Improving the Prognosis of Patients with *Staphylococcus aureus* Bloodstream Infections:

A Multifaceted Treatment Analysis

Zhanni Weber

A Thesis Submitted to the Faculty of Graduate Studies
in Partial Fulfillment of the Requirements
for the Degree of

MASTER OF SCIENCE

College of Pharmacy
University of Manitoba

Abstract

The treatment of *Staphylococcus aureus* bloodstream infections (SABSI) remains a major challenge. With an emphasis on complicated methicillin–sensitive *S. aureus* (MSSA), a comprehensive analysis of initial antibiotic treatment was conducted. The influence of treatment gaps on clinical outcomes were examined. Strategies were developed to improve the use of available antibiotics. Patient- and infection-related variables predictive for end-of-treatment failure included higher Charlson Comorbidity Index and healthcare-associated infection. Treatment variables of shorter duration of optimal targeted, shorter duration of optimal or adequate and lower TSE score were also predictive for end-of-treatment failure when tested separately in their own models. Strategies to optimize the treatment of complicated MSSA BSI at minimum should include: 1) Initiating at least an adequate therapy within 24 hours following the index blood culture draw and 2) Maintaining uninterrupted treatment, especially during the initial 7 days including at least 4 days of cloxacillin or cefazolin.

Acknowledgements

I would like to express my heartfelt appreciation to all those who have contributed to my study and supported me throughout my Masters program.

I would like to thank our Dean, Dr. Neal Davies and the College of Pharmacy for their support. The University of Manitoba's Pharmacy Graduate program has flourished under Dr. Davies' care and guidance.

I would like to thank Dr. Hope Anderson and the Graduate Committee for all their support and making my Masters program a seamless experience.

I would like to thank Dr. Keith Simons for providing me advice, encouragement and support throughout my graduate studies.

I would like to thank my committee members, Drs. Lavern Vercaigne, Philippe Lagacé-Wiens and Robert Ariano for their time and feedback on my study and thesis. Thank you for providing me with the resources for my study and the clinical experiences for my Masters program. They have been the most exceptional mentors.

I would like to thank Dr. Harris Iacovides for providing me with his time and guidance during my clinical rotations at St. Boniface Hospital.

I would like to thank Divna Calic, my friend and colleague for all her support, ideas and feedback whether it was for clinical rotations, presentations or for my thesis. I have made a very special friend from these experiences.

I would like to thank my parents, Thomas and Yan Weber for their encouragement and moral support through this challenging time in my life. Thank you for standing by my side throughout this whole process.

Lastly, I would like to express my sincerest gratitude to my advisor and role model, Dr. Sheryl Zelenitsky. I came into the Masters program with minimal knowledge and experience. I was also quite doubtful of my abilities. Dr. Zelenitsky saw my potential and invested countless hours to help me develop those skills. To have this kind of mentorship is rare and I am very fortunate to have been under her guidance. Dr. Zelenitsky, I cannot thank you enough.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

SECTION 1: *Staphylococcus aureus*

Microbiology and Resistance: *Staphylococcus aureus* (*S. aureus*) is one of 37 species in the *Staphylococcus* genus and is the most pathogenic amongst the 16 *Staphylococcus* species found in humans.[1] Similar to other Gram-positive bacteria, *S. aureus* has a thick peptidoglycan cell wall that provides strength and protection for the organism. *S. aureus* can withstand variable environments of desiccation, variable pH, osmotic stress, nutrient deprivation and elevated temperatures. In addition, *S. aureus* is more salt tolerant than most other bacteria.[2]

In 1959, methicillin (semi-synthetic penicillin) was introduced to treat penicillinase-producing staphylococcal strains. However soon after the introduction of this novel agent, the emergence of methicillin-resistant *S. aureus* (MRSA) was reported.[3,4] Located in the cell membrane, penicillin-binding proteins (PBPs) are an integral part of peptidoglycan cell wall synthesis. Beta-lactam antibiotics covalently bind and inactivate these peptidase enzymes in methicillin sensitive *S. aureus* (MSSA) disrupting cell wall synthesis and causing bacterial cell death. MRSA on the other hand, withstands the actions of beta-lactam antibiotics through the *mec* A gene that encodes for a modified PBP called PBP-2a. This specialized peptidase enzyme has low affinity for beta-lactam antibiotics enabling cell wall synthesis to proceed.[5] Methicillin resistance infers resistance to all penicillins, cephalosporins and carbapenems with the exception of the 5th generation cephalosporins (eg, ceftobiprole, ceftaroline) which retain affinity for the PBP-2a receptor.[6]

MRSA strains can be categorized as either community-acquired (CA-MRSA) or healthcare-associated (HCA-MRSA). The two types can differ with regards to genotype, phenotype (ie, antibiotic resistance) and virulence. They can also be associated with different infections and patient populations. The *mec* gene is part of a mobile chromosomal element called the staphylococcal cassette chromosome (SCCmec), which has five types. The majority of CA-MRSA are associated with SCCmec types IV and V, whereas the majority of HA-MRSA involve types I, II, and III.[7] HCA-MRSA tend to be associated with more resistance to non-beta-lactam antibiotics such as clarithromycin, clindamycin, tigecycline and trimethoprim/sulfamethoxazole (TMP/SMX).[8] The role of Panton and Valentine leukocidin (PVL) toxin as the cause of increased virulence in CA-MRSA infections remains controversial. PVL toxin has been previously linked to CA-MRSA infections including severe necrotizing pneumonia and skin and skin structure infections. [7, 12] More recent evidence has shown that *S. aureus* transformed with the PVL toxin did not lead to increased leukocyte destruction and tissue necrosis, which suggests that other factors are at play. [225] Since CA-MRSA infections occur in patients without healthcare exposure, the population tends to be younger and otherwise healthy. In contrast, HCA-MRSA infections most often include bloodstream infections (BSIs), nosocomial pneumonia, non-necrotizing skin and skin structure infections and catheter-related urinary tract infections (UTIs). Affected patients tend to be those with diabetes, dialysis dependence, indwelling catheters or devices, prolonged hospitalization, intensive care unit (ICU) admission or residence at a long-term care facility.[7] Over time the two categories of MRSA are becoming less distinct in regards to both acquisition and antimicrobial susceptibilities.[9]

Colonization and Infection: Aided by surface proteins, *S. aureus* colonizes [10] the nasal passages, axillae, vagina, pharynx and skin. *S. aureus* colonization occurs in approximately 30 to 50% of the population and is persistent in 10 to 20%.[11] With a breach in skin or mucosal barriers, colonization has the potential to progress into infection. The interplay between bacterial virulence factors and host immunity determines the risk and extent of infection. Virulence factors produced by *S. aureus* include exfoliatin toxin which can cause staphylococcal scalded skin syndrome [13] and superantigens such as toxic shock syndrome toxin (TSST-1) and staphylococcal enterotoxin (SE), both of which are pyrogenic and enteropathogenic.[14] Compromised immunity, whether innate or acquired, dramatically increases the frequency, duration and severity of infection. Chemotherapy-induced neutropenia, an acquired immune-deficiency, is associated with susceptibility to infections.[15] Amongst patients with *S. aureus* infections, depressed humoral immunity as demonstrated by low levels of antibodies to enterotoxin A and exfoliatin toxin has been associated with increased mortality.[16] Amongst human immunodeficiency virus (HIV) infected patients with depressed cell-mediated immunity, CD4 cell counts < 100 cells/μg were associated with a 31 times higher incidence of *S. aureus* BSI (SABSI).[17] Finally, Kaech et al. demonstrated that immunocompromised patients with SABSI were much more likely to die from the infection.[18]

S. aureus is the second most common cause of BSI and will be discussed in detail in the next section.[19] *S. aureus* is also a common pathogen in skin and skin structure infections and contributes to 75% of skin abscesses. Clinical manifestations are variable from mild infections with erythema, swelling and purulence, to life-threatening infections characterized by full

tissue necrosis and sepsis.[20] *S. aureus* is an important cause of cardiac infections including endocarditis involving native or prosthetic valves. The clinical presentation of endocarditis varies and can include the signs and symptoms of sepsis along with cardiac complications such as heart failure, perivalvular abscess and pericarditis. Septic embolization can result and cause infarction in organs such as the brain, lungs and, heart.[21] Risk factors for *S. aureus* endocarditis include cardiac devices or prosthetic valves, valvular abnormalities, intravenous drug use, hemodialysis and primary or secondary SABSI.[22] A study by Nadji et al. concluded that *S. aureus* endocarditis was associated with relatively high rates of severe sepsis, major neurological events, multi-organ failure and mortality compared with other pathogens.[23] Infected cardiac devices including pacemakers and defibrillators are associated with *S. aureus* or coagulase-negative staphylococci in 65 to 75% of superficial infections and up to 90% of deep-seated infections.[24-7]

S. aureus is the most common cause of hematogenous osteomyelitis and accounts for more than 50% of vertebral infections.[28] Clinical manifestations can include pain, tenderness, warmth, erythema, swelling and complications such as epidural abscess.[29] *S. aureus* is also the most common cause of septic arthritis in adults.[30-32] Due to the significant vascularization of the joint space, most cases of septic arthritis are a result of hematogenous spread.[33] Clinical presentation can include fever, joint pain, swelling, warmth and reduced mobility.[34] Finally, infected prosthetic joints are associated with *S. aureus* and coagulase-negative staphylococci in 22% and 19%, respectively.[35]

SECTION 2: *Staphylococcus aureus* Bloodstream Infections

Definition and Epidemiology: *S. aureus* is an important cause of BSI, which is also associated with significant complications, patient morbidity and mortality. As per the Centers of Disease Control and Prevention (CDC), the definition of a laboratory-confirmed BSI is a recognized pathogen cultured from one or more blood cultures.[36]

S. aureus is one of the most common bacterial causes of BSI. In a national surveillance study of over 8,000 bloodstream isolates collected in Canadian hospitals between 2007 and 2009, *Escherichia coli*, *S. aureus* and coagulase–negative staphylococci were the most common pathogens accounting for 22.6%, 17.7% and 11.0% of cases, respectively.[19] These data were consistent with a report of BSI in patients admitted to European medical centers where the same pathogens were isolated in 22.4%, 19.5% and 14.6% of cases, respectively.[37]

Other large surveillance studies of SABSI have reported annual incidence rates of 19.7 cases per 100,000 population in Canada [38], 26 per 100,000 in Scandinavia [39, 40] and 50 cases per 100,000 in the United States (US).[41, 42] A recent study by the International Bacteremia Surveillance Collaborative (IBSC) involving Finland, Sweden, Denmark, Canada and Australia described the annual incidence patterns of SABSI from 2000 to 2008 stratified according to methicillin resistance and community versus hospital acquisition. The overall incidence rate was 26.1 cases per 100,000 population including 24.2 cases of MSSA and 1.9 cases of MRSA. A closer look at the Canadian data suggests that MRSA accounted for 20 to 25% of all *S. aureus* [43], which was consistent with another national surveillance study of bloodstream isolates.[19] The overall

incidence rate of SABSI reported by the IBSC did not change over the 9-year study period (p = 0.8). Although there were no significant trends in the incidence of MSSA BSI over time, there was an increase in the proportion of community–acquired MSSA infections (p = 0.005). There were also significant increases in the overall incidence rate (p = 0.035) and proportion of community–acquired infections (p = 0.013) associated with MRSA.[43]

Risk Factors: There are several risk factors for SABSI. Nasal colonization with *S. aureus* has been observed to increase the rate of SABSI by three times compared to non-colonized patients (1.2% versus 0.4%, RR 3, 95% CI 2.0-4.7).[44] Studies have also shown that nasal colonization with MRSA is associated with a much higher rate of infection compared with colonization with MSSA.[45] *S. aureus,* a commensal organism of the skin, can colonize intravascular catheters and seed the bloodstream. Similarly, other foreign devices such as cardiac devices and prosthetic valves or joints can serve as reservoirs for *S. aureus* colonization, biofilm production and infection.[46-8] Serious *S. aureus* infections such as skin and skin structure infections, endocarditis, osteomyelitis or pneumonia can lead to secondary SABSIs. Finally, patient factors associated with the greatest risk for developing SABSI include those with cancer, HIV, organ transplantation, diabetes mellitus and hemodialysis dependence.[38]

Diagnosis: The isolation of *S. aureus* from blood rarely represents contamination so the microbiological techniques for its identification and characterization follow strict processes. Clinical *S. aureus* isolates are distinguished using a Gram-stain in addition to thermostable DNAse, catalase and coagulase tests. Blood samples should be collected from at least two

venipuncture sites. Samples can be inoculated into blood culture bottles which are then incubated and continuously monitored (eg, BacT/Alert™ system) for up to 5 days. If positive growth is detected, a Gram-stain can be performed. If Gram-positive cocci arranged in clusters are observed, a thermostable DNAse test can be done for the presumptive identification of *S. aureus.* Positive blood culture bottles can also be subcultured on sheep blood agar for definitive identification of *S. aureus* as smooth, translucent yellow/gold colonies with positive catalase and coagulase tests. Methicillin resistance can be presumptively identified using one of several methods (eg, Polymerase chain reaction, subculture to selective media, microarray technology). Definitive identification of methicillin resistance can then be carried out with antimicrobial susceptibility testing using broth dilution, agar dilution, Kirby-Bauer disc diffusion or an automated instrument (eg, Vitek™ 2). A minimum inhibitory concentration (MIC) of > 6 μg/mL for cefoxitin can be used to confirm the presence of methicillin resistance.[49] SABSI detection and identification turnaround times have been previously examined by Kim et al. The authors have reported mean microorganism detection time (using an automated system), Gram-stain and final susceptibility reporting times of 21.3, 32.1 and 82.9 hours, respectively. [213]

The clinical features of SABSI are variable and non-specific. The most common signs and symptoms are fever, chills, confusion, tachycardia and tachypnea. Physical examination and diagnostic work-up are important to identify possible sources of SABSI as well as metastatic infection.[50] For example, the presence of *S. aureus* bacteriuria should prompt careful investigation for SABSI since concurrent bacteriuria develops in approximately 25% of cases.[51] Infective endocarditis can be present in up to 30% of SABSI cases [52-4] and therefore

investigations such as transthoracic echocardiography (TTE) and/or transesophageal echocardiography (TEE) are important diagnostic tools. Although TEE is more invasive, it is also more sensitive [55-7] in detecting vegetations [52-4, 57], intracardiac abscesses and valvular perforations.[53] Signs of endocarditis can include new or worsening heart murmur, peripheral stigmata consistent with infective endocarditis (eg, septic emboli, Janeway lesions and Osler's nodes) and persistent SABSI despite appropriate antimicrobial therapy.[21]

Acquisition: Traditionally, BSIs have been classified as community or nosocomial (hospital-acquired). In 2002, Friedman et al. proposed a new classification for BSIs called "healthcare-associated" in order to define the emerging infections in patients from the community but with previous exposure to healthcare sites or services. Following this proposal, the authors conducted a prospective study of 504 BSIs, which described 35% as nosocomial, 28% as community-acquired and 37% as healthcare-associated. The study also found *S. aureus* as the most common cause of infection in each category.[58]

Nosocomial SABSI was defined by a positive *S. aureus* blood culture collected $\geq$ 48 hours since hospital admission. If the patient was transferred from another hospital, the calculation was from the time of that admission.[58] Patients with nosocomial SABSI are typically older with one or more comorbidity. Risk factors include surgical wound infection and presence of an intravascular catheter. Metastatic complications occur in approximately 20% of cases of nosocomial SABSI.[59]

Healthcare-associated, community-onset SABSI was defined by a positive *S. aureus* blood culture within 48 hours of admission. In addition, these patients had to have 1) received intravenous therapy, wound care or specialized nursing care at home within 30 days prior to the BSI, 2) attended a hospital, undergone hemodialysis or received chemotherapy within 30 days prior to the BSI, 3) been hospitalized in an acute care institution for > 2 days within 90 days prior to the BSI or 4) resided in a nursing home or long-term care facility.[58] Patients with healthcare-associated also tend to be older with multiple comorbidities. Healthcare-associated, community-onset SABSI is often associated with infected decubitus ulcers, diabetic foot ulcers or other wounds.[60]

Finally, community-acquired BSI was also defined by a positive *S. aureus* blood culture obtained within 48 hours of admission but without the criteria for health-care associated, community onset infection listed above.[58] Patients with community-acquired BSI are often younger and healthier, but also include more patients with a history of intravenous drug use. Patients with community acquisition are at the highest risk for developing metastatic infections with rates ranging from 40% to 90%.[59, 61-3] According to one study by Fowler et al., community-acquired SABSI was more likely to be complicated than nosocomial-acquired infection (OR 3.1, $p = 0.002$). Furthermore, infective endocarditis has been shown to be three times more common in community-acquired SABSIs.[64]

Following the advent of the "healthcare-associated infection" definition, numerous modified definitions have been used in clinical studies. Such heterogeneity in the literature has led to

confusion amongst clinicians and researchers. To standardize the classification of BSI, the CDC and National Healthcare Safety Network (NHSN) released new surveillance definitions in 2014 for categorizing acquisition type as either present-on-admission or healthcare-associated. Present-on-admission is defined as positive blood cultures drawn two days prior to admission, the first day of admission or the day after admission to an acute care facility. This category encompasses the previous community-acquired BSI and healthcare-associated, community-onset BSI. The new healthcare-associated is defined as positive blood cultures drawn on or after the third day of admission, and replaces the former nosocomial BSI.[36]

Classification: SABSI has also been classified as primary or secondary. Primary SABSI, shown to be an independent predictor of mortality [18], is not related to an infection at another site.[36, 65] Secondary SABSI is due to an infection from another site such as skin and skin structure infection or infected foreign device. In a Canadian study of 1440 cases of SABSI, 40.7% were primary infections whereas 59.3% were secondary to infections in the bone or joint (15.7%), skin and skin structure (15.5%), respiratory tract (15.3%), endovascular system (6.0%), abdomen (5.5%) or central nervous system (0.8%).[38]

