explore shorter duration of antibiotic therapy and transition to oral therapy as treatment approaches for uncomplicated streptococcal and enterococcal BSI. Other outcomes of interest for future research include determining the optimal time for transition to oral therapy.

Keywords: bacteremias, streptococcal infection, enterococcal infection, antimicrobial stewardship, bloodstream infection

RÉSUMÉ

Contexte : Les infections du sang (IS), ou bactériémies, se classent parmi les causes principales de décès en Amérique du Nord. Malgré leur prévalence, la pratique de la prescription d'antibiotiques continue de varier grandement.

Objectif : Étudier les pratiques actuelles de la prescription pour la gestion des bactériémies à streptocoque et à entérocoque non compliquées.

Méthodes : Une étude de cohorte rétrospective a été menée à l'aide de dossiers de patients admis à un centre de soins aigus en Colombie-Britannique entre le 16 novembre 2019 et le 20 octobre 2020. Des patients adultes (≥ 18 ans) ayant reçu un diagnostic de bactériémie a streptocoque ou à entérocoque non compliquée ont été inclus. Les patients étaient exclus s'ils présentaient une bactériémie polymicrobienne ou une infection profonde ou s'ils avaient été hospitalisés depuis moins de 48 heures. Les résultats principaux étaient la durée de l'antibiothérapie (IV et orale) et le temps écoulé avant la transition à une thérapie orale adaptée pour le traitement de l'IS. Les résultats secondaires étaient les taux observés de reprise des antibiotiques et de réadmission avec une IS récurrente. Des statistiques descriptives ont été calculées et une analyse de régression a été effectuée pour les résultats principaux et secondaires.

Résultats : Au total, 96 patients répondaient aux critères d'inclusion. La durée totale médiane du traitement pour les bactériémies à streptocoque et à entérocoque non compliquées était d'environ 2 semaines. Les bactériémies à *Streptococcus pneumoniae* étaient associées à une durée significativement plus courte du traitement IV et étaient plus susceptibles d'être associées à la transition vers des antibiotiques oraux. Aucune IS récurrente n'a été observée chez les patients pour lesquels le traitement était passé à des antibiotiques oraux.

Conclusions : Une étude plus approfondie est justifiée pour explorer une durée plus courte de l'antibiothérapie et la transition vers une thérapie orale en tant qu'approches de traitement pour les IS à streptocoque et à entérocoque non compliquées. D'autres résultats d'intérêt pour les recherches futures comprennent la détermination du moment optimal pour la transition vers la thérapie orale.

Mots-clés : bactériémies, infection à streptocoque, infection à entérocoque, gestion responsable des antimicrobiens, infections du sang

INTRODUCTION

Bloodstream infections (BSIs) have a major impact on morbidity and mortality and are ranked among the top 7 causes of death in North America.[1] Despite the prevalence of these infections, there remain significant practice variations in the prescribing of antibiotics for BSI.[2] Although the most commonly recommended duration of therapy for BSI is 14 days, the majority of respondents in a national survey of Canadian infectious diseases (ID) and critical care specialists recommended a duration of 10 days or less.[2] In the same survey, recommendations for uncomplicated BSI were also variable, with approximately half of respondents recommending antibiotic duration of 10 days or less for BSI associated with urinary tract infection (56.6%) and skin and soft-tissue infection (SSTI; 47.9%), and only slightly more respondents making the same recommendation for pneumonia-associated BSI (69.3%).[2] The management of gram-positive BSIs in particular may have more variability, given that definitive guidance is available for treatment of BSIs caused by certain gram-positive bacteria, such as *Staphylococcus aureus*,[3-5] but not others.

BSIs due to *Streptococcus* spp. and *Enterococcus* spp. can occur with common infectious syndromes, such as soft-tissue infections and infections of the urinary tract. Although guidelines exist for the treatment of such infections, there is no specific guidance regarding duration of therapy and use of oral therapy in the case of concurrent bacteremia. *Staphylococcus aureus* bacteremia has been associated with increased morbidity and mortality, whereby the 30-day all-cause mortality rate has been estimated at 20% and an infection-related mortality rate of 13% has been reported,[6] but the outcomes related to streptococcal and enterococcal BSI, particularly in the absence of intravascular infection or other deep-seated sources, are unclear. In previous studies, the reported mortality rate for streptococcal BSI was between 7% and 22% and that for enterococcal BSI ranged from 20% to 40%.[7,8] Even fewer data have been reported regarding mortality with uncomplicated BSI; however, the mortality rate has been lower overall, specifically 8% for cellulitis-related streptococcal BSI and 17.9% for urinary tract–associated enterococcal BSI.[7,9]

Furthermore, given the lack of robust clinical evidence, the approach to oral therapy seems to be based upon expert opinion. A single-centre retrospective cohort study examining oral definitive therapy for non-staphylococcal gram-positive BSI found no differences in outcomes between high- and low-bioavailability agents.[10] That study also found no risk factors related to type of agent used or the causative organism and its source that increased the risk of treatment failure.[10] Given uncertainty about optimal treatment for these BSIs, prescribers have been observed to deviate from typical guideline recommendations in terms of duration and route of administration of antibiotics.

The aims of this study were to investigate current prescribing practices at an acute care hospital for management of uncomplicated BSI due to *Streptococcus* spp. and *Enterococcus* spp. not associated with deep-seated infections and to determine the factors affecting optimal treatment of these infections.

METHODS

Setting and Participants

This retrospective cohort study involved patients admitted to a large tertiary care teaching centre in Vancouver, British Columbia, from November 16, 2019, to October 20, 2020. Eligible patients were adults (≥ 18 years of age) with a diagnosis of uncomplicated BSI due to *Streptococcus* spp. or *Enterococcus* spp. Patients with uncomplicated BSI were defined as those with adequate source control, relative clinical improvement, and clearance of BSI within 72 hours after diagnosis in the absence of endovascular and other septic complications.[11] Patients were excluded if they had polymicrobial bacteremia or a deep-seated infection (osteomyelitis, septic arthritis, endovascular infection, central nervous system infection, or infection involving a foreign body or prosthetic material), or if they died or were discharged within 48 hours of admission. Patients were identified from a list extracted from the microbiology laboratory's information system for patients admitted within the specified date range who had positive blood culture results for *Streptococcus* spp. and *Enterococcus* spp. Covariates of interest were age, immunocompromised status, community-acquired infection, ID consults, disease severity (according to the quick Pitt bacteremia score[12,13]), type of bacterial isolate, comorbidities, and suspected source of the BSI. For specific definitions of terms, see Appendix 1.

Primary outcomes were the duration of antibiotic therapy (IV and oral), reported in days, and the time to appropriate oral therapy for uncomplicated gram-positive non-staphylococcal BSI, also reported in days. Secondary outcomes were initiation of antibiotics for the same indication within 30 days after completion of treatment, reinitiation of IV antibiotics after transition to oral therapy, and readmission within 30 days after discharge because of BSI or complications of antibiotic administration (e.g., septic thrombophlebitis or infected IV line).

Data Analysis

Descriptive statistics were used to report the primary and secondary outcomes. The Wilcoxon rank–sum test was performed for continuous outcomes and the Fisher exact test to compare binary outcomes. The primary outcomes were analyzed according to bacterial isolate and suspected source of BSI. Bacterial isolates were grouped as α-hemolytic *Streptococcus* spp., β-hemolytic *Streptococcus* spp., *Enterococcus* spp., and *Streptococcus pneumoniae*. α-Hemolytic *Streptococcus*

spp. included viridans group *Streptococcus*, and β-hemolytic *Streptococcus* spp. included groups A, B, C, and G *Streptococcus*. Suspected sources of BSI were classified as respiratory, genitourinary, gastrointestinal (GI), SSTI, other, and unknown. Univariate and multivariate regression analyses were conducted to determine whether any of the prespecified covariates were associated with the dependent outcomes (duration of IV therapy, total duration of antibiotic therapy, time to oral therapy, and transition to oral antibiotics). The multivariate regression model was generated using a backward selection algorithm, with statistical significance for inclusion and exclusion set at $p < 0.05$.