SABSI has also been classified as complicated or uncomplicated based on severity of infection.[18] In general, the definition of complicated SABSI is based on infection characteristics associated with poor prognosis such as endocarditis, metastatic infection, presence of a foreign device (eg, prosthetic valves, cardiac devices), positive follow-up blood culture drawn 2 to 4 days after the

index blood culture draw or persistent signs and symptoms of infection beyond 72 hours after the index blood culture draw.[64, 66, 68]

Several studies have demonstrated that endocarditis is associated with poor outcomes. In a study by Chang et al., endocarditis was more often associated with recurrent *S. aureus* infections (49% versus 10%, p = 0.01).[61] Libert et al. examined risk factors for mortality amongst patients with SABSI and found that endocarditis was a significant predictor of infection-related mortality (OR 12.13, 95% CI 2.03-72.36, p = 0.002).[69] These results were consistent with other studies by Rieg et al. which linked endocarditis to in-hospital mortality (OR 2.8, 95% CI 1.4-4.7, p < 0.01) [70] and Turnridge et al. which linked left-sided endocarditis to 30-day mortality (OR 2.8, 95% CI 1.34-5.85, p = 0.006).[9] Metastatic infections are also associated with poor outcomes. In a study of MRSA BSI by Lin et al., metastatic infections were identified as significant predictors for both infection-related and 30-day mortality (OR 5.23, 95% CI 2.17-12.59, p < 0.001 and OR 3.01, 95% CI 1.45-6.28, p = 0.003, respectively).[71] Finally, Fowler et al. characterized the remaining factors including presence of foreign devices (OR 1.77, 95% CI 1.01-3.11, p = 0.05), positive follow-up blood culture (OR 4.94, 95% CI 3.37-7.25, p < 0.001) and persistent signs and symptoms (OR 2.00, 95% CI 1.36-2.92, p < 0.001) as important indicators of complicated SABSI.[48]

Complications and Prognosis: Approximately one–third of cases of SABSI metastasize to other sites. Risk factors for developing metastatic infections include immunosuppression [72-5], community-acquisition and the absence of an identifiable source.[76, 77] Hematogenous spread

occurs in up to 50% of SABSI cases with cardiac devices [78] and up to 34% with prosthetic joints.[79] Hematogenous spread to joints can occur in up to 10% of cases most often infecting the knee.[59]

Recurrence has been defined as the return of SABSI after completing a course of antimicrobial therapy resulting in an apparent clinical cure.[61] Recurrence encompasses both relapse and reinfection where the former is associated with the original isolate and the latter with a new *S. aureus* infection. In a study of 309 cases of SABSI, recurrence was documented in 38 patients (12.3%). Amongst the 29 patients available for further study, relapse was confirmed in 79.3% and reinfection in 20.7%. The study found that relapses were more likely to involve foreign devices and occur within 90 days of the initial infection (OR 18.2, 95% CI, 7.6– 43.6, $p < .001$).[80] Chang et al. also observed an earlier occurrence of SABSI relapse at a median of 36 days compared with reinfections at 99 days.[61]

Despite treatment with antimicrobials with *in vitro* susceptibility, all-cause mortality rates associated with SABSI are 20% or greater in high–risk populations.[9, 18, 39, 70] In patients with septic shock, all-cause mortality rates approach 50%.[81] In comparison with other infectious diseases in the US, SABSI is associated with an annual mortality rate of 2 to 10 deaths per 100,000 population [38, 82] compared with 3.0, 0.2 and 2.2 deaths per 100,000 associated with acquired immune deficiency syndrome (AIDS), tuberculosis and viral hepatitis, respectively.[83]

Risk Factors for Mortality in SABSI: Van Hal et al. conducted an extensive review of risk factors for mortality in patients with SABSI. Patient related factors associated with reduced survival were advanced age and higher Charlson Comorbidity Index score.[84] In a case control study of MRSA BSI by Tacconelli et al., all-cause mortality was significantly higher amongst those who were at least 65 years of age (36% versus 12%, OR 4.1, 95% CI 1.4-14, $p < 0.01$).[85] The Charlson Comorbidity Index score was also validated in patients with SABSI where higher scores were associated with greater mortality and values $\geq$ 3 were independent predictors of death (OR 3, 95% CI 1.3 to 5.5, $p = 0.006$).[86]

Soriano et al. investigated whether the source of SABSI was predictive of mortality. Sources were categorized into low (intravascular catheter, urinary tract, ear/nose/throat or gynecological), intermediate (skin and skin structure, bone, joint or unknown) or high risk (endovascular, lower respiratory tract, intra-abdominal or central nervous system). The study found that low risk sources were associated with a mortality rate of 5%, whereas intermediate and high-risk sources corresponded to rates of 13% and 30%, respectively.[87] The same authors conducted a subsequent study in MRSA BSI and identified that intermediate (OR 2.18, 95% CI 1.17-4.04, $p = 0.014$) and high-risk (OR 3.6, 95% CI 1.89-6.99, $p < 0.001$) sources were predictive of mortality.[88]

Other infection-related factors predictive of mortality include complicated and persistent SABSI. Lautenschalger examined outcomes between complicated and uncomplicated SABSI and found that the former was associated with a significantly higher mortality rate (40% versus 24%, p <

0.01).[59] Persistent BSI has been identified to be an independent predictor of mortality (OR 17.5, 95% CI 1.5-212, p = 0.024).[89] Similar to endocarditis and metastatic infection, persistent BSI can be viewed as a surrogate for complicated SABSI.

Acquisition of SABSI in the ICU and severity of acute illness are risk factors for mortality. A study of 334 patients with SABSI by Ammerlaan et al. identified ICU stay at onset of SABSI (OR 2.9, 95% CI 1.5-5.6, p < 0.001) and severe sepsis or septic shock (OR 2.7, 95% CI 1.5-4.8, p < 0.001) as independent predictors of 30-day mortality.[90] Since ICU stay and severity of illness are inter-related, the conclusions of these studies suggest that the severity of the SABSI, irrespective of the measure used, is an important predictor of mortality.

Several studies have reported higher mortality rates in patients with BSI associated with MRSA compared with MSSA. Despite evidence suggesting that methicillin resistance is associated with poor outcomes, case-control studies by Harbarth [91] and Park et al. [92] found no difference in mortality between MRSA BSI and MSSA BSI. A recent study by Yaw et al. also found no difference in mortality after adjusting for important prognostic factors such as age, comorbidities, severity of acute illness and metastatic infections suggesting the role of other confounding factors on the all-cause mortality rate associated with MRSA BSI.[93] These factors, in addition to treatment variables including empirical therapies without MRSA coverage and definitive therapies such as vancomycin against MRSA which is less active than beta-lactams against MSSA, could all contribute to less favourable clinical outcomes for MRSA BSI. Due to

the lack of consensus, the causal relationship between methicillin resistance and mortality remains uncertain.

Finally, several studies have suggested that increased vancomycin MICs are associated with increased mortality. In a study of 414 patients with MRSA BSI conducted by Soriano et al., a vancomycin MIC of 2 μg/mL was an independent predictor of 30-day mortality (OR 6.39, 95% CI 1.68-24.3, $p < 0.001$).[88] This study was subsequently supported by two additional studies.[94, 95] In contrast, no association between vancomycin MIC and mortality was observed in a large study of 814 cases of SABSI.[96] While the majority of studies point to increased mortality with higher vancomycin MICs, the actual role of MIC independent of other confounders remains unclear.

Healthcare and Economic Burden: A study of approximately 1000 US hospitals reported that the length of stay for patients with *S. aureus* infections was three times longer than for patients without a *S. aureus* infection (14.3 versus 4.5 days, $p < 0.001$). This study also reported a three-fold increase in treatment costs.[82] Similar observations were reported in a study by Primo et al. which documented prolonged hospital stays and significant costs in patients with SABSI. This case-control study found that patients with healthcare-associated SABSI (cases) required significantly longer hospitalization compared with patients without SABSI (controls) (48.3 versus 16.2 days, $p < 0.01$). In addition, amongst 84 cases and 84 controls, SABSI was associated with three times the hospitalization cost ($123,065 versus $40,247 US, respectively, $p < 0.01$) including 6.7 times the antibiotic cost.[97]

Treatment costs also differ between MRSA and MSSA BSI. Reed et al. examined the difference in treatment costs between MRSA and MSSA BSI suggesting that MRSA infection was associated with significantly higher cost after 12 weeks ($25,518 versus $17,354, p = 0.015).[98] Higher treatment costs were confirmed by Lodise et al. who found a 2-fold increase in the cost of hospitalization for MRSA compared with MSSA BSI ($21,577 versus $11,668, p = 0.001). Furthermore, patients with MRSA BSI had a 1.5-fold longer hospital stay (19.1 versus 14.2 days, p = 0.005).[99]

SECTION 3: TREATMENT OF SABSI

Important aspects of antibiotic therapy in the treatment of SABSI include: 1) Antibiotic selection, 2) Time to initiation, 3) Duration of therapy and 4) Antimicrobial dosing. Other adjuvant treatment measures may also be required.

1) Antimicrobial Selection

Empiric versus definitive therapy: The choice of antibiotic therapy is mainly guided by pathogen identification and susceptibility results. Patient-related factors (eg, previous antibiotics, comorbidities, allergies) as well as infection-related factors (eg, acquisition, severity of infection, concurrent infections) also can also be important in antibiotic selection.[104] Despite the global awareness to decrease the use of unnecessary antibiotics, initial broad-spectrum empiric therapy may be warranted. This is especially true for critically ill patients where there is little room for error in selecting and administering antibiotic therapy. Piperacillin/tazobactam, meropenem and ceftriaxone are examples of commonly used broad-spectrum empiric therapies with the addition of vancomycin for MRSA coverage if required. Following a Gram-stain report of Gram-positive cocci in clusters, broad-spectrum empiric therapy can be narrowed to empiric coverage for *S. aureus*. Vancomycin in combination with cloxacillin which includes optimal agents for MRSA and MSSA, respectively, is considered the best available therapy. Studies have supported this empiric combination for serious *S. aureus* infections including SABSI. Amongst high-risk patients, combination therapy has been associated with better outcomes than initial vancomycin monotherapy with de-escalation to a penicillinase-resistant penicillin such as cloxacillin or nafcillin.[105, 106]

Beta-lactams in MSSA BSI: Beta-lactam antibiotics such as cloxacillin, cefazolin, ceftriaxone, piperacillin/tazobactam and meropenem have similar bactericidal mechanisms of action against MSSA by inhibiting PBPs and disrupting peptidoglycan cell wall synthesis. MSSA susceptibility to these beta-lactam antibiotics has been inferred from the results of oxacillin testing. Since cefoxitin testing is more reliable, it is currently used as a surrogate for oxacillin. A cefoxitin MIC of $\leq$ 4 μg/ml is considered oxacillin susceptible whereas an MIC of > 6 μg/ml is indicative of oxacillin resistance.[36, 49] As discussed previously, the beta-lactam antibiotics listed above have low affinity for the modified PBP 2a in MRSA.

Cloxacillin and Cefazolin in MSSA BSI: Cloxacillin is a penicillinase-stable penicillin. As per a global surveillance study, where the majority of isolates were from North America and Europe (83.2%), the oxacillin MIC_{50} and MIC_{90} values for MSSA were $\leq$ 0.25 μg/ml and 0.5 μg/ml, respectively.[107] Cefazolin is a first generation cephalosporin, which according to the Canadian Antimicrobial Resistance Alliance (CARA) has MIC_{50} and MIC_{90} values of $\leq$ 0.5 μg/ml for MSSA.[8, 108]

Cloxacillin is the mainstay therapy for primary and secondary MSSA BSI, serious skin and skin structure infections, endocarditis, septic arthritis, osteomyelitis and pneumonia.[109] The classification of cefazolin as second-line therapy is based on *in vitro* studies showing that cefazolin is more prone to the inoculum effect of high density bacteria and beta-lactamase production. Sabath et al. examined the inoculum effect of 118 MSSA isolates on 13 penicillins and cephalosporins. The authors calculated the MIC ratio of undiluted and diluted (10^{-4})

inocula with higher values corresponding to greater vulnerability to the inoculum effect. The authors found that cloxacillin, methicillin and nafcillin were most resistant to the inoculum effect with ratios of approximately 2. Cefazolin on the other hand, was one of the most vulnerable with ratios of 16.[110] Another study by Nannini et al. examined the inoculum effect on various cephalosporins. Amongst the 85 beta-lactamase-positive *S. aureus* isolates, cephalexin was most prone to the inoculum effect with mean MIC_{50} and MIC_{90} values of 3.9 and 4.0 µg/ml, respectively, with standard inocula of 5×10^5 colony-forming units (CFU)/mL compared with values of 10.7 and 32 µg/ml with high inocula of 5×10^7 CFU/mL. Cephalothin was the next most vulnerable whereas ceftriaxone, cefuroxime and ceftobiprole were resistant to the inoculum effect.[111]

However, the *in vitro* findings of the inoculum effect with cefazolin have not been translated to human studies. Amongst the few published studies, clinical outcomes between cloxacillin and cefazolin have been similar. A retrospective study by Paul et al. evaluated the efficacy of different beta-lactam antibiotics in 498 patients with MSSA BSI. The study found that 90-day mortality did not differ between patients treated definitively with cloxacillin compared with cefazolin (OR 0.91, 95% CI 0.47-1.77, $p = 0.781$). There was also no difference in mortality amongst a subgroup of 204 patients treated empirically and definitively with these antibiotics (OR 0.81, 95% CI 0.18-3.62, $p = 0.782$).[112] Lee et al. conducted a retrospective case-control study evaluating the efficacy of nafcillin and cefazolin in 133 patients. The study found that treatment failure was similar at 4 weeks (10% versus 10%, $p > 0.99$) and 12 weeks (15% versus 15%, $p > 0.99$).[113] Despite larger clinical trials finding no difference between these antibiotics,

numerous clinical reports of endocarditis treatment failures with cefazolin have been published.[114-7] It has been suggested that the inoculum effect may compromise the efficacy of cefazolin for infections with high bacterial burden such as endocarditis, osteomyelitis, septic arthritis and pneumonia.[116] However, in situations where cloxacillin is unavailable or inappropriate due to intolerance or allergy (non-Type I), for example, cefazolin is still considered the most appropriate alternative.

Ceftriaxone in MSSA BSI: Ceftriaxone is a broad-spectrum third generation cephalosporin with relatively high MIC_{50} and MIC_{90} values of 4 μg/ml for MSSA.[118] Although ceftriaxone is used for broad-spectrum empiric therapy, its spectrum and pharmacokinetic profile has resulted in its use as definitive MSSA therapy especially in outpatient programs. The role of ceftriaxone in treating MSSA infections is controversial. [112] A few studies have reported favourable outcomes with ceftriaxone compared with cefazolin.[119-22] However these studies were often conducted in non-serious infections where favourable outcomes may have occurred irrespective of antibiotic selection. In addition, two studies compared cefazolin and ceftriaxone as outpatient therapy for MSSA infections after receiving optimal therapy in hospital.[119, 120] To truly assess the efficacy of ceftriaxone for MSSA infections, studies need to examine early selection in treating serious MSSA infections. In a retrospective study of 541 patients with MSSA BSI, Paul et al. found that empiric therapy with ceftriaxone or cefotaxime was associated with more than double the mortality compared to cloxacillin or cefazolin (OR 2.24, 95% CI 1.23-4.08, p = 0.008).[112] Inferior clinical outcomes observed with ceftriaxone may be explained by inadequate pharmacodynamics achieved with standard recommended doses. Based on estimates using

population pharmacokinetic parameters, a 2 g dose of ceftriaxone once daily in a 70 kg patient with normal renal function would be expected to yield free concentrations exceeding the MIC_{50} for *S. aureus* of 4 μg/ml approximately 69% of the time, which is well below an optimal target of 100% for serious infections like SABSI. Such suboptimal pharmacodynamics would significantly increase the risk of treatment failure. Since *S. aureus* has a high ceftriaxone MIC_{50} of 4 μg/ml, an increase in ceftriaxone's daily dose to 4 g/day would be more appropriate. Based on estimates using population pharmacokinetic parameters, a 2 g dose of ceftriaxone twice daily in a 70 kg patient with normal renal function would be expected to yield 100% fT> MIC_{50}.