RESULTS

Patient Characteristics

In total, 210 patients were identified on initial screening, of whom 96 met the eligibility criteria (Figure 1). The mean age of included patients was 54.5 years, 70 (72.9%) were male (Table 1), and 54 (56.3%) had at least one comorbidity. The most common comorbidities were chronic kidney disease (17.7%), HIV infection (14.6%), and diabetes (14.6%). Overall, patients had low quick Pitt bacteremia scores, which suggested relatively low severity of disease. Just over half of patients (n = 49, 51.0%) received an ID consult, whereas 25 (26.0%) had a documented assessment by the antimicrobial stewardship program.

Of the pathogens identified, *Streptococcus* spp. were isolated most frequently, with *S. pneumoniae* being the most common species (30.2%), followed by Group A *Streptococcus* (25.0%), and much smaller proportions of other *Streptococcus* species. *Enterococcus* spp. was isolated in 15.6% of cases. There were no significant differences in baseline characteristics among the bacterial isolates, except that among patients with *S. pneumoniae*, α-hemolytic and β-hemolytic *Streptococcus* isolates were more likely to be related

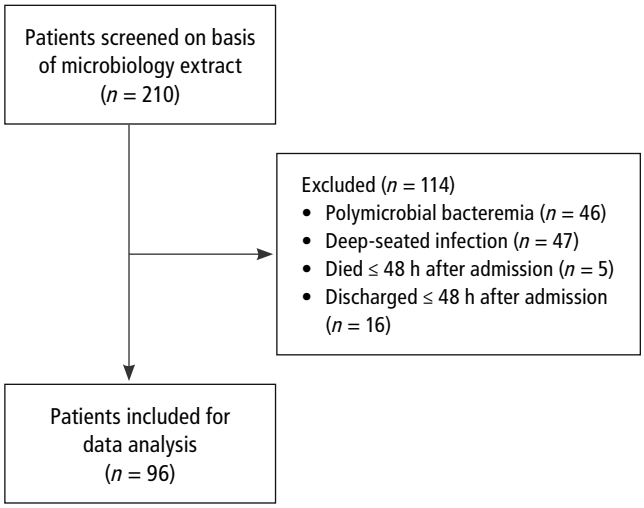

FIGURE 1. Study flow chart.

TABLE 1 (part 1 of 2). Patient Baseline Characteristics

Characteristic	No. (%) of Patients[a] (n = 96)
Age (years) (mean ± SD)	54.5 ± 17.5
Sex, male	70 (72.9)
Community-acquired infection	85 (88.5)
Infectious diseases consult	49 (51.0)
Source control	13 (13.5)
Quick Pitt bacteremia score	
0	55 (57.3)
1	28 (29.2)
2	13 (13.5)
Comorbidities	
Chronic kidney disease	17 (17.7)
Diabetes	14 (14.6)
HIV	14 (14.6)
Chronic obstructive pulmonary disease	13 (13.5)
Congestive heart failure	10 (10.4)
Cirrhosis	10 (10.4)
Solid organ malignancy	7 (7.3)
Asthma	3 (3.1)
Solid organ transplant	2 (2.1)
Hematological malignancy	1 (1.0)
Immunocompromise[b]	12 (12.5)
HIV and CD4 count < 200 cells/μL	4 (33)
Active malignancy	4 (33)
History of solid organ transplant	3 (25)
Azathioprine–6-mercaptopurine	1 (8)
Bacteria isolated	
Streptococcus pneumoniae	29 (30.2)
Group A *Streptococcus*	24 (25.0)
Enterococcus spp.	15 (15.6)
Viridans group *Streptococcus*	7 (7.3)
Group B *Streptococcus*	7 (7.3)
Group C *Streptococcus*	5 (5.2)
Group G *Streptococcus*	5 (5.2)
Mixed species	4 (4.2)
Type of infection	
Respiratory	38 (39.6)
Skin and soft tissue	26 (27.1)
Genitourinary	11 (11.5)
Gastrointestinal	6 (6.2)
Other	4 (4.2)
Unknown	11 (11.5)
Patient ward at time of positive blood culture result	
Medical	67 (69.8)
Surgical	1 (1.0)
Critical	14 (14.6)
Other	14 (14.6)

TABLE 1 (part 2 of 2). Patient Baseline Characteristics

Characteristic	No. (%) of Patients[a] (*n* = 96)
Transitioned to oral antibiotics	50 (52.1)
Patient ward at time of oral therapy[c]	
Medical	39 (78)
Critical care	1 (2)
Other	10 (20)
Clinical markers at time of initiation of oral therapy[c]	
Temperature (°C) (mean ± SD)	36.7 ± 0.2
Systolic/diastolic blood pressure (mm Hg) (mean ± SD)	122.9 ± 21.9 / 69.3 ± 13.5
Respiratory rate (per minute) (mean ± SD)	17.6 ± 5.7
White blood cell count (× 10^9/L) (mean ± SD)	9.8 ± 4.6
Glasgow Coma Score (mean ± SD)	14.7 ± 1.3
No vasopressor use	49 (98)
No mechanical ventilation or O_2 requirement	47 (94)
No poorly functioning gastrointestinal tract	48 (96)
Patient able to take medications orally	48 (96)

SD = standard deviation.
[a]Except where indicated otherwise.
[b]For reasons for immunocompromise, percentages are calculated in relation to number of patients with immunocompromise (*n* = 12).
[c]Among patients for whom transition to oral therapy was noted (*n* = 50).

to community-acquired infection. The most common suspected source of BSI was respiratory (39.6%), followed by SSTI (27.1%). Respiratory, SSTI, and genitourinary sources of infection were more likely to be related to community-acquired infection. Respiratory sources of infection were most often associated with *S. pneumoniae* isolates (*n* = 27), SSTI sources with β-hemolytic *Streptococcus* isolates (*n* = 25), genitourinary sources with *Enterococcus* spp. isolates (*n* = 9), and unknown sources with α-hemolytic or β-hemolytic *Streptococcus* isolates (*n* = 4 each) (see Appendix 2).

All of the patients were initiated on IV therapy, and 50 (52.1%) of them were subsequently transitioned to oral therapy. At the time of transition to oral therapy, all patients were afebrile, had stable vital signs, and normal mean white blood cell counts. Nearly all patients (96%) had a functioning GI tract and were tolerating oral medications at the time of initiation of oral therapy.

Primary Outcomes

Total Duration of Antibiotic Therapy

Among the most common suspected sources of infection by bacterial isolate, respiratory sources of infection with *S. pneumoniae* isolates had the shortest duration of therapy (median 14.0 days) (Table 2). For both SSTI sources with β-hemolytic *Streptococcus* and genitourinary sources with *Enterococcus* spp. isolates, the median total duration of antibiotic therapy was 15.0 days. Unknown sources with α-hemolytic *Streptococcus* isolates had the longest duration of therapy (16.0 days).

There were no statistically significant differences in total duration of therapy according to bacterial isolate (Table 3) or among suspected sources of infection (Table 4) ($p = 0.28$ for both).

The median duration of antibiotic therapy for patients with an ID consult was 17 days compared with 14 days for those without an ID consult ($p < 0.001$). The total duration of antibiotic therapy was longer, by an estimated 0.498 day (95% confidence interval 0.094-0.901), for patients with GI sources of infection than for those with suspected respiratory sources ($p = 0.016$). No other covariates had a significant impact on total duration of antibiotic therapy.

Duration of IV Antibiotic Therapy

Patients with α-hemolytic *Streptococcus* BSI had the longest duration of IV therapy (median 15.0 days, interquartile range [IQR] 7.0–23.0 days) (Table 3); in the few cases in which this isolate was identified (*n* = 7), the source of infection could not be confirmed. Patients with *S. pneumoniae* BSI, most commonly associated with respiratory infection, had the shortest duration of IV therapy (median 5.0 days, IQR 5.0–8.0 days). BSI due to β-hemolytic *Streptococcus*, the predominant pathogen for SSTIs, had a median duration of IV therapy of 13.0 days (IQR 8.0–17.0 days). BSI due to *Enterococcus* spp., for which the majority of cases were from urinary infection, had a median duration of IV therapy of 11.0 days (IQR 7.0–15.0 days). These differences in duration were statistically significant among the various bacterial isolates ($p < 0.001$). Duration of IV antibiotic therapy according to source of infection is presented in Table 4.