Piperacillin/tazobactam and Meropenem in MSSA BSI: Piperacillin is a broad-spectrum penicillin which is combined with tazobactam, a beta-lactamase inhibitor. MSSA has piperacillin/tazobactam MIC_{50} and MIC_{90} values of $\leq$ 1 μg/ml.[118] Meropenem is a broad-spectrum carbapenem that is stable to most beta-lactamases. MSSA has meropenem MIC_{50} and MIC_{90} values of 0.12 μg/ml and 0.25 μg/ml, respectively.[118] *In vitro* and *in vivo* studies examining piperacillin/tazobactam and meropenem in MSSA BSI are lacking. These agents are assumed to be as effective as cloxacillin. The retrospective study by Paul et al. referred to above also found that empiric therapy with beta-lactam/beta-lactamase combinations was associated with a significantly higher 30-day mortality compared with cloxacillin or cefazolin (OR 2.68, 95% CI 1.23-5.85, p = 0.013). The limitation of these results, however, is that those who received the former were more seriously ill and although the authors attempted to adjust for such differences they stated that no method could fully do so.[112]

Vancomycin: Vancomycin is a glycopeptide that inhibits peptidoglycan cell wall cross-linking during cell wall synthesis which lead to slow bactericidal activity.[123] Resistance with vancomycin has been observed with vancomycin intermediate *S. aureus* (VISA) and vancomycin resistant *S. aureus* (VRSA). While VISA and VRSA have almost exclusively developed in MRSA, their resistance mechanisms are completely separate. Resistance in VISA is associated with a thickened cell wall that is rich in un-crosslinked peptidoglycan precursors (D-Ala-D-Ala) that act as decoy targets for vancomycin. Resistance in VRSA is associated with the vanA operon acquired from vancomycin-resistant *Enterococcus*. The vanA operon encodes for peptidoglycan precursors (D-Ala-D-Lac) for which vancomycin has low affinity.[124] *S. aureus* isolates with a vancomycin MIC of $\leq$ 2 μg/ml are considered vancomycin-susceptible whereas MICs of 4-8 μg/ml are considered intermediate and MICs $\geq$ 16 μg/ml are labeled resistant.[6] Both MRSA and MSSA have vancomycin MIC_{50} and MIC_{90} values of 1 μg/ml.[8, 108]

Vancomycin versus Cloxacillin or Cefazolin in MSSA BSI: Vancomycin is recommended as third-line therapy for MSSA BSI. The superiority of cloxacillin and cefazolin over vancomycin has been exemplified in several *in vitro* and *in vivo* studies. Small et al. examined 10 MSSA strains isolated from intravenous drug users with endocarditis and found that at 4 times the MIC, vancomycin was less rapidly bactericidal than nafcillin. After 24 hours, the mean reduction from the initial inoculum was 1.4 $\log_{10}$ CFU/mL ($p > 0.05$) for vancomycin compared with 2.8 $\log_{10}$ CFU/mL ($p < 0.001$) for nafcillin.[125] Guerrero et al. conducted an *in vivo* study examining the bactericidal activities of cloxacillin and vancomycin in cardiac vegetations in an experimental rabbit model of aortic endocarditis. At 24 hours, the control had a mean

inoculum of 9.86 $\pm$ 0.81 $\log_{10}$ CFU/g compared to 3.5 $\pm$ 2.18 $\log_{10}$ CFU/g with cloxacillin and 6.25 $\pm$ 1.28 $\log_{10}$ CFU/g with vancomycin. Despite cloxacillin and vancomycin being equally effective in preventing mortality in rabbits after 24 hours, cloxacillin produced a significantly greater reduction in bacterial count ($p < 0.05$). Furthermore, rabbits treated with cloxacillin had a significantly greater percentage of sterile vegetations at 24 hours (41% versus 0%, $p = 0.035$).[126]

The following are four observational studies comparing the efficacy of cloxacillin or cefazolin to vancomycin. The first was a prospective observational study by Chang et al. that evaluated risk factors for poor outcomes in 324 patients with SABSI. In a subgroup of 88 MSSA infections evaluable for bacteriologic outcomes, treatment with nafcillin was superior to vancomycin in preventing bacteriologic failure including persistent BSI or relapse (0% versus 19%, $p = 0.058$). The same study identified vancomycin treatment (OR 6.5, 95% CI 1.0-52.8, $p < 0.048$) as an independent predictor of relapse.[61] The second was a prospective observational study by Stryjewski et al. that evaluated 123 hemodialysis-dependent patients with MSSA treated with either cefazolin or vancomycin. The study found that treatment failure was significantly more common in patients receiving vancomycin (31.2% versus 13%, $p = 0.02$) despite this treatment group being younger with lower rates of metastatic complications at presentation. The same study identified vancomycin treatment (OR 3.53, 95% CI 1.15-13.45, $p = 0.04$) as an independent risk factor for treatment failure.[127] The third was a retrospective case-control study by Kim et al. that evaluated 294 patients with MSSA BSI treated with vancomycin (cases) or beta-lactams (controls). The study found that patients treated with vancomycin had a significantly higher infection-related mortality (37% versus 11%, $p = 0.01$), and once again

identified vancomycin as an independent predictor of poor outcomes including infection-related mortality (OR 3.3, 95% CI 1.2-9.5, p = 0.02).[128] Finally, a retrospective cohort study by Schweizer et al. of 267 patients with MSSA BSI found that those who received either nafcillin or cefazolin were significantly less likely to die than those treated with vancomycin (HR 0.21, 95% CI 0.09-0.47). In addition, patients who received empirical vancomycin and were subsequently switched to nafcillin or cefazolin had a 69% lower in-hospital mortality hazards compared with those who remained on vancomycin (HR 0.31, 95% CI 0.10-0.95).[129] In summary, given the available evidence that vancomycin is inferior to cloxacillin or cefazolin for serious MSSA infections, vancomycin should only be used in cases where cloxacillin and cefazolin are contraindicated.

Vancomycin in MRSA BSI: A recent report released by the CDC identified antibiotic resistance as one of the most urgent threats to human health.[130] A review by van Hal et al. examined predictors of mortality in SABSI and identified the impact of methicillin resistance on mortality.[84] It has been postulated these poor outcomes may be due to confounders such increased age and severity of illness associated with the MRSA BSI population along with fewer therapies available for treating MRSA infections.[93] Vancomycin has slow bactericidal activity with pharmacodynamics that are still being characterized. Furthermore, there are challenges in the dosing and monitoring of vancomycin to achieve pharmacodynamic targets in patients. The presence of VISA and VRSA strains within a "susceptible" population may also explain the relatively high rates of treatment failures in some patient populations.[67]

Despite its limitations, vancomycin remains the mainstay therapy for MRSA BSI as the alternatives have failed to show superiority. Fowler et al. conducted a large prospective open-label trial from 2002 to 2005 comparing standard therapy (vancomycin plus gentamicin) with daptomycin in 235 patients with SABSI and endocarditis. The study found that amongst 89 patients with MRSA infections, treatment success was similar (44.4% for daptomycin versus 31.8% for standard therapy, p = 0.28).[131] Subsequently, Moore et al. conducted a retrospective case-control study of 177 patients with MRSA BSI and vancomycin MICs of > 1 μg/ml who received either vancomycin (n = 118) or daptomycin (n = 59) therapy. The study found that treatment with vancomycin was associated with a greater 60-day mortality (20.0% versus 9%, p = 0.046) and was independently associated with clinical failure (OR 3.13, 95% CI 1.00-9.76).[132] These results were supported by a similar retrospective study conducted by Murray et al. which found that daptomycin treatment was associated with a significantly lower 30-day mortality (3.5% versus 12.9%, p = 0.047).[133] These two recent studies suggest that daptomycin therapy should be considered in some cases of MRSA BSI.

Wilcox et al. conducted an open-label non-inferiority trial comparing vancomycin with linezolid in complicated skin and skin-structure infections and catheter-related BSI. The study found that microbiological cure was similar in those with MRSA BSI treated with vancomycin or linezolid (85.7% versus 80.8%, 95% CI -26.2 to 16.5). Furthermore, end-of-treatment response was similar for the two treatments (76.2% versus 88.0%, 95% CI -10.4 to 34.0).[134] Studies comparing vancomycin with TMP/SMX in the treatment of MRSA are limited. An early randomized, double-blind trial conducted by Markowitz et al. compared vancomycin with TMP/SMX in 101

patients with *S. aureus* infections, with SABSI in most cases. The study found that patients treated with TMP/SMX had a lower clinical success rate compared with those treated with vancomycin (86% versus 98%, $p < 0.02$). However, since all the failures occurred in the MSSA population, the authors suggested that TMP/SMX could be considered as an alternative in select cases of MRSA.[135] Despite this recommendation, the use of TMP/SMX in serious MRSA infections is questionable. Theoretically, thymidine release from damaged cells could reduce the activity of folate antagonists.[136] Compared with vancomycin monotherapy, the addition of rifampin has not been shown to improve the clinical outcomes of MRSA native valve endocarditis.[137, 138] Telavancin has been effective in MRSA endocarditis animal models and some case reports.[139, 140] Lastly, ceftaroline, a fifth generation cephalosporin with activity against MRSA, has shown the ability to reduce vegetations comparable to vancomycin in a rabbit endocarditis model but human studies are lacking.[141] In the absence of better alternatives, vancomycin remains the best available therapy for MRSA BSI.

Linezolid in MRSA BSI: Linezolid is an oxazolidinone that binds to the 23S ribosomal RNA of the 50S subunit, thereby inhibiting protein synthesis resulting in bacteriostasis. Although rare, resistance mechanisms including changes at the 23S ribosomal RNA binding site have been identified.[124] *S. aureus* isolates with linezolid MICs $\leq$ 4 µg/ml are considered susceptible whereas isolates with MICs $\geq$ 8 µg/ml are reported as resistant.[6] *S. aureus* has linezolid MIC_{50} and MIC_{90} values of 2 µg/ml.[8, 108]

Linezolid monotherapy does not have a role in MRSA BSI. Results from available *in vitro* and *in vivo* studies have been mixed. Despite large studies supporting linezolid use in MRSA pneumonia and skin and skin structure infections [142, 143], evidence for linezolid in MRSA BSI is lacking. As such, the Infectious Diseases Society of America (IDSA) has recommended linezolid to be used only in salvage therapy for MRSA BSI.[66] *In vitro* studies have shown that unlike the bactericidal effects of glycopeptides and daptomycin, linezolid has bacteriostatic activity.[144] In contrast, an *in vivo* study of rabbit endocarditis reported that linezolid achieved similar reductions in bacterial counts compared with vancomycin and suggested that linezolid may be an alternative to vancomycin in the treatment of serious MRSA infections.[145] Despite positive outcomes with this *in vivo* study, numerous treatment failures have been observed in MRSA BSI and endocarditis.[146-8] The role of linezolid-based salvage therapy for MRSA BSI has been investigated in a retrospective observational study of 35 patients with persistent MRSA BSI. This study showed that linezolid with or without a carbapenem was associated with better microbiological responses and survival rates than vancomycin-based salvage therapy with an aminoglycosides or rifampin.[149]

Daptomycin in MRSA BSI: Daptomycin is a lipopeptide that rapidly depolarizes the bacterial cell membrane and causes cell death. There is evidence of cross-resistance with vancomycin where cases with prior exposure to vancomycin and elevated vancomycin MICs are associated with increased daptomycin MICs.[66, 124] *S. aureus* isolates with an MIC $\leq$ 1 µg/ml are considered daptomycin-susceptible. No breakpoint has been set for daptomycin resistance.[6] *S. aureus* has daptomycin MIC_{50} and MIC_{90} values of 0.25 and 0.5 µg/ml, respectively.[8, 108]

Daptomycin has been recommended as an alternative to vancomycin in MRSA BSI.[66] Daptomycin has been shown to be more rapidly bactericidal compared with vancomycin in *in vitro* studies.[144] These results were confirmed in an in *vivo* study of rabbit MRSA endocarditis, which found that daptomycin was more effective in reducing bacterial vegetation density and sterilizing vegetations.[150] While two recent studies showed more favourable outcomes with daptomycin in cases with vancomycin MICs > 1 μg/ml, such findings are limited by their retrospective design. Furthermore, there is considerable evidence regarding the development of resistance during daptomycin therapy. [223, 224] In conclusion, further studies are needed to elucidate the role of daptomycin in MRSA BSI.

2) Time to Initiation

A study by Kumar et al. showed that in patients with septic shock, each hour of delay in antibiotic therapy in the 6 hours following hypotension onset corresponded to a 7.6% decrease in survival.[100] The importance in prompt initiation of antibiotic therapy has been highlighted in the SABSI population. A retrospective study in 1998 by Conterno et al. examined the influence of antibiotic initiation on 14-day mortality amongst 116 patients with SABSI (MSSA or MRSA). Early and delayed treatments were defined as antibiotics with *in vitro* susceptibility initiated within, or after 48 hours of the index blood culture draw, respectively. The study found that delayed treatment was significantly associated with increased 14-day mortality (57.1% versus 29.7%, $p = 0.02$).[199] Subsequently, Lodise et al. conducted a similar study of 167 patients with SABSI (MSSA or MRSA). Early and delayed treatment were defined as antibiotics with *in vitro* susceptibility initiated within, or after 44.75 hours of the index blood culture draw. The study

found that delayed treatment was associated with a higher infection-related mortality rate compared with early treatment (33.3% versus 20.2%, p = 0.05).[101] The critical need for prompt antibiotic therapy was addressed in two additional studies of MRSA BSI where early treatment was defined as initiation of antibiotics with *in vitro* susceptibility within 48 hours of the index blood culture draw. The first, a retrospective study of 510 cases by Paul et al. found that delayed treatment was associated with a mortality of 49.1% compared with 33.3% (p= 0.001).[102] Marchaim et al. also observed a significantly higher mortality when antibiotics were initiated after 48 hours in a case-control study of 202 patients who were 65 years of age and older (OR 2.35, 95% CI 1.01-5.44, p = 0.047).[103]

3) Duration of Antibiotic Therapy

The recommended duration of antibiotic therapy is dependent on the severity of the infection. For uncomplicated SABSI, a treatment duration of at least 2-3 weeks has been suggested.[66, 188] Subsequent to these recommendations, Chong et al. evaluated treatment duration (< versus $\underline{\geq}$ 14 days) in a prospective study of 111 patients with uncomplicated SABSI. Although there were no differences in treatment failure or all-cause mortality rates between short-course [median 8.5 days (IQR 7, 11)] and longer courses of therapy [median 16 days (IQR 14, 21)], the former was associated with more relapse infections (7.9% versus 0%, p = 0.036).[189]

Patients with endocarditis-related SABSI have a high bacterial load (up to 10^9 CFU/g of tissue) within their valvular vegetations and may remain febrile for 5 to 7 days after institution of antibiotic therapy.[190] As such, prolonged therapy is critical. Depending on the type and extent

of the infection, complicated SABSI should be treated for at least 4 to 6 weeks.[66] This recommendation was based on studies examining streptococcal endocarditis where a 2-week course was associated with approximately 20% relapse rate [192] and a 4-week course was associated with no relapse.[191] The necessity for longer treatment duration in complicated cases was reinforced in a study by Dimar et al., which showed that in patients with *S. aureus* vertebral osteomyelitis, a 6-week antibiotic course following surgical debridement and fusion was associated with full resolution and no recurrence.[193]

4) Antibiotic Dosing

Intravenous versus oral therapy: Even with *in vitro* susceptibility, oral antibiotics are often faced with issues of decreased bioavailability and administration of lower doses compared with their intravenous counterparts (eg, cloxacillin, cephalexin). As such, oral antibiotics are associated with delayed antibiotic exposure and lower drug concentrations.[151] Due to achievement of suboptimal pharmacodynamics with oral antibiotics and the severity of SABSI, initial treatment should only be with parenteral therapy.

The role of oral therapy in uncomplicated SABSI remains uncertain. The *Staphylococcus aureus* Bacteremia Antibiotic Treatment Options (SABATO) trial is currently underway to investigate the role of oral therapy in uncomplicated SABSI. This trial aims to demonstrate that an early switch from intravenous to oral therapy is non-inferior to the conventional 14-day intravenous therapy, with benefits of earlier discharge, fewer adverse reactions and increased quality of life and cost savings.[152]

General pharmacokinetics, pharmacodynamics and dosing: Knowledge of antimicrobial pharmacokinetics and pharmacodynamics are critical in determining optimal antimicrobial dosing. Population pharmacokinetic data of cloxacillin, cefazolin, ceftriaxone, piperacillin/tazobactam, meropenem, vancomycin, linezolid and daptomycin are provided in Table 1.[109,167-85] Recommended parenteral doses for cloxacillin, cefazolin, ceftriaxone, piperacillin/tazobactam, meropenem, vancomycin, linezolid and daptomycin are provided in Table 2.[109, 167-73]

Three types of pharmacodynamic parameters are used to predict *in vitro* activity and *in vivo* efficacy: 1) % free time above the MIC (%fT > MIC), 2) free peak concentration divided by the MIC (free C_{max}/MIC) and 3) area under the concentration–time curve over 24 hours divided by the MIC (AUC_{24}/MIC).

Anti-staphylococcal beta-lactam antibiotics that correspond best with %fT > MIC include cloxacillin, cefazolin, ceftriaxone, piperacillin/tazobactam and meropenem. Minimal improvements in bactericidal activity are observed when concentrations are increased beyond the point of maximal killing (approximately 4 times the MIC). Rather, greater bacterial kill is associated with increasing the time that free concentrations exceed the MIC.[151] %fT > MIC can be maximized with various administration methods including increased dosing frequency, prolonged or continuous infusion. For serious infections, a %fT > MIC of 75-100% should be achieved, with the optimal aim of 100% for SABSI.[153-5]

The clinical study of cloxacillin dosing and pharmacodynamics is limited. One study by Jensen et al. evaluated dicloxacillin dosing in 186 patients with MSSA BSI and found that daily doses of < 4 g, was a predictor of infection-related mortality (OR 3.7, 95% CI 1.3-11.2, p = 0.02).[155] This observation suggests that there may be a dose-response relationship in treating serious infections. The recommended dosing regimen for cloxacillin ranges from 2g q4-6h, however, the maximum dose of 2g q4h is preferred since it achieves superior pharmacodynamic attainment. Based on estimates using population pharmacokinetic parameters, a 2 g dose of cloxacillin given every 4 hours in a 70 kg patient with normal renal function would achieve the optimal target of 100% fT > MIC for serious infections like SABSI when the MIC_{50} for *S. aureus* $\leq$ 0.25 μg/ml. In contrast, the %fT > MIC would be reduced by 33% when dosed at 2 g q6h.