Oral Therapy

A total of 50 patients were stepped down to oral therapy. Among the most common suspected sources of infection by bacterial isolate, the rate of transition to oral therapy was highest for patients with respiratory sources of infection and *S. pneumoniae* isolates (23/27, 85%). The rate of transition was 67% (6/9) for patients with a genitourinary tract infection and *Enterococcus* spp. isolates, 50% (2/4) for patients with infection from an unknown source and α-hemolytic *Streptococcus* isolates, and 48% (12/25) for patients with SSTI with β-hemolytic *Streptococcus* isolate. A much greater proportion of patients with *S. pneumoniae* BSI were transitioned to oral therapy (83%) compared with the other bacterial isolates ($p < 0.001$) (Table 3). For both α-hemolytic and β-hemolytic *Streptococcus* BSI, the median time to oral therapy was 9.0 days (IQR 6–12 and 6–11 days, respectively), whereas for *Enterococcus* spp. BSI it was 8.0 days (IQR 4–12 days) and for *S. pneumoniae* BSI it was 6.0 days (IQR 5–8.5 days). These differences in time to oral therapy were not statistically different among the various bacterial isolates ($p = 0.19$). Time to oral antibiotics by source of infection is presented in Table 4.

Among patients with transition to oral therapy, those infected with *Enterococcus* spp. were given amoxicillin (4/7, 57%), linezolid (2/7, 29%), or amoxicillin–clavulanate (1/7, 14%). Patients infected with α-hemolytic *Streptococcus* were given either amoxicillin–clavulanate (2/3, 67%) or amoxicillin (1/3, 33%). Patients infected with β-hemolytic *Streptococcus* were given amoxicillin (6/16, 38%), cephalexin (4/16, 25%), amoxicillin–clavulanate (3/16, 19%),

TABLE 2. Primary Outcome According to Most Common Suspected Source of BSI for Each Bacterial Isolate (*n* = 65)

	Source of BSI; Median Duration or Time (IQR)[a]			
Outcome	**Unknown Source with α-Hemolytic *Streptococcus* Isolate (*n* = 4)**	**SSTI Source with β-Hemolytic *Streptococcus* Isolate (*n* = 25)**	**GU Source with *Enterococcus* spp. Isolate (*n* = 9)**	**Respiratory Source with *Streptococcus pneumoniae* Isolate (*n* = 27)**
Duration of IV therapy (days)	11.0 (6.5–18.5)	11.0 (7.0–16.0)	8.0 (6.0–12.0)	5.0 (5.0–7.0)
Total duration of antibiotic therapy (days)	16.0 (14.5–20.0)	15.0 (13.0–17.0)	15.0 (13.0–17.0)	14.0 (11.0–16.75)
No. (%) with transition to oral antibiotics	2 (50)	12 (48)	6 (67)	23 (85)
Time to oral therapy (days)[b]	7.5 (8.25–18.5)	10.0 (7.0–16.0)	7.0 (6.0–12.0)	6.0 (5.0–7.75)

BSI = bloodstream infection, GU = genitourinary, IQR = interquartile range, SSTI = skin and soft-tissue infection.
[a]Except where indicated otherwise.
[b]Among patients for whom transition to oral therapy was noted (*n* = 43).

TABLE 3. Primary Outcome According to Type of Bacterial Isolate (*n* = 96)

	Bacterial Isolate; Median Duration or Time (IQR)[a]				
Outcome	**α-Hemolytic *Streptococcus* (*n* = 7)**	**β-Hemolytic *Streptococcus* (*n* = 43)**	***Enterococcus* spp. (*n* = 17)**	***Streptococcus pneumoniae* (*n* = 29)**	***p* Value**
Duration of IV therapy (days)	15.0 (7.0–23.0)	13.0 (8.0–17.0)	11.0 (7.0–15.0)	5.0 (5.0–8.0)	< 0.001
Total duration of antibiotic therapy (days)	17.0 (15.0–29.0)	16.0 (13.0–18.0)	15.0 (11.0–19.0)	15.0 (11.0–17.0)	0.28
No. (%) with transition to oral antibiotics	3 (43)	16 (37)	7 (41)	24 (83)	< 0.001
Time to oral therapy (days)[b]	9.0 (6.0–12.0)	9.0 (6.0–11.0)	8.0 (4.0–12.0)	6.0 (5.0–8.5)	0.19

IQR = interquartile range.
[a]Except where indicated otherwise.
[b]Among patients for whom transition to oral therapy was noted (*n* = 50).