For cephalosporins, a %fT > MIC of 60-70% has been recommended to achieve maximum bactericidal effect.[156] McKinnon et al. examined the relationship between %fT > MIC and clinical outcomes for cefepime and ceftazidime, in patients with BSI and sepsis. The study found patients that maintained %fT > MIC of 100% was associated with significantly greater clinical cure (82% versus 33%, p = 0.002) and bacteriologic eradication (97% versus 44%, p < 0.001) compared with those that did not maintain %fT > MIC of 100% .[154]

Meropenem pharmacodynamic targets have been examined by Li et al. identifying that the free minimum drug concentration divided by the MIC (free C_{min}/MIC) > 5, which achieves %fT > MIC of 100%, as the most significant predictor of both clinical (OR 3.58, 95% CI 1.05-13.13, p = 0.043) and microbiological response (OR 4.36, 95% CI 1.32-15.82, p = 0.018) in patients with

lower respiratory tract infections.[157] Lastly, Ariano et al. reported a clinical response rate of 80% amongst febrile neutropenic patients with BSIs when %fT > MIC exceeded 75%.[153]

The antibiotic activity and treatment response of vancomycin, linezolid and daptomycin corresponds best with AUC_{24}/MIC. This parameter blends the importance of both concentration and time into an index of exposure.[151, 158] Current therapeutic drug monitoring guidelines for vancomycin recommend an AUC_{24}/MIC target of $\geq$ 400 based on total levels (free AUC_{24}/MIC $\geq$ 200).[159, 160] More recent studies have shown that even higher values of > 600 total (> 300 free) may be associated with better survival in critically ill patients with septic shock.[81] In the practice setting, total plasma trough concentrations are used to monitor appropriateness in dosing and achieving optimal pharmacodynamic targets. The guidelines suggest trough levels of $\geq$ 10 mg/L for preventing resistance and more aggressive targets of 15 to 20 mg/L for treating complicated infections like SABSI. The latter is used as a surrogate for attaining AUC_{24}/MIC values of $\geq$ 400 when the organism has an MIC of 1 µg/ml.[161]

Available data for linezolid suggest that a total AUC_{24}/MIC of $\geq$ 100 is associated with improved clinical outcomes [162, 163], whereas limited data for daptomycin show that total AUC_{24}/MIC ranges of 250 to 550 and 800 to 4000 correspond to bacteriostasis and 2 log bacterial kill, respectively.[164-6]

Other Adjuvant Treatment Measures

In certain scenarios, only a combination of source control and antibiotic therapy can provide clinical cure. Source control encompasses several different clinical measures to rapidly reduce the bacterial inoculum. Such measures include drainage of fluids, debridement of tissues or removal or replacement of foreign devices. Infections amenable to source control include furunculosis, mediastinitis, necrotizing soft tissue infection, intra-abdominal abscess, empyema, endocarditis and foreign device-related SABSI.[104] The importance of source control has been demonstrated in several studies.[195-7] Fowler et al. found that amongst 244 patients with intravascular device-related SABSI, patients without removal of the device were 6.5 times more likely to relapse and die (OR 6.5, 95% CI 2.1-20.2, $p < 0.01$).[195] Furthermore, Kim et al. reported that not draining or removing an eradicable focus was associated with increased mortality (OR 4.17, 95% CI 1.09-3.62, $p = 0.04$).[197]

In addition to antibiotic therapy and source control, patients with SABSI induced sepsis or septic shock may require management with hemodynamic support, mechanical ventilation, sedation or continuous renal replacement therapy (CRRT). Hemodynamic supportive therapies include fluids, vasopressors and inotropes. Rapid fluid resuscitation (eg, crystalloids, albumin solutions) is used as initial treatment for restoring perfusion. Vasopressors (eg, norepinephrine, dopamine) and inotropes (dobutamine) are used when hypoperfusion persists despite adequate fluid resuscitation. Acute respiratory failure can develop in patients with sepsis or septic shock. As such, mechanical ventilation and endotracheal intubation are used in conjunction with sedative agents (eg, propofol, midazolam) to provide comfortable airway

protection and oxygen delivery allowing the stabilization and reduction in work of breathing and the healing of injured lungs. Lastly, CRRT may be necessary in patients who develop acute kidney injury (AKI).[104]

SECTION 4: KNOWLEDGE GAPS & SIGNIFICANCE OF RESEARCH

In a review on management strategies for SABSI, Thwaites et al. states that the evidence guiding optimal management for SABSI is poor.[198] Antibiotic treatment is a dynamic process involving the interplay between antibiotic selection, initiation and duration, yet current literature examines these important aspects individually.

Several clinical studies have characterized differences among antibiotics used in the treatment of SABSI. For MSSA BSI, such investigations have shown that cloxacillin and cefazolin are superior to vancomycin.[61, 127, 129] Data also suggest that cloxacillin and cefazolin are similar in effectiveness.[112, 113] However, according to Paul et al., empiric therapy with ceftriaxone is less effective than cloxacillin or cefazolin.[112] For MRSA BSI, a prospective study suggested that daptomycin is non-inferior to vancomycin [131], whereas subsequent retrospective studies showed that daptomycin treatment may be superior in cases where vancomycin MICs are > 1 μg/ml.[132, 133] A prospective study by Khatib et al. in 2006 was the only study that attempted to use these data to broaden the definitions of antibiotic selection. "Appropriate" therapy for MRSA BSI was defined as either vancomycin or linezolid. "Optimal" therapy for MSSA BSI was defined as a beta-lactam, whereas "suboptimal" was vancomycin or other antibiotics with *in vitro* susceptibility. The study found that amongst 342 patients with SABSI, initial inappropriate or suboptimal selection was associated with a significantly higher all-cause mortality compared with appropriate/optimal selection (35.0% versus 20.9%, p = 0.02).[202]

This approach focused on only one aspect of antibiotic therapy. Antibiotic selection was evaluated irrespective of time to antibiotic initiation and duration.

Several human studies have investigated the influence of time to antibiotic initiation on clinical outcomes. Conterno et al. found that in patients with SABSI (MSSA or MRSA), the 14-day mortality rate doubled when antibiotics with *in vitro* susceptibility were initiated after 48 hours of the index blood culture draw.[199] Subsequently, Lodise et al. conducted a similar study of patients with SABSI (MSSA or MRSA) and found that antibiotics with *in vitro* susceptibility initiated after 44.75 hours had a 50% higher infection-related mortality.[101] The remaining four studies examined time to initiation of antibiotics for MRSA BSI with early and delayed treatments defined as antibiotics with *in vitro* susceptibility initiated within or after 48 hours of the index blood culture draw. Both Paul and Marchaim et al. found that initiating delayed antibiotics were associated with a significantly higher mortality rate [102, 103] In contrast, a retrospective study of 127 patients by Kim et al. reported no difference in infection-related mortality between early and delayed treatments.[200] Finally, Fang et al. also found that infection-related mortality did not differ between early and delayed treatments.[201] While considerable effort has been placed on examining time to initiation, little attention has been placed on antibiotic selection. The evaluation of antibiotic selection has been relatively general, with the majority of studies examining antibiotics with *in vitro* susceptibility. Furthermore, these studies failed to evaluate antibiotic duration.

A few recent studies assessed more than one aspect of antibiotic therapy concurrently. Nevrekar et al. conducted a retrospective study examining antibiotic selection in conjunction with time to antibiotic initiation. This study compared the effectiveness of oxacillin with cefazolin in the treatment for MSSA BSI and only included patients who received these

antibiotics within 48 hours of the index blood culture draw. By limiting initiation times to within 48 hours, antibiotic selection was evaluated more stringently compared with previous selection studies. Despite this, the study found no difference in treatment failures between oxacillin and cefazolin.[203] Miller et al. examined antibiotic selection in conjunction with duration of antibiotic therapy. This study compared the effectiveness of nafcillin with cefazolin in MSSA BSI and only included patients who received these antibiotics for at least 75% of a 14-day minimum treatment course. Here, antibiotic selection was evaluated more stringently by controlling for duration of antibiotic therapy. This study also found no difference in clinical success between nafcillin and cefazolin.[204] Although the first study by Nevrekar et al. evaluated antibiotic selection and time to initiation concurrently, duration was not taken into account. The latter study by Miller et al. assessed antibiotic selection and duration of therapy concurrently but failed to incorporate time to initiation.

In a study of MRSA BSI, Joo et al. identified early response to antibiotic therapy as the most important predictor of end-of-treatment outcome.[205] To achieve a rapid positive response, intervention with early aggressive antibiotic therapy is necessary. Despite a consensus that early and effective antibiotic therapy is crucial to patient outcomes, no studies have incorporated the significance of maintaining effective exposure during that initial timeframe.

This is the first study to comprehensively evaluate initial antibiotic treatment. By examining all three aspects of selection, time to initiation and duration of antibiotic exposure, along with standardizing initial treatment definition to within 7 days following the index blood culture

draw, key parts of treatment will not missed. This multifaceted approach will be able to examine antibiotic treatment in much greater detail compared with previous studies during the most crucial timeframe. Key treatment variables associated with improved clinical outcomes will be identified and optimal treatment strategies will be provided, all in hopes of improving the prognosis of patients with SABSI.

SECTION 5: OBJECTIVES

1) The prognosis of patients with SABSI is dependent on initial antibiotic treatment. This study seeks to comprehensively evaluate initial antibiotic treatment in the clinical setting by examining important aspects of: antibiotic selection, time to initiation, duration and exposure.
2) To examine and identify treatment-related variables associated with positive clinical outcomes so that optimal treatment strategies can be provided to improve the prognosis of patients with SABSI.

SECTION 6: HYPOTHESIS

1) Patients with SABSI are receiving suboptimal antibiotic treatment with opportunities to improve in antibiotic selection, time to initiation, duration and exposure.
2) Patients who receive suboptimal initial antibiotic treatment are at a greater risk of poor clinical outcomes compared with those who receive optimal treatment.

SECTION 7: METHODS

Study Design

A retrospective review and analysis of antibiotic treatment variables predictive of clinical outcomes was conducted in adult patients with SABSI admitted to the St. Boniface Hospital (SBH, Winnipeg, Canada) during a 5-year period from January 1, 2009 to December 31, 2013. The SBH is a tertiary care, 554-bed academic hospital, which admits approximately 25,000 patients annually. The study followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for sample size selection.[206] According to the STROBE guidelines, sample size selection could either be based on statistical calculations or be determined by the number of cases available in the research discipline during the study period. Our study followed the latter and arrived at a sample size based on the available number of SABSI cases over a 5-year period. Previous studies in the same research discipline achieved sample sizes ranging from 111 to 167.[101, 113, 205]

Approval to conduct the study was obtained from the University of Manitoba Health Research Ethics Board on January 16, 2013 (#HS160240) and from the SBH Research Review Committee on May 6, 2013 (#RRC/2013/1290).

Case Selection

Adults patients (≥ 18 years) with SABSI admitted to SBGH were identified using the blood culture database maintained by the Clinical Microbiology Laboratory. All study data were collected on a comprehensive data collection sheet (Appendix 1) and then transcribed into

Excel®. As per CDC's definition of laboratory-confirmed BSI, cases had a recognized pathogen (ie, *S. aureus*) known to cause BSI isolated from one or more blood cultures.[36] Eligible cases also required clinically significant signs and symptoms of infection including one or more of: temperature > 37.8°C, heart rate > 90 beats per minute, hypotension, respiratory rate > 20 breaths per minute, leukocytosis [white blood cells (WBC) > 11,000 cells/μL] or neutrophilia [absolute neutrophil count (ANC) > 5,400 cells/μL or percent neutrophils ≥ 80%].

Exclusion criteria included cases with early mortality within 2 days of initiating antibiotic therapy, a concurrent bloodstream pathogen other than *S. aureus* and relapsing SABSI within 3 months of completing therapy yielding an apparent clinical cure. Finally, patients undergoing chronic dialysis were excluded.

Patient Demographics and Medical History

Patient characteristics including age, gender, height, weight, BMI and creatinine clearance [207] were documented. Alcohol use, smoking status and history of intravenous drugs were also noted. The presence of comorbidities were detailed including: diabetes mellitus with or without organ damage (eg, neuropathy, retinopathy, nephropathy), congestive heart failure, ischemic heart disease, myocardial infarction, hypertension, malignancy, cerebrovascular disease, peripheral vascular disease, chronic pulmonary disease (eg, asthma, chronic bronchitis, chronic obstructive pulmonary disease), chronic kidney disease defined as serum creatinine > 265 μmol/L and without evidence of acute kidney injury as the cause of serum creatinine elevation, liver disease defined as cirrhosis or chronic hepatitis [208], connective tissue disease,

hemiplegia, peptic ulcer disease, autoimmune disease, neutropenia (ANC < 500 cells/μL), and HIV/AIDS. These data were used to calculate the Charlson Comorbidity Index, a prognostic score for mortality at one year.[209] The parameter incorporates 17 comorbid conditions with assigned scores from 1 to 6. For example, diabetes mellitus and congestive heart failure are scored 1, diabetes with end organ damage and lymphoma and leukemia are assigned 2, liver failure is assigned 3 and AIDS is assigned 6. The original study found that the summative Charlson Comorbidity Index was associated with risk of death with scores of 0, 1 to 2, 3 to 4 and $\geq$ 5 corresponding to mortality rates of 12%, 26%, 52% and 85%, respectively. In addition, a Charlson Comorbidity Index of 3 was identified as a significant threshold and risk factor for death at one year.[209] Lesens et al. validated this value in patients with SABSI where a Charlson Comorbidity Index of $\geq$ 3 was an independent predictor of mortality (OR 3, 95% CI 1.3-5.5, p = 0.006).[86]

Other relevant medical information such as the presence of foreign devices including indwelling vascular catheters, prosthetic heart valves, other cardiac devices and prosthetic joints were documented. Prior hospitalization within 3 months and surgical procedures within 30 days of admission were also noted. Antibiotic therapy for at least 5 days within 3 months of admission was retrieved from the electronic patient records (EPR), if available. Chemotherapy and other immunosuppressive therapies within 30 days of admission were also recorded.

***S. aureus* Bloodstream Infections**

All blood samples drawn during hospitalization were recorded along with the sampling sites and times. The Gram stain (ie, Gram positive cocci in clumps), pathogen identification (ie, *S. aureus*), susceptibility results and reporting times were also recorded. The acquisition of SABSI was classified as present-on-admission if the index blood culture was drawn 2 days before or on the first or second day of hospitalization and healthcare-associated if the index blood culture was drawn later.[36] The sampling time of the index blood culture draw was considered time zero and was used to determine the time to reporting microbiology results and initiating antibiotic therapy. Antibiotic susceptibilities to oxacillin, clindamycin, erythromycin, linezolid, TMP/SMX, tetracycline and vancomycin were obtained from the Clinical Microbiology Laboratory. Antibiotic susceptibilities were reported as susceptible (S), intermediate (I) or resistant (R). Susceptibility breakpoints set by the Clinical and Laboratory Standards Institute are listed in Table 3.[6]

Other concurrent *S. aureus* infections were noted including: skin and skin structure infection, endocarditis, pneumonia, UTI, osteomyelitis, meningitis and indwelling vascular catheter or other device-related infections. All other concurrent infections associated with other pathogens and identified within 7 days of the index blood culture draw were also recorded.

Clinical signs and symptoms of infection including temperature, heart rate, blood pressure, respiratory rate, WBC, ANC and percent neutrophils were documented from admission to discharge or death. Plasma creatinine, urea and albumin were also monitored during

hospitalization. Clinical status associated with infection such as ICU admission, presence of circulatory shock, respiratory failure, acute renal failure and altered mentation were documented.

The clinical data were used to calculate the Pitt Bacteremia Score, an index of acute illness. The Pitt Score was originally developed to predict mortality associated with BSIs and was subsequently validated in patients with SABSI.[210] The parameter incorporates five infection-related variables for 48 hours prior to and on the day of the index blood culture draw. The presence of fever, hypotension, mechanical ventilation, cardiac arrest and altered mental status are assigned scores ranging from 0 to 4. Hill et al. validated the Pitt Score in patients with SABSI and found cumulative scores of 0, 1, 2, 3 and $\geq$ 4 were associated with mortality rates of 12%, 13%, 31%, 42% and 68%, respectively.[210] Furthermore, the same study identified a Pitt Score of 4 as a significant threshold for infection-related mortality with scores of $\geq$ 4 associated with a relative risk for infection-related death of 5.2 (95% CI 2.9-9.5).[210] In a more recent study of MRSA BSI, a Pitt Score of $\geq$ 4 was an independent predictor of in-hospital all-cause mortality with an odds ratio of 2.9 (95% CI 1.21-7.09).[211]

Finally, SABSI was classified as complicated as defined by: endocarditis, metastatic infection (ie, pneumonia, central nervous system, pyelonephritis, bone/joint, foreign device-related), presence of a foreign device (ie, prosthetic heart valve, other cardiac device, prosthetic joint) or persistent signs and symptoms of infection beyond 3 days of antibiotic therapy. [64, 66, 68]

Treatment of *S. aureus* Bloodstream Infections

All antibiotic therapy including agent, route, dose and duration were detailed. Changes to therapy including de-escalation or step-down were also documented. Each antibiotic was categorized as optimal, adequate or inadequate in regards to treatment for SABSI. For MSSA, optimal therapy encompassed both targeted and broad antibiotics. Optimal targeted therapy was cloxacillin or cefazolin, whereas optimal broad included piperacillin/tazobactam or meropenem. Vancomycin was considered adequate therapy. Other antibiotics to which the organism had *in vitro* susceptibility (ie, azithromycin, ceftriaxone, clindamycin, linezolid) were considered inadequate, as was the initial selection of oral therapy. For MRSA, optimal therapy was defined as vancomycin. There were no antibiotic therapies defined as adequate. Again, other antibiotics to which the organism had *in vitro* susceptibility (ie, clindamycin, linezolid, TMP/SMX) and oral therapy were considered inadequate initial therapy. Daptomycin, a non-formulary alternative at the time, was not used during the study period.

A descriptive evaluation of antibiotic therapy was conducted according to: i) Antibiotic selection and time to initiation, ii) Antibiotic duration and exposure and iii) Antibiotic dosing within 7 days following the index blood culture draw.

i) Antibiotic selection and time to initiation: First, cases were reviewed for the use of any optimal targeted, optimal broad, adequate or inadequate antibiotic sometime during treatment. Only antibiotics administered for at least 24 hours were considered. The time to initiation was calculated for each antibiotic in relation to when the index blood culture was

drawn. Next, the time to each optimal targeted, optimal broad and adequate therapy were assessed individually. The data were then collated for each case to determine the earliest time to initiating any optimal (targeted or broad) therapy. Similarly, the earliest time to initiating any optimal or adequate therapy was calculated. Finally, the "time to initiation" data were assessed based on the target of within 48 hours, as identified by previous studies.[102, 103, 199-202]

In addition, a snapshot assessment of early antibiotic selection within 3 days following the index blood culture draw was conducted. As such, the best antibiotic therapy administered during 0 to 23.9 hours, 24 to 47.9 hours, and 48 to 72 hours was categorized as optimal targeted, optimal broad, adequate and inadequate. Changes in antibiotic selection over each 24-hour interval were examined.

ii) Antibiotic duration and exposure: The duration of each antibiotic selected within 7 days following the index blood culture draw was characterized. First, the duration of optimal targeted, optimal broad and adequate therapies was calculated individually. Next, the total duration of optimal (targeted or broad) therapy was determined. If therapies overlapped, for example, optimal broad given on days 1 and 2 and optimal targeted on days 2 and 3, the total duration would be 3 days. Similarly, the total duration of optimal or adequate therapy was calculated.

As a comprehensive measure of antibiotic exposure within 7 days following the index blood culture draw, a scoring system incorporating antibiotic selection and duration was developed.

The TSE (timing, selection and exposure) used ordinal ranking with higher points corresponding to more appropriate antibiotic selection and greater antibiotic exposure. Three (3) points were assigned to optimal (targeted or broad), 2 points to adequate, and 1 point to inadequate therapy. The latter was assigned 1 point with the assumption that these antibiotics, despite *in vitro* susceptibility, were inferior to optimal (3 points) or adequate (2 points) agents but superior to no therapy (0 points). Antibiotic points were assigned for whole or partial days of therapy. For example, optimal therapy would be assigned 3 for a full day (3 points x 1 day) versus 1.5 for half a day (3 points x 0.5 days) of therapy. If therapies overlapped, the best antibiotic would be counted. For example, adequate therapy given for full days on days 1, 2, 3 and 4 with optimal on days 3, 4, 5, 6 and 7 would give a TSE score of 19 (2 points x 2 days + 3 points x 5 days). The TSE score could range from a minimum of 0 (ie, no therapy) to a maximum of 21 (ie, optimal therapy for 7 days).

iii) Antibiotic dosing: Dosing of the three most common antibiotic therapies (ie, cloxacillin, cefazolin and vancomycin) were reviewed. The percentages of cases that received maximum recommended doses of cloxacillin and cefazolin within 7 days of the index blood culture draw were determined. A dose of 2 g every 4 hours was considered the maximum recommended and optimal dose for cloxacillin, whereas doses ranging from 1 to 2 g every 8 to 24 hours were considered optimal for cefazolin depending on patient characteristics such as body weight and renal function. Vancomycin dosing was assessed according to trough concentrations achieved within the first 3 days of therapy. Based on current guidelines, levels of 15-20 mg/L were considered therapeutic.

Other adjuvant or supportive therapies for SABSI and its complications such as antipyretics, intravenous fluids, vasopressors, inotropes, sedation, mechanical ventilation and CRRT were noted. Finally, all source control measures such as intravascular catheter removal, surgery, debridement and drainage were documented.

Clinical Outcomes

Clinical response was evaluated on day 3, 5 and 7 following the index blood culture draw. Full response required complete resolution of fever ($\leq$ 37.8°C), leukocytosis ($\leq$ 11,000 cells/μL), neutrophilia (< 80%) and other signs of infection (respiratory rate $\leq$ 20 breaths per minute, heart rate $\leq$ 90 beats per minute, normotensive). Partial response was defined as an improvement in these conditions without complete resolution. No response was defined as no improvement or worsening of signs and symptoms. Evidence of fever, hypotension or positive follow-up blood culture was evaluated as no response.[205, 212]

End-of-treatment clinical cure was defined as complete resolution of all signs and symptoms of infection without relapse. Treatment failure was persistent signs or symptoms of infection, positive blood culture at the end of therapy, death or relapse. The latter was defined as a positive *S. aureus* blood culture drawn within 3 months of completing antibiotic therapy. Early clinical responses on days 3, 5 and 7 were also examined as predictors of end-of-treatment response.

Mortality rates were determined as in-hospital all-cause mortality due to any cause, and infection-related mortality associated with SABSI or its complications such as septic shock, acute respiratory distress or endocarditis-related heart failure.[86] Length of hospitalization was documented.

Data Analysis

Descriptive statistics were used to characterize patient–, infection– and treatment–related variables. Variables with Gaussian distributions were presented as means and standard deviations, whereas other data were reported as medians and inter–quartile ranges.

A clinical outcome analysis was conducted to examine patient–, infection– and treatment–related variables in relation to end-of-treatment response. Patient characteristics such as age, gender, BMI and Charlson Comorbidity Index; infection characteristics such as acquisition, ICU admission, Pitt Score, presence of endocarditis and complicated classification; and treatment variables such as antibiotic selection, time to initiation, duration and exposure (ie, TSE score) were tested.

Univariate statistical comparisons were made using the two-tailed Students t–test, Mann Whitney U, Pearson Chi–square or Fisher's exact test, as appropriate. Optimal breakpoints for continuous treatment variables were identified using positive and negative predictive values derived from univariate logistic regression. Significant predictors were included in multivariable logistic regression models to assess their conditional significance and joint predictive ability.

Although a p-value of < 0.1 has been suggested as threshold for determining which variables to include in multivariate logistic regression, we were more strict with our variable selection and only included the most significant variables with a p-value of $\leq$ 0.05. Additionally, model size was limited by the number of observed events. All statistical tests were conducted using SAS version 9.3 (SAS Institute, Cary NC). Statistical analyses were conducted in consultation with a biostatistician in the George and Fay Yee Center for Healthcare Innovation at the University of Manitoba.

SECTION 8: RESULTS

Study Subjects

The process for case selection is outlined in Figure 1. A total of 352 positive *S. aureus* blood cultures were identified. Two-hundred and ninety (n = 290) were index blood cultures whereas 62 were repeat cultures. One hundred and eighteen (n = 118) cases were excluded due to hemodialysis (n = 91), early mortality (n = 14), concurrent bloodstream pathogen other than *S. aureus* (n = 12) and under 18 years of age (n = 1). Another 56 cases were excluded for incomplete medical records (n = 54) and ongoing treatment at the time of study closure (n = 2). Upon further inspection, three cases with concurrent non-*S. aureus* pneumonia were excluded since the clinical response of SABSI could not be evaluated with confidence. For the same reason, five cases with severe neutropenia due to chemotherapy were excluded. There were 108 evaluable cases of SABSI.

Patient demographics and medical history are provided in Table 4. The mean age was 66.0 $\pm$ 19.0 years with 58.3% (63/108) over 65 years. Thirty-four percent (37/108) were female. The mean weight and height were 83.6 $\pm$ 29.8 kg and 1.7 $\pm$ 0.1 m, respectively. The mean BMI was 29.2 $\pm$ 8.9 kg/m^2 with 30.9% (30/97) of cases being obese ($\geq$ 30 kg/m^2). Obesity was further categorized as class 1 (30.0 to 34.9 kg/m^2), class 2 (35.0 to 39.9 kg/m^2) and class 3 ($\geq$ 40.0 kg/m^2) with 15.5% (15/97), 7.2% (7/97) and 8.2% (8/97) of cases, respectively. The mean creatinine clearance was 62.0 $\pm$ 38.0 mL/min/1.73m^2. Smoking was documented in 21.3% (23/108) of cases and social drinking in 37.0% (40/108) of cases. Intravenous drug use was present in 3.7% (4/108) of cases; all of which presented with endocarditis.

The three most prominent comorbidities were related to cardiac disease, diabetes and cancer. Seventy-two percent (78/108) of cases had hypertension, 37.0% (40/108) had congestive heart failure, 38.0% (41/108) had ischemic heart disease and 16.7% (18/108) had a history of myocardial infarction. Diabetes mellitus was observed in 39.8% (43/108) of cases and 69.8% (30/43) of those had diabetes-associated end organ damage. Twenty percent (21/108) of patients had been diagnosed with cancer within the last 5 years including 9.3% (10/108) with a solid tumor, 6.5% (7/108) with a solid tumor and metastases, 2.8% (3/108) with lymphoma and 0.9% (1/108) with leukemia. Forty-three percent (9/21) of patients with cancer received chemotherapy within 30 days of admission. Furthermore, 18.5% (20/108) of patients had pulmonary disease, 18.5% (20/108) had cerebral vascular disease, 13.0% (14/108) had peripheral vascular disease, 11.1% (12/108) had autoimmune disease, 9.3% (10/108) had dementia, 5.6% (6/108) had liver disease, 3.7% (4/108) were hemiplegic, 2.8% (3/108) had chronic renal failure, 1.9% (2/108) had peptic ulcer disease and 0.9% (1/108) had connective tissue disease (Table 5).

The Charlson Comorbidity Index ranged from 0 to 9 with a mean of 2.7 $\pm$ 2.1 [median 2.0 (IQR 1.0, 4.0)]. Forty-five percent (49/108) of cases had scores of $\geq$ 3.0, with a predicted one year mortality rate of $\geq$ 52%. The remainder had scores of < 3.0, with a predicted mortality rate of $\leq$ 26%.

Prosthetic heart valves were present in 9.3% (10/108) of cases and 60% (6/10) of those presented with endocarditis. Prosthetic joints were documented in 1.8% (2/108) of cases.

Thirty-six percent (39/108) of cases had a hospital admission within 3 months and 17.6% (19/108) had an elective or emergency surgery within 30 days of admission. Forty-one percent (44/108) of cases had antibiotic therapy for at least 5 days within 3 months of admission.

Eight percent (9/108) of cases reported penicillin allergy including 66.7% (6/9) with IgE mediated reactions and 33.3% (3/9) with other rashes. In addition, allergies to TMP/SMX and vancomycin were reported in 4.6% (5/108) and 1.9% (2/108) of cases, respectively. There was one case of multiple allergies to penicillin, TMP/SMX and vancomycin.

***S. aureus* Bloodstream Infections**

The median day of the index blood culture draw was 2.0 [IQR 1.0, 6.0] with 37.0% (40/108) classified as healthcare-associated infections. Gram stain results were reported 24.5 $\pm$ 13.1 hours [median 21.5 hours (IQR 18.0, 27.0)] after the index blood culture was drawn. Antibiotic susceptibility results were reported in 97.5 $\pm$ 154.2 hours [median 60.0 hours (IQR 47.9, 71.8)] (Table 6). With 85.2% (92/108) of *S. aureus* isolates reported as susceptible to oxacillin, the MRSA incidence rate in SABSI was 14.8%. All MRSA isolates were susceptible to vancomycin and linezolid. Ninety-six percent (104/108) of isolates were susceptible to tetracycline, 95.4% (103/108) were susceptible to TMP/SMX, 75.9% (82/108) were susceptible to clindamycin and 69.4% (75/108) were susceptible to erythromycin.

Sixty-three percent (68/108) of cases had one or more repeat blood cultures drawn including 32.4% (35/108) with one, 20.4% (22/108) with two, 7.4% (8/108) with three and 2.8% (3/108)

with five cultures. The mean time to the first repeat blood culture was 5.1 ± 5.9 days [median 3.5 days (IQR 1.0, 6.0)]. The times to the second, third, fourth and fifth repeat blood cultures were 11.0 [IQR 6.0, 19.0], 20.0 [IQR 12.5, 31.0], 34.0 [IQR, 27.5, 41.5], and 53.0 days [IQR 39.0, 53.5], respectively. Amongst the first repeat blood cultures, 10.3% (7/68) were positive for *S. aureus*. Only 3.0% (1/33) of second repeat cultures and none of the subsequent repeat cultures were positive for *S. aureus*

As listed in Table 7, 90.7% (98/108) of cases had one or more concurrent *S. aureus* infections including 68.5% (74/108), 18.5% (20/108) and 3.7% (4/108) with one, two or three concurrent infections, respectively. The most common infections involved skin and skin structure including surgical site (27.0%, 34/126), followed by endocarditis (15.1%, 19/126), intravascular catheter (14.3%, 18/126), urinary tract (13.5%, 17/126), bone or joint (11.9%, 15/126), pneumonia (9.5%, 12/126), central nervous system (4.7%, 6/126) and device-related infections (4.0%, 5/126).

Clinical presentation on the day the index blood culture was drawn was characterized by heart rate, respiratory rate, temperature, WBC and percent neutrophils as shown in Table 8. Seventy-eight percent (84/108) of patients were tachycardic (> 90 beats per minute) and 59.2% (64/108) were tachypneic (> 20 breaths per minute). Seventy-five percent (81/108) of patients had leukocytosis (> 11,000 cells/μL) with a mean WBC of 16,100 ± 7000 cells/μL, and 88.0% (95/108) had neutrophilia (≥ 80%). Seventy-six percent (82/108) of patients were febrile (> 37.8°C) and antipyretics (eg, acetaminophen) were administered in 62.0% (67/108) of cases.

Nineteen percent (20/108) of cases were admitted to the ICU. Inotrope or vasopressor support, mechanical ventilation and CRRT were required in 13.0% (14/108), 13.9% (15/108) and 0.9% (1/108) of cases, respectively.

The Pitt Score ranged from 0 to 16 with a mean of 1.8 $\pm$ 1.8 [median 1.0 (IQR 0.0, 3.0)]. Fifteen percent (16/108) of cases were high risk, with scores of $\geq$ 4.0 and a predicted mortality rate of $\geq$ 68%. The majority (85.2%, 92/108) had scores of < 4.0 and a predicted mortality rate of $\leq$ 42%.

The 77.8% (84/108) of cases classified as complicated SABSI are described in Figure 2. These included 22.6% (19/84) with endocarditis including six involving prosthetic heart valves, 44.0% (37/84) with metastatic infection and 6.0% (5/84) with a foreign device. The remaining complicated cases (27.4%, 23/84) had persistent signs and symptoms of infection beyond 3 days of antibiotic therapy.

Treatment of *S. aureus* Bloodstream Infections

i) Antibiotic selection and time to initiation: The use of any optimal targeted, optimal broad, adequate or inadequate antibiotic sometime during treatment is shown in Figure 3. An optimal targeted antibiotic (cloxacillin or cefazolin for MSSA, vancomycin for MRSA) was given for at least 24 hours sometime during treatment in 83.3% (90/108) of all cases. Amongst cases of MSSA BSI (n = 92), 37.0% (34/92) received an optimal broad antibiotic (piperacillin/tazobactam or meropenem) and 87.0% (80/92) received an adequate agent. Overall an optimal (targeted or

broad) antibiotic was given in 88.0% (95/108) of cases, whereas either an optimal or adequate antibiotic was given in 98.1% (106/108) of cases.

The mean time to initiating optimal targeted antibiotics was 63.9 ± 44.9 hours [median 63.8 hours (IQR 27.3, 88.0)] compared with optimal broad antibiotics at 6.9 ± 9.9 hours [median 4.5 hours (IQR 0.0, 9.6)]. The time to initiating the earliest optimal antibiotic was 42.1 ± 47.5 hours [median 24.5 hours (IQR 4.0, 71.3)]. There was a delay in the initiation of optimal targeted antibiotics, with the majority of cases (64.4%, 58/90) having initiation times after 48 hours of the index blood culture draw. The patterns of time to initiation for optimal targeted antibiotics are shown in Figure 4. In contrast to optimal targeted, optimal broad antibiotics were initiated much earlier, with the majority (82.4%, 28/34) being initiated within 12 hours (Figure 5). The pattern for initiation of earliest optimal (targeted or broad) antibiotics was more evenly distributed with approximately one-third of cases (41.1%, 39/95) initiated with 12 hours, one-third (33.7%, 32/95) from 12 to 71.9 hours and another one-third (25.3%, 24/95) at 72 hours or later (Figure 6).

The mean time to initiating adequate antibiotics was 19.3 ± 15.7 hours [median 19.0 hours (IQR 5.0, 26.5)]. The mean time to initiating the earliest optimal or adequate antibiotic was 21.6 ± 29.5 hours [median 10.0 hours (IQR 2.1, 25.9)]. The pattern of time to initiation of earliest optimal or adequate antibiotic is displayed in Figure 7. More than half of the cases were initiated within 12 hours with decreasing percentage of cases having optimal or adequate antibiotics initiated in each subsequent timeframe. Based on the previously suggested target

for antibiotic initiation, 62.1% (59/95) of cases receiving optimal (targeted or broad) antibiotics and 84.9% (90/106) of those receiving any optimal or adequate antibiotics were initiated within 48 hours of the index blood culture draw.