TABLE 4. Primary Outcome According to Suspected Source of BSI (*n* = 96)

	Suspected Source of BSI; Median Duration or Time (IQR)[a]						
Outcome	**GI (*n* = 6)**	**GU (*n* = 11)**	**Respiratory (*n* = 38)**	**SSTI (*n* = 26)**	**Other (*n* = 4)**	**Unknown (*n* = 11)**	***p* Value**
Duration of IV therapy (days)	22.0 (15.0–23.0)	8.0 (6.0–13.0)	7.0 (5.0–9.0)	11.0 (7.0–16.0)	17.0 (12.0–21.0)	15.0 (7.0–16.0)	< 0.001
Total duration of antibiotic therapy (days)	23.0 (15.0–28.0)	15.0 (13.0–17.0)	15.0 (11.0–17.0)	15.0 (13.0–17.0)	17.0 (12.0–21.0)	16.0 (15.0–17.0)	0.28
No. (%) with transition to oral antibiotics	1 (17)	6 (55)	27 (71)	12 (46)	0 (0)	4 (36)	0.011
Time to oral therapy (days)[b]	20.0 (20.0–20.0)	7.0 (4.0–8.0)	7.0 (5.0–9.0)	8.5 (5.0–11.0)	NA	8.5 (7.0–9.0)	0.29

BSI = bloodstream infection, GI = gastrointestinal, GU = genitourinary, IQR = interquartile range, NA = not applicable, SSTI = skin and soft-tissue infection.
[a]Except where indicated otherwise.
[b]Among patients for whom transition to oral therapy was noted (*n* = 50).

cefuroxime (2/16, 13%), or penicillin VK (2/16, 13%). Patients with *S. pneumoniae* were given amoxicillin (14/24, 58%), moxifloxacin (5/24, 21%), amoxicillin–clavulanate (3/24, 13%), penicillin VK (1/24, 4%), or levofloxacin (1/24, 4%). Some patients received combination treatment with 2 or more oral antibiotics (2/50, 4%).

Secondary Outcomes

The overall rate of clinical failure in this study was 1% (1/96); more specifically, 1 patient was readmitted within 30 days after discharge with recurrent BSI. This patient had recurrent BSI due to group G *Streptococcus*, which occurred 18 days after discharge. The patient had completed an 18-day course of IV antibiotics with empiric ceftriaxone and vancomycin, as well as definitive IV therapy with cefazolin for a suspected hospital-acquired line infection. This patient had a previous medical history of HIV with CD4 count below 200 cells/μL and solid organ malignancy.

None of the patients with transition to oral therapy met the criteria for clinical failure, and no patients had re-initiation of antibiotics for the same infection within the same admission.

DISCUSSION

There is limited evidence to guide the use of oral antibiotics and the duration of treatment for uncomplicated streptococcal and enterococcal BSI. Hence, antibiotic treatment for such infections is typically based upon expert opinion and individual clinical judgment. The purpose of this study was to describe the variability in prescribing practice for uncomplicated streptococcal and enterococcal BSI at our institution, to better determine how best to optimize the use of antibiotics. The patients included this study were relatively healthy and had non-severe infections.

Patients with *S. pneumoniae* BSI, typically from a respiratory source, had a significantly shorter duration of IV therapy (median 5.0 days) but a similar duration of total antibiotic therapy (median 15.0 days) compared with other pathogens and other infectious sources. Despite a willingness to transition early to oral therapy, clinicians remain hesitant to shorten the overall duration of antibiotics in patients with BSI. This reflects the lack of robust evidence for treatment duration for streptococcal BSIs. In a systematic review and meta-analysis that compared shorter and longer duration of antibiotic therapy for BSI (5–7 days versus 7–21 days), there were no significant differences in clinical cure, microbiological cure, or survival among patients with non–*Staphylococcus aureus* infections.[14] The authors also noted that in 3 studies looking at BSI related to community-acquired pneumonia, clinical cure was achieved for 19 of 21 patients who received 5–7 days of therapy and 17 of 19 patients who received 7–10 days of therapy.[14] Unfortunately, this systematic review did not differentiate between gram-positive and gram-negative pathogens, and it is therefore unclear whether the results can be strictly applied to BSIs due to gram-positive bacteria. The Association of Medical Microbiology and Infectious Disease Canada published guidelines on the duration of antibiotic therapy for common infections in 2020. These guidelines recommend a duration of 5–7 days of therapy for *S. pneumoniae* BSI associated with pneumonia,[15] but there was little evidence supporting this recommendation.