The snapshot assessment of early antibiotic selection within 3 days following the index blood culture draw is shown in Figure 8. At 0 to 23.9 hours, optimal antibiotics were given in 42.6% (46/108) of cases including 14.8% (16/108) optimal targeted and 27.8% (30/108) optimal broad. Adequate antibiotics were given in 25.9% (28/108), inadequate in 16.7% (18/108) and no therapy in 14.8% (16/108) of cases. At 24 to 47.9 hours, optimal antibiotic use increased to 51.9% (56/108) of cases including optimal targeted in 28.7% (31/108) and optimal broad in 23.1% (25/108). Adequate antibiotics were given in 30.6% (33/108), inadequate in 9.3% (10/108) and no therapy in 8.3% (9/108) of cases. Finally at 48 to 72 hours, optimal antibiotic use increased further to 62.0% (67/108) of cases with 49.1% (53/108) receiving optimal targeted and 13.0% (14/108) receiving optimal broad. Adequate antibiotics were given in 25.9% (28/108), inadequate in 6.5% (7/108) and no therapy in 5.6% (6/108) of cases. There was a significant change in antibiotic selection with an increase in optimal antibiotics and decrease in inadequate antibiotics or no therapy over time ($p = 0.004$). Amongst the optimal antibiotics, there was a significant increase in the proportion of targeted agents ($p < 0.0001$).

ii) Antibiotic duration and exposure: Within 7 days following the index blood culture draw, 81.5% (88/108) of cases received optimal targeted therapy for an average of 4.3 $\pm$ 1.6 days [median 4.2 days (IQR 3.3, 5.7)] (Figure 9). Optimal broad therapy given in 37.0% (34/92) of

cases was administered for an average of 2.8 ± 2.0 days [median 2.0 days (IQR 1.3, 3.9)]. Optimal therapy given in 87.0% (94/108) of cases was administered for an average of 5.0 ± 1.7 days [median 5.5 days (IQR 3.8, 6.6)]. Lastly, optimal or adequate therapy was given in 98.1%, (106/108) of cases with the total duration of 5.5 ± 1.7 days [median 6.2 days (IQR 4.7, 6.9)].

Antibiotic exposure within 7 days following the index blood culture draw as per the TSE score was 16.3 ± 4.2 [median 17.1 (IQR 13.0, 19.8)]. As shown in Figure 10, TSE scores were grouped with 6.5% (7/108), 12.0% (13/108), 14.8% (16/108), 22.2% (24/108) and 44.4% (48/108) of cases within 6 to 8.9, 9 to 11.9, 12 to 14.9, 15 to 17.9 and 18 to 21, respectively.

iii) Antibiotic dosing: There were 56 cases that received cloxacillin therapy within 7 days of the index blood culture draw. Of these, 87.5% (49/56) received the maximum recommended dose of 2 g every 4 hours within the first 24 hours of therapy.

There were 17 cases that received cefazolin within 7 days of the index blood culture draw. Cefazolin was administered at the maximum recommended or pharmacodynamically equivalent dose in 88.2% (15/17) of cases. There were two cases of suboptimal dosing where 1 g instead of 2 g was administered every 8 hours. In one case, 1 g every 8 hours was selected instead of the recommended 2 g every 12 hours. Although the former had a lower daily dose (3.0 versus 4.0 g/day), it achieved optimal pharmacodynamics as demonstrated by the predicted %fT > MIC (129% versus 103%) using a cefazolin MIC of 0.5 μg/ml.

Ninety percent (97/108) of cases received vancomycin sometime during treatment (Figure 11). Seventeen percent (16/97) of these cases did not have any troughs drawn within 3 days of initiating vancomycin therapy. This included cases that either had vancomycin discontinued early on in therapy or troughs drawn after 3 days of initiating therapy. The remaining 57.7% (56/97) had one trough drawn and another 25.8% (25/97) with two troughs. The average concentration of first vancomycin troughs was 12.3 $\pm$ 6.1 mg/L [median 11.3 mg/L (IQR 7.4, 15.0)]. Of these, 44.4% (36/81) of cases were < 10 mg/L, 29.6% (24/81) were 10 to 14.9 mg/L and only 26.0% (21/81) were $\geq$ 15 mg/L. The average concentration of second vancomycin troughs was 15.2 $\pm$ 4.7 mg/L [median 13.6 mg/L (IQR 12.9, 16.4)]. Of these, 8.0% (2/25) were < 10 mg/L, 48.0% (12/25) were 10 to 14.9 mg/L and 44.0% (11/25) were $\geq$ 15 mg/L. This represented a significant improvement in achieving therapeutic vancomycin troughs ($p = 0.003$).

Source control was performed in 38.9% (42/108) of cases. The mean time to source control was 4.6 $\pm$ 5.8 days [median 2.0 days (IQR 0.0, 7.0)]. The most common intervention was intravascular catheter removal in 40.5% (17/42) of cases followed by surgery in 26.2% (11/42), drainage in 19.0% (8/42), superficial debridement in 16.7% (7/42), device removal in 9.5% (4/42) and urinary catheter removal in 4.8% (2/42) of cases.

Clinical Outcomes of SABSI (n = 108)

As detailed in Figure 12, there was significant progression in clinical response characterized from day 3 through day 7 following the index blood culture draw ($p = 0.008$). On day 3, 31.5%

(34/108) of cases had a full response, 24.1% (26/108) had a partial response and 44.4% (48/108) had no response. On day 5, full responses increased to 45.4% (49/108) while no responses were reduced to 31.5% (34/108) of cases. The partial response rate was similar at 23.1% (25/108). On day 7, 55.6% (60/108) of cases had a full response, 15.7% (17/108) had a partial response and 28.7% (31/108) had no response. Clinical improvement was also evaluated with measures of time to afebrile and normalization of percent neutrophils. Seventy-six percent (82/108) of cases were febrile (> 37.8°C) on the day the index blood culture was drawn. Amongst these, 96.3% (79/82) became afebrile over a mean time of 4.1 $\pm$ 4.9 days [median 2.0 days (IQR 1.0, 5.0)]. Eighty-eight percent (95/108) of cases presented with neutrophilia ($\geq$ 80%). Of these, 95 cases, 73.7% (70/95) normalized over a mean time of 7.0 $\pm$ 6.8 days [median 5.0 days (IQR 3.0, 7.8)].

End-of-treatment clinical cure was documented in 70.4% (76/108) of cases with treatment failure in 29.6% (32/108) (Figure 13). Amongst those that failed, 68.8% (22/32) died due to infection, 25.0% (8/32) had persistent signs or symptoms of infection and 6.3% (2/32) relapsed.

Clinical response on days 3, 5 and 7 were predictive of end-of-treatment cure with days 5 and 7 having the best predictive performances ($p = 0.0002$, $p < 0.0001$ and $p < 0.0001$, respectively). Amongst responders on day 5, end-of-treatment cure was observed in 95.9% (47/49) compared with 49.2% (29/59) in partial or non-responders. Amongst responders on day 7, end-of-treatment cure was observed in 96.7% (58/60) compared with 37.5% (18/48) in partial or non-responders.

The in-hospital all-cause mortality rate was 22.2% (24/108) with an infection-related mortality rate of 20.4% (22/108). The mean time to death following the index blood culture draw was 21.0 $\pm$ 17.8 days [median 13.5 days (IQR 9.0, 32.0)]. The duration of hospitalization was 32.5 $\pm$ 30.4 days [median 23.0 days (IQR 12.8, 38.5)].

Univariate analyses showed that age (75.3 $\pm$ 18.2 years versus 62.0 $\pm$ 18.3 years, $p < 0.001$), Charlson Comorbidity Index (3.4 $\pm$ 1.9 versus 2.4 $\pm$ 2.0, $p = 0.01$), healthcare-associated infection (62.5% versus 26.3%, $p < 0.001$), complicated infection (93.8% versus 71.1%, $p = 0.01$) and Pitt Score (2.4 $\pm$ 2.2 versus 1.5 $\pm$ 1.6, $p = 0.02$) were significantly higher in those with end-of-treatment failure (Table 9). The proportion of cases with endocarditis (25.0% versus 14.5%, $p = 0.19$) and admitted into the ICU (28.1% versus 14.5%, $p = 0.10$) were not significantly different between clinical cures and treatment failures.

For any antibiotic selection during treatment (Table 9), optimal targeted antibiotics were more commonly used in cases with end-of-treatment cure compared with failure (89.5% versus 68.8%, $p = 0.008$). This observation also extended to optimal (targeted or broad) antibiotics (93.4% versus 75.0%, $p = 0.02$). There were no significant differences in the time to initiation of optimal targeted antibiotics (64.1 $\pm$ 46.5 versus 63.4 $\pm$ 40.6, $p = 0.95$), the earliest optimal (targeted or broad) (42.3 $\pm$ 48.6 versus 41.5 $\pm$ 45.1 hours, $p = 0.95$) or the earliest optimal or adequate (20.8 $\pm$ 27.7 versus 23.5 $\pm$ 34.0 hours, $p = 0.87$) antibiotics.

Results of the snapshot assessment of early antibiotic selection within 3 days following the index blood culture draw are also shown in Table 9. There were no significant differences in antibiotic selection during 0 to 23.9 hours (p = 0.78) or 24 to 47.9 hours (p = 0.76) between cases with end-of-treatment cure and failure. At 48 to 72 hours, however, the selection of optimal targeted antibiotics was significantly more common in cases with end-of-treatment cure compared with failure (55.3% versus 34.3%, p = 0.047).

The duration of optimal targeted antibiotic therapy within 7 days following the index blood culture draw was 3.8 $\pm$ 2.1 days in cases with end-of-treatment cure compared with 2.9 $\pm$ 2.3 in those with failure (p = 0.05). Antibiotic exposure was not significantly different with TSE scores of 16.6 $\pm$ 3.9 and 15.5 $\pm$ 4.7 in those that were cured and failed, respectively (p = 0.20) (Table 9).

Comprehensive Antibiotic Treatment Analysis and Clinical Outcomes of Complicated MSSA BSI (n = 71)

Based on the significant antibiotic treatment variables described above, a more targeted and comprehensive treatment analysis was conducted. Since my study included both MSSA and MRSA infections, the predominant subgroup of those with MSSA BSI (n = 92) were selected. Furthermore, cases with more serious and difficult-to-treat infections were identified using the established, objective definition of complicated SABSI (n = 71).

On day 3, 19.7% (14/71) of cases had a full response, 31.0% (22/71) had a partial response and 49.3% (35/71) had no response. On day 5, full response was documented in 35.2% (25/71),

partial in 29.6% (21/71) and no response in 35.2% (25/71) of cases. On day 7, 45.1% (32/71), 19.7% (14/71) and 35.2% (25/71) of cases had full, partial and no response, respectively. End-of-treatment clinical cure was documented in 63.4% (45/71) of cases with treatment failure in 36.6% (26/71) (Figure 14). Clinical response on days 3, 5 and 7 were predictive of end-of-treatment cure with day 5 and 7 having the best predictive performances ($p = 0.01$, $p < 0.0001$ and $p < 0.0001$, respectively). Amongst responders on day 5, end-of-treatment cure was observed in 96.0% (24/25) compared with 45.7% (21/46) in partial or non-responders. Amongst responders on day 7, end-of-treatment cure was observed in 96.9% (31/32) compared with 35.9% (14/39) in partial or non-responders.

Univariate analysis showed that age (73.7 $\pm$ 19.5 versus 62.4 $\pm$ 20.3 years, $p = 0.03$), Charlson Comorbidity Index (3.3 $\pm$ 2.1 versus 2.0 $\pm$ 1.8, $p = 0.007$) and healthcare-associated infection (57.7% versus 24.4%, $p = 0.005$) were significantly higher in those with end-of-treatment failure (Table 10).

For any antibiotic selection during treatment (Table 10), optimal targeted antibiotics were more commonly used in cases with end-of-treatment cure compared with failure (91.1% versus 65.4%, $p = 0.007$). This observation also extended to optimal (targeted or broad) antibiotics (93.3% versus 73.1%, $p = 0.02$).

Results of the snapshot assessment of early antibiotic selection for 3 days following the index blood culture draw are shown in Table 10. There were no significant differences in antibiotic

selection during 0 to 23.9 hours (p = 0.41) or 24 to 47.9 hours (p = 0.95) between cases with end-of-treatment cure and failure. At 48 to 72 hours, however, the selection of optimal targeted antibiotics was significantly more common in cases with end-of-treatment cure compared with failure (60.0% versus 34.6%, p = 0.04).

The total duration of any optimal or adequate therapy was 6.1 $\pm$ 1.2 days in cases with end-of-treatment cure compared with 5.0 $\pm$ 2.3 days in those with failure (p = 0.02). Cure rates were significantly higher in cases given at least 6 days of any optimal or adequate therapy (71.7%, 33/46 versus 48.0%, 12/25; p = 0.047). The duration of optimal targeted therapy within 7 days following the index blood culture draw was significantly greater in cases with end-of-treatment cure (3.9 $\pm$ 1.9 versus 2.6 $\pm$ 2.3 days, p = 0.02). Cure rates were significantly higher in cases given at least 3.9 days of optimal targeted therapy (74.4%, 29/39 versus 50.0%, 16/32; p = 0.03). Finally, cure rates were significantly higher in cases with TSE scores of at least 15.2 (72.0%, 36/50 versus 42.9%, 9/21, p = 0.02) (Table 10).

In the multivariate analysis of end-of-treatment response, patient and infection variables of Charlson Comorbidity Index and healthcare-associated infection were significant for end-of-treatment failure. Increasing age, a patient variable identified in univariate analyses (p = 0.03), was not significantly associated with end-of-treatment failure upon multivariate analysis. Continuous treatment variables of duration of optimal targeted therapy, duration of optimal or adequate therapy and TSE scores were highly correlated with each other. As such, three separate models were created to examine each treatment variable's effect on model

performance. The first model found that higher Charlson Comorbidity Index (p = 0.03), healthcare-associated infection (p = 0.024) and decreased duration of optimal targeted therapy (p = 0.025) were predictive of end-of-treatment failure. Similar results were found in the second and third models examining treatment variables of duration of optimal or adequate therapy and TSE scores, respectively (Table 12).

SECTION 9: DISCUSSION

Study Subjects

Amongst 108 cases of SABSI, the mean age was 66.0 ± 19.0 years [median 68.5 (IQR 54.8, 80.3)] and 34.3% were female. Other studies have reported patients of slightly younger age ranging from 54.2 ± 16.6 to 60.0 ± 15.8 years [61, 101, 213] and female patients comprising 30% to 40% of cases. [61, 101, 131, 189, 199, 213] Although the patients in my study had a median BMI of 28.0 kg/m^2 (IQR 24.3, 31.2), which is above the normal range (18.5 -25.0 kg/m^2), this was similar to Fowler et al.'s study population where a median BMI of 26.9 kg/m^2 (IQR 17.6, 49.7) was reported. [131]

The most common comorbidities identified in my study were cardiac disease (72.2% of cases with hypertension, 38.0% with ischemic heart disease, 37.0% with congestive heart failure, and 16.7% with a history of myocardial infarction), diabetes mellitus (39.8%) and cancer (19.5%). Cardiac disease, diabetes mellitus and cancer were also prominent in other studies of SABSI. Other studies of SABSI have reported similar rates for diabetes mellitus ranging from 22% to 37%. [61, 131, 189, 213] Despite some variations in comorbidities, the Charlson Comorbidity Index score found in my study, 2.7 ± 2.1 [median 2.0 (IQR 1.0, 4.0)], was consistent with the scores reported by several other studies. [90, 93, 189, 213-5] The mean Charlson Comorbidity Index score for my study subjects corresponds to a one-year mortality rate of 26% to 52%.

S. aureus Bloodstream Infection & Clinical Outcomes

In my study, the mean time to Gram stain reporting was 24.5 ± 13.1 hours with a median of 21.5 hours (IQR 18.0, 27.0). Furthermore, the mean time to susceptibility reporting was 97.5 ±

154.2 hours with a median of 60.0 hours (IQR 47.9, 71.8). These results are consistent with a study by Kim et al. where mean times to Gram stain and susceptibility reporting were 32.1 hours and 82.9 hours, respectively. [213] The new CDC definition of healthcare-associated infection is the same as what was previously referred to as nosocomial infection. Compared with other studies that reported rates of nosocomial SABSIs from 47% to 82%, my study had a lower rate of healthcare acquisition in 37.0% of cases. [90, 189, 213,216] While my study observed decreased MRSA rates, it was consistent with a national surveillance study which reported MRSA rates of 18.2% in 2012. [108] According to my study, 100% of the MRSA isolates were susceptible to vancomycin and linezolid. Susceptibility rates to other antibiotics such as clindamycin (75.9%), erythromycin (69.4%), tetracycline (96.3%) and TMP/SMX (95.4%) were also consistent with national surveillance data. [108]

The three most common concurrent infections identified in my study were skin and skin structure infections (27.0%), followed by endocarditis (15.1%) and intravascular catheter-associated infections (14.3%). Similar distributions of concurrent infections in patients with SABSI have been observed. [155, 199, 210, 213] The percentage of complicated SABSI cases in my study at 77.8% was consistent with the complicated SABSI rate characterized by Fowler et al. (74.0% of 235 cases). [131]

As with the Charlson Comorbidity Index, the severity of acute illness as demonstrated by the mean Pitt Score in my study, 1.8 $\pm$ 1.8 [median 1.0 (IQR 0.0, 3.0)], was consistent with those reported in other studies of SABSI. [189, 213] The mean Pitt Score for my study subjects predicted

an infection-related mortality rate of 13% to 31%. Of note, the infection-related mortality rate in my study was 20.4%, which was in line with what was predicted by the Pitt Score. Lastly, both the infection-related and all-cause mortality rates (22.2%) observed in my study were consistent with the range of 21% to 39% reported in other studies. [61, 101, 155, 199, 213]

Treatment failure rates for SABSI in the literature are variable ranging from 23% to 61%. Uncomplicated infections (eg, catheter-related) are typically associated with less treatment failure compared with complicated infections such as endocarditis. Furthermore, MRSA BSIs have a higher risk of treatment failure than MSSA infections. [127, 189, 205, 217-9] With low rates of MRSA (14.8%) and high rates of complicated infections (77.8%), my study's treatment failure rate of 29.6% fell in between the previously reported ranges.

My study set out to examine whether initial clinical response on days 3, 5 and 7 following the index blood culture draw was associated with end-of-treatment response. The predictive performance of each initial timeframe for end-of-treatment response was evaluated by examining the positive predictive (PPV) and negative predictive values (NPV). PPV is the probability or likelihood that full responders will have treatment cure whereas NPV is the probability or likelihood that partial or non-responders will experience treatment failure. My study showed that a full response on as early as day 3 was highly predictive of clinical cure as shown with the high PPVs of clinical responses on days 3 (94.1%), 5 (95.9%), and 7 (96.7%). Although a partial or no response was less predictive of treatment failure, the NPVs did increase considerably from 40.5% on day 3 to 50.9% on day 5 to 62.5% on day 7. My study

found that initial clinical response was indicative of end-of-treatment outcomes with a full response on as early as day 3 being highly predictive of clinical cure. These findings are consistent with a study of MRSA BSI by Joo et al. that identified a lack of clinical response after 3 days of starting vancomycin therapy as a strong indicator of end-of-treatment failure. [205]

Antibiotic Treatment Analysis

Previous studies have examined important aspects of antibiotic therapy separately. Studies have analyzed antibiotic selection without regard to time to initiation, duration or exposure. Others have assessed time to antibiotic initiation without considering other treatment-related variables. Furthermore, studies have analyzed duration of antibiotic therapy without accounting for what antibiotics were given, when they were initiated or how much initial exposure was maintained and uninterrupted. As discussed previously, such analyses are incomplete, omitting important confounders and leading to potentially misleading results. The novelty of my study is its a comprehensive analysis of initial treatment that includes selection, time to initiation, duration and exposure.

The snapshot assessment of early antibiotic selection in 108 SABSI cases showed that with the first day (0 to 23.9 hours) following the index blood culture draw, 14.8% of cases were not receiving antibiotic therapy while 16.7% received inadequate antibiotics. The empiric selection of ceftriaxone comprised 61.1% of these cases and 10.2% of all cases. Within the second day (24 to 47.9 hours), antibiotic selection was being streamlined as Gram stain results were reported. As such, fewer cases (8.3%) were not receiving antibiotic therapy and inadequate

antibiotics decreased to 9.3% of cases. Finally, within the third day (48 to 72 hours), as susceptibility results were being reported, 5.6% of cases still were not receiving antibiotics while inadequate antibiotics declined further to 6.5% of cases. In summary, 68.5% of cases received at least adequate therapy within the first day whereas 82.4% and 88.0% were administered such therapy within the second and third days, respectively. This snapshot assessment shows opportunities for improvement in prompt diagnosis and antibiotic initiation, as well as in antibiotic selection. While matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) offers high sensitivity and specificity and can improve the laboratory process, it does not significantly reduce time-to-results for pathogen detection and identification for SABSI. Polymerase chain reaction (PCR) based assay tests for whole blood (eg, Sepsi*FAST®*) is the only approach that currently enables pathogen detection and identification within a few hours, allowing for earlier administration of appropriate empiric therapy for *S. aureus*. [220] Despite more rapid turnaround times, this approach is resource intensive. As such, the most realistic strategy to improve early antibiotic treatment in the meantime is prompt initiation of empiric *S. aureus* coverage with cloxacillin or cefazolin plus vancomycin after Gram stain reports for Gram-positive cocci in clusters, followed by streamlining therapy to either cloxacillin or cefazolin for MSSA or vancomycin for MRSA after susceptibility reports return.

Previous studies have identified that poor antibiotic choice (eg, empiric selection with ceftriaxone/cefotaxime for MSSA BSI) and delayed antibiotic initiation (eg, after 48 hours following the index blood culture draw) were predictive of mortality. By comprehensively analyzing antibiotic treatment, during the most crucial timeframe and amongst complicated

cases, my study was able to show that antibiotic treatment along with Charlson Comorbidity Index and healthcare-associated infection were predictive of outcomes. To elaborate, my univariate analyses identified patient age, Charlson Comorbidity Index, healthcare-associated infection, duration of optimal targeted therapy, duration of optimal or adequate therapy and TSE score as factors to include in the subsequent multivariate logistic regression analysis. Since the three treatment variables were highly correlated, each was independently tested in the model. In my analysis, patient age, an established predictor of poor outcomes in other studies, fell out of the regression model, while the Charlson Comorbidity Index remained. This could be explained by the relationship between age and number of comorbid conditions with the latter showing a stronger correlation with infection-related outcomes. My first multivariate model showed that by holding variables of healthcare-associated infection and Charlson Comorbidity Index constant, with every one day increase in duration of optimal targeted therapy, the odds of end-of-treatment cure increased by 36% [1.36 (95% CI 1.04, 1.76)]. The same model also showed that by holding variables of healthcare-associated infection and duration of optimal targeted therapy constant, with every one-point increase in the Charlson Comorbidity Index score, the odds of end-of-treatment cure decreased by 27% [0.73 (95% CI 0.55, 0.97)]. Lastly, by holding Charlson Comorbidity Index and duration of optimal targeted therapy constant, present-on-admission infection was associated with almost four times greater odds of end-of-treatment cure compared with healthcare-associated infection [3.66 (95% CI 1.19, 11.30)]. The second and third models that incorporated duration of optimal or adequate therapy and TSE score, respectively, also showed similar results.

Unlike the traditional analysis, my comprehensive analysis took into account initiation times and antibiotic selection changes with their varying durations of therapy. With my more thorough analysis, I was able to characterize significant differences in therapy between clinical cures and treatment failures. These findings suggest that the treatment of complicated MSSA BSI should, at minimum, include: 1) Initiating at least adequate antibiotic therapy within 24 hours following the index blood culture draw and 2) Maintaining uninterrupted treatment, especially during the initial 7 days including at least 4 days with cloxacillin or cefazolin. The recommendations for initiating therapy within 24 hours and maintaining treatment in the initial 7 days were based on results from both univariate and multivariate analyses. Univariate analysis showed that patients who had $\geq$ 6 days of at least adequate therapy within 7 days of the index blood culture draw had significantly higher cure rates compared with those who received shorter durations of therapy (71.7% versus 48.0%, p = 0.047). Such a high threshold of 6 days suggests that the initiation and maintenance of antibiotic therapy is important. My multivariate analysis also showed that increased duration of at least adequate therapy was predictive of clinical cure. The recommendation for incorporating at least 4 days of cloxacillin or cefazolin within those 6 or more days of therapy was also based on both univariate and multivariate findings. Univariate analysis showed that patients who had $\geq$ 3.9 days of cloxacillin or cefazolin had significantly higher cure rates compared with those who received shorter durations of therapy (74.4% versus 50.0%, p = 0.03). Again, my multivariate analysis found that increased duration of cloxacillin or cefazolin was predictive of clinical cure. Upon further examination, the clinical cure rate amongst those that received the best treatment (ie, $\geq$ 6 days

of at least adequate therapy including $\geq$ 3.9 days of cloxacillin or cefazolin), was significantly higher compared with those who did not (75.8%, 25/33 versus 52.6%, 20/38, p = 0.04).

Similar to the Charlson Comorbidity Index and Pitt Score developed to assess severity of illness, the TSE score was developed to characterize the degree of antibiotic exposure within the first 7 days following the index blood culture draw. The TSE score was also able to examine inadequate exposure like ceftriaxone. My study found that higher TSE scores, which corresponded to more appropriate antibiotic selection administered for a longer duration, was associated with improved end-of-treatment response by both univariate and multivariate analyses. Univariate analysis showed that patients who had TSE scores of $\geq$ 15.2 had significantly higher cure rates compared with patients who had lower scores (72.0% versus 42.9%, p = 0.02). My multivariate analysis showed that increased TSE scores was predictive of clinical cure. With a TSE score of 15.2 identified as a breakpoint, this suggests that a 7-day exposure of ceftriaxone (7 points) within 7 days following the index blood culture draw would fall below the target for MSSA BSI, as would a 7-day exposure of vancomycin (14 points). A score of 15.2 suggests that treatment with cloxacillin or cefazolin is necessary within those first 7 days. Although this significant breakpoint is not explicit as to the optimal duration of vancomycin, cloxacillin or cefazolin therapy, a score of 15.2 would correspond to a 6-day exposure with approximately 4 days being cloxacillin or cefazolin and 2 days being vancomycin. This consistency with my previous analyses suggests that the TSE scoring system may be a useful tool in evaluating antibiotic therapy.

Limitations

Randomized controlled trials (RCT) are considered the "gold standard" for reducing the spurious causality and bias in the study of medications. However, such studies would be unethical in certain clinical situations (eg, comparing treatment outcomes of SABSI between various levels of appropriate and inappropriate antibiotic therapy). According to Ligthelm et al., observational studies are less affected by ethical considerations and are an important means of optimizing treatment decisions and enhancing patient care. [221] The retrospective observational nature of my study to evaluate antibiotic therapy in the clinical setting and identify strategies to optimize the treatment of serious infections was very fitting. As will be discussed, the significant findings and strategies as well as challenges identified in my study can help catalyze future prospective studies.

There were both advantages and disadvantages to evaluating clinical response retrospectively. Not being able to evaluate response both subjectively and objectively could have lead to misclassification of some of the cases. Not being able to evaluate response at the bedside, however, limited subjective bias and thus response was standardized to objective evaluation. Due to the lack of daily blood cultures and with only 63% of cases having one or more repeat blood cultures, evaluation of clinical response relied heavily on clinical and laboratory data (eg, temperature, percent neutrophils and blood pressure).

There were 11.1% of SABSI cases (12/108) and 7.0% (5/71) of MSSA complicated cases where patients were either discharged or had died earlier than 7 days following the index blood

culture draw. As such, there was some missing data for initial clinical response, end-of-treatment response as well as for antibiotic therapy. Since cases were stabilized prior to discharge, I assumed that the early discharges had either a partial or full response with an end-of-treatment cure. For cases that were discharged or died earlier, the duration of antibiotic therapy was adjusted by normalizing the actual duration to 7 days.

Antibiotic dosing and vancomycin trough levels were not examined in my antibiotic treatment analysis of clinical outcomes for MSSA BSI. Amongst those treated with cloxacillin or cefazolin within 7 days of the index blood culture, 87.5% (49/56) and 88.2% (15/17) received the maximum recommended doses, respectively. From this, dosing was not a significant factor in the clinical outcomes of MSSA BSI. Furthermore, the small number of MRSA BSI made an analysis of vancomycin trough levels and clinical outcomes unreliable. It would also not have been appropriate to examine associations between vancomycin levels and outcomes in the majority of MSSA cases since the treatment of MSSA involved other beta-lactam agents.

Additional limitations include the inability to fully evaluate relapse and infection-related mortality. Chang et al. prospectively monitored SABSI patients for a total of 6 months after the time of the index blood culture draw and found a relapse rate of 7.4%. In comparison, my study's relapse rate was much lower at 1.9%. This may be explained by the inability to follow up with patient records at other institutions. It was difficult to evaluate infection-related mortality due to insufficient documentation of signs and symptoms of infection at the time of death, as well as the causes of death. Furthermore infection-related mortality could not be

monitored after hospital discharge. Despite these drawbacks, the infection-related mortality rate identified in my study was consistent with the available literature. [86, 101, 199]

Previous literature has demonstrated that not draining or removing an eradicable foci was a significant predictor for relapse and mortality. [195, 197] Due to limited chart documentation on source control, my study was unable to fully evaluate both the population that received source control and the population that required but did not receive these measures. As a result, source control was not examined in univariate analysis. Furthermore, this variable was not controlled for in multivariate analyses.

Future Directions

The strategies as discussed can aid future researchers in developing an evidence-based treatment intervention that can be utilized in a prospective observational pre and post-intervention study. After propensity-matching the pre and post-intervention populations, treatment practices as well as cure rates between the two populations can be examined to see whether optimizing treatment practices can provide increased cure rates.

Similar to the Pitt Score and Charlson Comorbidity Index developed to evaluate severity of illness due to BSI and chronic comorbidities, my study developed the TSE score as an overall measure of antibiotic therapy. However, the TSE score has not been prospectively validated to predict clinical outcomes. Therefore, further work needs to be done to validate this novel and potentially valuable tool for evaluating antibiotic therapy.

Antibiotic dosing, although evaluated in my study, was not examined in great detail. The main focus of my study was to develop a method that could concurrently analyze antibiotic therapy in terms of time to initiation, selection and duration and exposure. The next step in such research is to incorporate the variable of dosing and pharmacodynamic target attainment. Pharmacodynamic target attainments can be estimated from drug level predictions and MIC assumptions based on susceptibility data. However, research needs to evolve from making inferences to measuring antibiotic plasma concentrations and pathogen MICs. This way, true pharmacodynamic exposure can be determined. Since initial antibiotic exposure may involve several antibiotic changes, there may be more than one pharmacodynamic parameter (eg, %fT > MIC and AUC_{24}/MIC) and antibiotic combination therapy to evaluate. Future research lies in examining the effects of 1) Antibiotic selection, 2) Time to initiation, 3) Duration, 4) Exposure and 5) Pharmacodynamic target attainment on treatment outcomes.

SECTION 10: CONCLUSION

A recent commentary published in the Lancet [222] stated that "Patient and management factors have the key role in patient prognosis". Since many antibiotic treatment variables are modifiable, a patient's prognosis is heavily dependent on their treatment in the clinical setting. As such, strategies to optimize antibiotic therapy are crucial. The treatment of complicated MSSA BSI at minimum should include initiating at least adequate therapy within 24 hours following the index blood culture draw and maintaining uninterrupted treatment, especially during the initial 7 days including at least 4 days with cloxacillin or cefazolin.

Given the severity of *S. aureus* infection, poor prognosis of SABSI with current therapies and absence of new antimicrobial development, it is imperative that treatment practices with available antibiotics be optimized to achieve the best patient outcomes possible.

SECTION 11: REFERENCES

(1) Holt JG et al. Bergey's Manual of Determinative Bacteriology. 9th ed. Philadelphia: Lippincott Williams & Wilkins; c1994.

(2) Barcia-Macay M. Activity of antibiotics towards extracellular and intracellular Staphylococcus aureus: Pharmacodynamic studies in vitro using a model of human THP-1 macrophages [doctoral dissertation]. [Leuven(BE)]: Université catholique de Louvain; 2007.

(3) Barber M. Methicillin-resistant staphylococci. J Clin Pathol 1961 July;14:385-393.

(4) Benner EJ and Kayser FH. Growing clinical significance of methicillin-resistant Staphylococcus aureus. Lancet 1968 Oct;2(7571):741-744.

(5) Fuda C et al. The basis for resistance to beta-lactam antibiotics by penicillin-binding protein 2a of methicillin-resistant Staphylococcus aureus. J Biol Chem 2004 Sept;279(36):40802-40806.

(6) Clinical and Laboratory Standard Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing; 24th Information Supplement (January 2014 Update) CLSI document M100-S24. Wayne, PA, USA: CLSI; 2014.

(7) Chambers HF. Community-associated MRSA--resistance and virulence converge. N Engl J Med 2005 Apr;352(14):1485-1487.

(8) Zhanel GG et al. Antimicrobial susceptibility of 22746 pathogens from Canadian hospitals: results of the CANWARD 2007–11 study. J Antimicrob Chemother 2013 May;68 Suppl 1:i7-i22.

(9) Turnridge JD et al. Staphylococcus aureus bacteraemia: a major cause of mortality in Australia and New Zealand. Med J Aust 2009 Oct 5;191(7):368–373.

(10) Clarke SR and Foster SJ. Surface adhesins of Staphylococcus aureus. Adv Microb Physiol 2006;51:187-224.

(11) Lowy F. Staphylococcus aureus infections. N Engl J Med. 1998 Aug 20;339(8) 520-532.

(12) Lina G et al. Involvement of Panton-Valentine leukocidin-producing Staphylococcus aureus in primary skin infections and pneumonia. Clin Infect Dis 1999 Nov;29(5):1128-1132.

(13) Amagai M et al. Staphylococcal exfoliative toxin B specifically cleaves desmoglein 1. J Invest Dermatol 2002 May;118(5):845-850.

(14) McCormick JK, Yarwood JM and Schlievert PM. Toxic shock syndrome and bacterial superantigens: an update. Annu Rev Microbiol 2001;55:77-104.

(15) Neth OW et al. Susceptibility to infection in patients with neutropenia: the role of the innate immune system. Br J Haematol 2005 Jun;129(6):713-722.

(16) Jacobsson G et al. Antibody responses in patients with invasive Staphylococcus aureus infections. Eur J Clin Microbiol Infect Dis 2010 Jun;29(6):715-725.

(17) Larsen MV et al. Major but differential decline in the incidence of Staphylococcus aureus bacteraemia in HIV-infected individuals from 1995 to 2007: a nationwide cohort study. HIV Med 2012 Jan;13(1):45-53.

(18) Kaech C et al. Course and outcome of Staphylococcus aureus bacteraemia: a retrospective analysis of 308 episodes in a Swiss tertiary-care centre. Clin Microbiol Infect 2006 Apr;12(4):345–352.

(19) Adam HJ et al. Prevalence of antimicrobial resistant pathogens from blood cultures from Canadian hospitals: results of the CANWARD 2007-2009 study. Diagn Microbiol Infect Dis 2011 Mar;69(3):307–313.

(20) Meade RH. Staphylococcal bacteremia and endocarditis. Circulation 1959;19:440-457.

(21) Baddour LM et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: endorsed by the Infectious Diseases Society of America. Circulation 2005 Jun 14;111(23):e394-434.

(22) Kaasch AJ et al. Use of a simple criteria set for guiding echocardiography in nosocomial Staphylococcus aureus bacteremia. Clin Infect Dis 2011 Jul 1;53(1):1-9.

(23) Nadji G et al. Comparison of clinical and morphological characteristics of Staphylococcus aureus endocarditis with endocarditis caused by other pathogens. Heart 2005 Jul;91(7):932-937.