In the current study, we observed a median total of 2 weeks of antibiotic therapy across all bacterial pathogens, despite the absence of evidence for deep-seated infection. A possible explanation for the longer-than-recommended duration of therapy is because non-staphylococcal gram-positive organisms, such as *Enterococcus* and *Streptococcus*, can also cause invasive and severe infections. Although we did exclude patients with endocarditis or deep-seated infection as a suspected source of BSI, clinicians may still be hesitant to completely rule out these possibilities. BSI due to viridans group *Streptococcus* also tended to have a longer duration of therapy, despite the lack of findings confirming endocarditis. The BALANCE (Bacteremia Antibiotic Length Actually Needed for Clinical Effectiveness) study is an ongoing randomized controlled trial looking at whether a shorter duration of therapy is adequate for hospitalized patients with non-*Staphylococcus* aureus BSI.[16] The BALANCE study will randomly assign patients to receive 7 or 14 days of antimicrobial therapy and will then analyze various clinical outcomes.

Another observation from this study was that patients with ID consults tended to have longer duration of IV and total antibiotic therapy and longer time to oral therapy than patients without ID consults. Possible reasons could be that patients with complicated disease are more likely to receive an ID consult or that ID consultants tend to treat more conservatively given uncertainty of an infection. This observation was also reflected in a previous retrospective cohort study looking at the association between ID consults and clinical outcomes in patients with *S. aureus* BSI at low risk of endocarditis, in which patients with ID consults had a longer duration of IV antimicrobial therapy than those without ID consults (31 versus 15 days, $p < 0.01$).[17] The same result was obtained for duration of antimicrobial treatment for BSI in critically ill Canadian patients.[18] More specifically, in their retrospective cohort study, Daneman and others[18] found that ID consults were less common among those receiving shorter duration of treatment, both at the time of antibiotic initiation (26.1% versus 32.6%; $p = 0.047$) and at the time of discontinuation (32.9% versus 50.3%; $p < 0.001$).

More than half of the patients included in our study were able to transition to oral antibiotics. Given the low number of clinical failures observed, this suggests that appropriate transition to oral antibiotics can be effective and safe for the treatment of uncomplicated streptococcal

and enterococcal BSI. In a single-centre, retrospective cohort study, Quinn and others[10] examined the effectiveness of oral antibiotics as definitive therapy for non-staphylococcal gram-positive BSI in 103 patients. In that study, 90-day all-cause mortality was 4.9%, 1.9% of patients had recurrent BSI within 90 days of switching to oral therapy, and 4.9% of patients had a switch from oral therapy back to IV therapy.[10]

In the current study, we evaluated prescribing practices related to treatment of streptococcal and enterococcal BSI, in a context of limited guidance for therapy, and the rate of clinical failure with current practices. The results provide insight into differences in antibiotic therapy according to bacterial isolates and suspected sources of BSI and allow us to address possible clinical factors that could have affected prescribing choices. The limitations included the small sample size of 96 patients within the prespecified data collection period. Additionally, stratification on the basis of pathogen and suspected source of BSI further reduced the sample sizes for statistical analysis. The study results should be interpreted in the context of a patient population with overall low severity of BSI. Furthermore, the patients were discharged with oral antibiotics to be completed in the community, where prolongation of therapy and adherence to the prescribed regimen could not be assessed and where secondary outcomes could have been missed if discharged patients were readmitted to another hospital.

CONCLUSION

At this acute tertiary care teaching hospital, approximately 2 weeks of total therapy was prescribed for uncomplicated streptococcal and enterococcal BSI. In this study, BSIs due to *S. pneumoniae* were associated with a significantly shorter duration of IV therapy, and transition to oral antibiotics was more likely. No recurrent BSIs were observed for patients with transition to oral antibiotics or for patients with shorter duration of therapy (< 14 days). Further study is warranted to explore shorter duration of antibiotic therapy and early transition to oral therapy as treatment approaches for this type of infection.

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APPENDIX 1 (part 1 of 2). Definition of Terms

Term	Definition
Bacteremia	Positive blood culture results from a central and peripheral line with one of the bacterial isolates specified in the inclusion criteria
Community-acquired or hospital-acquired infection	Community-acquired if the infection was diagnosed by blood culture of a sample obtained within 48 h of hospital admission Hospital-acquired if the infection was diagnosed by blood culture of a sample obtained more than 48 h after hospital admission
Immunocompromised	Presence of one or more of the following conditions during period with positive blood culture results: • Chemotherapy within 30 days before diagnosis of BSI • HIV and CD4 count < 200 cells/μL • Systemic lupus erythematosus • Hemolytic anemia • Aplastic anemia • Neutropenia (white blood cells $< 0.5 \times 10^9$/L) • History of solid organ transplant • Active malignancy (solid organ or hematological) • Splenectomy OR Receipt of one or more of the following medications during period of positive blood culture results: • Methotrexate > 25 mg weekly • Tumour necrosis factor-α inhibitors • Biologics • Azathiopurine–6-mercaptopurine • Prednisone or equivalent > 20 mg/day for at least 7 days
Polymicrobial bacteremia	Single culture with potential contaminants or cultures yielding *Staphylococcus aureus*, gram-positive bacilli, gram-negative bacteria, or fungal species
Deep-seated infection	At time of positive blood culture results, diagnosis of any of the following: • Osteomyelitis • Septic arthritis • Endovascular infection, including infective endocarditis • Meningitis or infection involving the CNS • Prosthetic material or foreign-body infection
Persistent bacteremia	Multiple positive blood culture results during admission, > 48 h apart, after initiation of antibiotics
Appropriate transition to oral therapy	Appropriate transition to oral therapy from empiric IV therapy for treatment of bacteremia
Re-initiation of antibiotics for same infection within the same admission	Re-initiation of antibiotics within 30 days after end of documented antibiotic treatment (IV or oral) or re-initiation of IV antibiotics if still receiving oral antibiotics for the same bacterial isolate in blood culture
Readmission within 30 days with recurrent bacteremia or complications of antibiotic treatment	Within 30 days after discharge date, patient was readmitted to Providence Health Care because of bacteremia or complications of antibiotic treatment (specifically, septic thrombophlebitis or infected IV line)
Source controlled	Documentation in patient chart that source of bacteremia was controlled or drainage was adequate OR Documentation of any of the following: • Drainage of abscess • Removal of line or tubes • Successful endoscopic retrograde cholangiopancreatography • Successful surgical intervention
Patient unable to take antimicrobial medications orally	Patient meets at least one of the following criteria: • NPO • Nasogastric or orogastric tube in use for suctioning • Active GI bleeding • Difficulty swallowing • Loss of consciousness without nasogastric or orogastric tube present • Recurring emesis

APPENDIX 1 (part 2 of 2). Definition of Terms

Term	Definition
Poorly functioning GI tract	Patient meets at least one of the following criteria: • Documented ileus or GI obstruction • Short GI transit time (e.g., malabsorption syndrome, partial or total gastrectomy, short bowel syndrome) • Shock or septic shock
Patient unable to tolerate other oral medications	Patient does not tolerate other medications, fluids, and/or food given orally or enterally while in hospital

BSI = bloodstream infection, CNS = central nervous system, GI = gastrointestinal, NPO = nothing by mouth.

APPENDIX 2. Suspected Source of Bloodstream Infection According to Type of Bacterial Isolate (n = 96)

	Bacterial Isolate; No. of Cases			
Source of Infection	**α-Hemolytic *Streptococcus* (*n* = 7)**	**β-Hemolytic *Streptococcus* (*n* = 43)**	***Enterococcus* spp. (*n* = 17)**	***Streptococcus pneumoniae* (*n* = 29)**
Gastrointestinal (*n* = 6)	1	2	3	0
Genitourinary (*n* = 11)	0	2	9	0
Respiratory (*n* = 38)	2	8	1	27
Skin and soft tissue (*n* = 26)	0	25	0	1
Other (*n* = 4)	0	2	2	0
Unknown (*n* = 11)	4	4	2	1