(24) Smith PN et al. Infections with nonthoracotomy implantable cardioverter defibrillators: can these be prevented? Pacing Clin Electrophysiol 1998 Jan;21(1 Pt 1):42-55.

(25) Sohail MR et al. Risk factor analysis of permanent pacemaker infection. Clin Infect Dis 2007 Jul15;45(2):166-173.

(26) Massoure PL et al. Pacemaker endocarditis: clinical features and management of 60 consecutive cases. Pacing Clin Electrophysiol 2007 Jan;30(1):12-19.

(27) Sohail MR et al. Management and outcome of permanent pacemaker and implantable cardioverter-defibrillator infections. J Am Coll Cardiol 2007 May 8;49(18):1851-1859.

(28) Lew DP and Waldvogel FA. Osteomyelitis. N Engl J Med 1997 Apr 3;336(14):999-1007.

(29) Carek PJ, Dickerson LM and Sack JL. Diagnosis and management of osteomyelitis. Am Fam Physician 2001 Jun 15;63(12):2413-2420.

(30) Mathews CJ and Coakley G. Septic arthritis: current diagnostic and therapeutic algorithm. Curr Opin Rheumatol 2008 Jul;20(4):457-462.

(31) Goldenberg DL and Reed JI. Bacterial arthritis. N Engl J Med. 1985 Mar 21;312(12):764-771.

(32) Frazee BW, Fee C and Lambert L. How common is MRSA in adult septic arthritis? Ann Emerg Med 2009 Nov;54(5):695-700.

(33) Morgan DS et al. An 18 year clinical review of septic arthritis from tropical Australia. Epidemiol Infect. 1996 Dec;117(3):423-428.

(34) Goldenberg DL. Septic arthritis. Lancet 1998 Jan 17;351(9097):197-202.

(35) Berbari EF et al. Risk factors for prosthetic joint infection: case-control study. Clin Infect Dis 1998 Nov;27(5):1247-1254.

(36) Centers for Disease Control and Prevention (CDC). CDC/NHSN Surveillance Definitions for Specific Types of Infections Manual 2014. http://www.cdc.gov/nhsn/pdfs/pscmanual/17 pscnosinfdef_current.pdf. Retrieved on January 25, 2014.

(37) Biedenbach DJ, Moet GJ and Jones RN. Occurrence and antimicrobial resistance pattern comparisons among bloodstream infection isolates from the SENTRY Antimicrobial Surveillance Program (1997-2002). Diagn Microbiol Infect Dis 2004 Sep;50(1):59-69.

(38) Laupland KB, Ross T and Gregson DB. Staphylococcus aureus bloodstream infections: risk factors, outcomes, and the influence of methicillin resistance in Calgary, Canada, 2000-2006. J Infect Dis 2008 Aug1; 198(3):336–343.

(39) Benfield T et al. Increasing incidence but decreasing in-hospital mortality of adult Staphylococcus aureus bacteraemia between 1981 and 2000. Clin Microbiol Infect 2007 Mar;13(3):257–263.

(40) Jacobsson G et al. The epidemiology of and risk factors for invasive Staphylococcus aureus infections in western Sweden. Scand J Infect Dis 2007;39(1):6–13.

(41) Klevens RM et al. Invasive methicillin-resistant Staphylococcus aureus infections in the United States. JAMA 2007 Oct 17;298(15):1763–1771.

(42) Morin CA and Hadler JL. Population-based incidence and characteristics of community-onset Staphylococcus aureus infections with bacteremia in 4 metropolitan Connecticut areas, 1998. J Infect Dis 2001 Oct 15;184(8):1029–1034.

(43) Laupland KB et al. The changing epidemiology of Staphylococcus aureus bloodstream infection: a multinational population-based surveillance study. Clin Microbiol Infect 2013 May;19(5):465-471.

(44) Wertheim HF et al. Risk and outcome of nosocomial Staphylococcus aureus bacteraemia in nasal carriers versus non-carriers. Lancet 2004 Aug21-27;364(9435):703-705.

(45) Bert F et al. Association between nasal carriage of Staphylococcus aureus and infection in liver transplant recipients. Clin Infect Dis 2000 Nov;31(5):1295-1299.

(46) Jensen AG et al. Risk factors for hospital-acquired Staphylococcus aureus bacteremia. Arch Intern Med 1999 Jul 12;159(13):1437-1444.

(47) Steinberg JP, Clark CC and Hackman BO. Nosocomial and community-acquired Staphylococcus aureus bacteremias from 1980 to 1993: impact of intravascular devices and methicillin resistance. Clin Infect Dis 1996 Aug; 23(2):255-259.

(48) Morin CA and Hadler JL. Population-based incidence and characteristics of community-onset Staphylococcus aureus infections with bacteremia in 4 metropolitan Connecticut areas. J Infect Dis 2001; 184:1029.

(49) Lagacé-Wiens, P. (Summary of laboratory identification of Staphylococcus aureus bloodstream infections [Internet]. Message to: Zhanni Weber. 2014 Jul 25 [cited 2014 Aug 2]. [6 paragraphs].

(50) Mitchell DH and Howden BP. Diagnosis and management of Staphylococcus aureus bacteraemia. Intern Med J 2005 Dec;35 Suppl 2:S17-S24.

(51) Lee BK, Crossley K and Gerding DN. The association between Staphylococcus aureus bacteremia and bacteriuria. Am J Med 1978 Aug;65(2):303–306.

(52) Abraham J et al. Staphylococcus aureus bacteremia and endocarditis: the Grady Memorial Hospital experience with methicillin-sensitive S aureus and methicillin-resistant S aureus bacteremia. Am Heart J 2004 Mar;147(3):536-539.

(53) Fowler VG Jr et al. Role of echocardiography in evaluation of patients with Staphylococcus aureus bacteremia: experience in 103 patients. J Am Coll Cardiol 1997 Oct;30(4):1072-1078.

(54) Sullenberger AL, Avedissian LS and Kent SM. Importance of transesophageal echocardiography in the evaluation of Staphylococcus aureus bacteremia. J Heart Valve Dis 2005 Jan;14(1):23-28.

(55) Rosen AB et al. Cost-effectiveness of transesophageal echocardiography to determine the duration of therapy for intravascular catheter-associated Staphylococcus aureus bacteremia. Ann Intern Med 1999 May 18;130(10):810-820.

(56) Sochowski RA and Chan KL. Implication of negative results on a monoplane transesophageal echocardiographic study in patients with suspected infective endocarditis. J Am Coll Cardiol 1993 Jan;21(1):216-221.

(57) Reynolds HR et al. Sensitivity of transthoracic versus transesophageal echocardiography for the detection of native valve vegetations in the modern era. J Am Soc Echocardiogr 2003 Jan;16(1):67–70.

(58) Friedman ND et al. Health care--associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. Ann Intern Med 2002 Nov 19;137(10):791-797.

(59) Lautenschlager S, Herzog C and Zimmerli W. Course and outcome of bacteremia due to Staphylococcus aureus: evaluation of different clinical case definitions. Clin Infect Dis 1993 April;16(4):567-573.

60) Bishara J et al. Healthcare-associated vs. hospital-acquired Staphylococcus aureus bacteremia. Int J Infect Dis 2012 Jun;16(6):e457-463.

(61) Chang FY et al. A prospective multicenter study of Staphylococcus aureus bacteremia: incidence of endocarditis, risk factors for mortality, and clinical impact of methicillin resistance. Medicine (Baltimore) 2003 Sept;82(5):322-332.

(62) Bayer AS et al. Staphylococcus aureus bacteremia. Clinical, serologic, and echocardiographic findings in patients with and without endocarditis. Arch Intern Med 1987 Mar;147(3):457-462.

(63) Willcox PA, Rayner BL and Whitelaw DA. Community-acquired Staphylococcus aureus bacteraemia in patients who do not abuse intravenous drugs. QJM 1998 Jan;91(1):41-47.

(64) Fowler VG Jr et al. Clinical identifiers of complicated Staphylococcus aureus bacteraemia. Arch Intern Med 2003 Sept 22;163(17):2066-2072.

(65) del Rio A et al. Patients at risk of complications of Staphylococcus aureus bloodstream infection. Clin Infect Dis 2009 May 15:48 Suppl 4:S246-253.

(66) Liu C et al. Clinical practice guidelines by the infectious diseases society of america for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. Clin Infec Dis 2011 Feb 1;52(3):e18-55.

(67) Charles PG et al. Clinical features associated with bacteremia due to heterogeneous vancomycin intermediate Staphylococcus aureus. Clin Infect Dis 2004 Feb 1;38(3):448–451.

(68) Cosgrove S and Fowler VG Jr. Management of methicillin-resistant Staphylococcus aureus bacteremia. Clin Infect Dis 2008 Jun 1;46 Suppl 4:S386-393.

(69) Libert M et al. Risk factors for meticillin resistance and outcome of Staphylococcus aureus bloodstream infection
in a Belgian university hospital. J Hosp Infect 2008 Jan;68(1):17-24.

(70) Rieg S et al. Mortality of S. aureus bacteremia and infectious diseases specialist consultation-a study of 521 patients in Germany. J Infect 2009 Oct;59(4):232-239.

(71) Lin SH et al. Risk factors for mortality in patients with persistent methicillin-resistant Staphylococcus aureus bacteraemia in a tertiary care hospital in Taiwan. J Antimicrob Chemother 2010 Aug;65(8):1792-1798.

(72) Jacobson MA, Gellermann H and Chambers H. Staphylococcus aureus bacteremia and recurrent staphylococcal infection in patients with acquired immune deficiency syndrome and AIDS-related complex. Am J Med 1988 Aug;85(2):172-176.

(73) Furuno JP et al. Community-associated methicillin resistant Staphylococcus aureus bacteremia and endocarditis among HIV patients: a cohort study. BMC Infect Dis 2011 Oct 31;11:298.

(74) Ghanem GA et al. Catheter-related Staphylococcus aureus bacteremia in cancer patients: high rate of complications with therapeutic implications. Medicine (Baltimore) 2007 Jan;86(1):54-60.

(75) Gopal AK et al. Prospective analysis of Staphylococcus aureus bacteremia in nonneutropenic adults with malignancy. J Clin Oncol 2000 Mar;18(5):1110-1115.

(76) Finkelstein R et al. Staphylococcus aureus bacteremia and endocarditis: comparison of nosocomial and community-acquired infection. J Med 1984;15(3):193-211.

(77) Nolan CM and Beaty HN. Staphylococcus aureus bacteremia. Current clinical patterns. Am J Med 1976 Apr;60(4):495-500.

(78) Chamis AL et al. Staphylococcus aureus bacteremia in patients with permanent pacemakers or implantable cardioverter-defibrillators. Circulation 2001 Aug 28;104(9):1029-1033.

(79) Murdoch DR et al. Infection of orthopedic prostheses after Staphylococcus aureus bacteremia. Clin Infect Dis 2001 Feb;32(4):647-649.

(80) Fowler VG Jr et al. Recurrent Staphylococcus aureus bacteremia: pulsed field gel electrophoresis findings in 29 patients. J Infect Dis 1999 May;179(5):1157-1161.

(81) Zelenitsky SA et al. Vancomycin pharmacodynamics and survival in patients with methicillin-resistant Staphylococcus aureus-associated septic shock. Int J Antimicrob Agents 2013 Mar;41(3):255-260.

(82) Noskin GA et al. The burden of Staphylococcus aureus infections on hospitals in the United States: an analysis of the 2000 and 2001 Nationwide Inpatient Sample Database. Arch Intern Med 2005 Aug 8-22;165(15):1756–1761.

(83) Kochanek KD et al. Deaths: Final data for 2009. National vital statistics reports, vol 60 no 3. Hyattsville, MD: National Center for Health Statistics. 2012.

(84) van Hal SJ et al. Predictors of mortality in Staphylococcus aureus bacteremia. Clin Microbiol Rev 2012 Apr;25(2):362-386.

(85) Tacconelli E, Pop-Vicas AE and D'Agata EM. Increased mortality among elderly patients with meticillin-resistant Staphylococcus aureus bacteraemia. J Hosp Infect 2006 Nov;64(3):251-256.

(86) Lesens O et al. Role of comorbidity in mortality related to Staphylococcus aureus bacteremia: a prospective study using the Charlson weighted index of comorbidity. Infect Control Hosp Epidemiol 2003 Dec;24(12):890-896.

(87) Soriano A et al. Pathogenic significance of methicillin resistance for patients with Staphylococcus aureus bacteremia. Clin Infect Dis 2000 Feb;30(2):368-373.

(88) Soriano A et al. Influence of vancomycin minimum inhibitory concentration on the treatment of methicillin-resistant Staphylococcus aureus bacteremia. Clin Infect Dis 2008 Jan 15;46(2):193-200.

(89) Liao CH et al. Outcome of patients with meticillin-resistant Staphylococcus aureus bacteraemia at an emergency department of a medical centre in Taiwan. Int J Antimicrob Agents 2008 Oct;32(4):326-332.

(90) Ammerlaan H et al. Adequacy of antimicrobial treatment and outcome of Staphylococcus aureus bacteremia in 9 Western European countries. Clin Infect Dis 2009 Oct 1;49(7):997-1005.

(91) Harbarth S et al. Impact of methicillin resistance on the outcome of patients with bacteremia caused by Staphylococcus aureus. Arch Intern Med 1998 Jan 26;158(2):182–189.

(92) Park SY et al. Clinical impact of methicillin-resistant Staphylococcus aureus bacteremia based on propensity scores. Infection 2011 Apr;39(2):141–147.

(93) Yaw LK, Robinson JO and Ho KM. A comparison of long-term outcomes after methicillin resistant and meticillin-sensitive Staphylococcus aureus bacteraemia: an observational cohort study. Lancet Infect Dis 2014 Oct;14(10):967-975.

(94) Wang JL et al. Comparison of both clinical features and mortality risk associated with bacteremia due to community-acquired methicillin resistant Staphylococcus aureus and methicillin-susceptible S. aureus. Clin Infect Dis 2008 Mar 15;46(6):799–806.

(95) Takesue Y et al. Clinical characteristics of vancomycin minimum inhibitory concentration of 2 μg/ml methicillin-resistant Staphylococcus aureus strains isolated from patients with bacteremia. J Infect Chemother 2011 Feb;17(1):52–57.

(96) Schweizer ML et al. Increased mortality with accessory gene regulator (agr) dysfunction in Staphylococcus aureus among bacteremic patients. Antimicrob Agents Chemother 2011 Mar;55(3):1082–1087.

(97) Primo MG et al. Healthcare-associated Staphylococcus aureus bloodstream infection: length of stay, attributable mortality, and additional direct costs. Braz J Infect Dis 2012 Nov-Dec;16(6):503-509.

(98) Reed SD et al. Costs and outcomes among hemodialysis-dependent patients with methicillin-resistant or methicillin-susceptible Staphylococcus aureus bacteremia. Infect Control Hosp Epidemiol 2005 Feb; 26(2):175–183.

(99) Lodise TP and McKinnon PS. Clinical and economic impact of methicillin resistance in patients with Staphylococcus aureus bacteremia. Diagn Microbiol Infect Dis 2005 Jun;52(2):113-122.

(100) Kumar A et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 2006 Jun;34(6):1589-1596.

(101) Lodise TP et al. Outcomes analysis of delayed antibiotic treatment for hospital-acquired Staphylococcus aureus bacteremia. Clin Infect Dis 2003 Jun 1;36(11):1418–1423.

(102) Paul M et al. Importance of appropriate empirical antibiotic therapy for methicillin-resistant Staphylococcus aureus bacteraemia. J Antimicrob Chemother 2010 Dec;65(12):2658–2665.

(103) Marchaim D et al. Case-control study to identify factors associated with mortality among patients with methicillin-resistant Staphylococcus aureus bacteraemia. Clin Microbiol Infect 2010 Jun;16(6):747–752.

(104) Dellinger RP et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Intensive Care Med 2013 Feb;39(2):165-228.

(105) McConeghy KW, Bleasdale SC and Rodvold KA. The empirical combination of vancomycin and a β-lactam for Staphylococcal bacteremia. Clin Infect Dis. 2013 Dec;57(12):1760-1765.

(106) Lodise TP Jr et al. Impact of empirical-therapy selection on outcomes of intravenous drug users with infective endocarditis caused by methicillin-susceptible Staphylococcus aureus. Antimicrob Agents Chemother 2007 Oct;51(10):3731-3733.

(107) Fritsche TR, Sader HS and Jones RN. Antimicrobial activity of ceftobiprole, a novel anti-methicillin-resistant Staphylococcus aureus cephalosporin, tested against contemporary pathogens: results from the SENTRY Antimicrobial Surveillance Program (2005-2006). Diagn Microbiol Infect Dis 2008 May;61(1):86-95.

(108) Baxter M et al. CANWARD 2012: Antimicrobial resistance in pathogens isolated from Canadian hospital clinics, emergency rooms, medical/surgical wards and intensive cure units. Presented at: Canadian Association for Clinical Microbiology and Infectious Diseases (CACMID); 2013 Apr 4-6; Quebec City, QC, Canada.

(109) e-CPS [Internet]. Ottawa (ON): Canadian Pharmacists Association; 2005 Nov [updated 2009 Mar; cited 2014 Jul 15]. Cloxacillin [product monograph]. Available from: https://www-e-therapeutics-ca.proxy2.lib.umanitoba.ca/cps.select.preliminaryFilter.action?simplePreliminaryFilter=cloxacillin+sodium#. Also available in paper copy from the publisher.

(110) Sabath LD et al. Effect of inoculum and of beta-lactamase on the anti-staphylococcal activity of thirteen penicillins and cephalosporins. Antimicrob Agents Chemother 1975 Sept;8(3):344-349.

(111) Nannini EC et al. Determination of an inoculum effect with various cephalosporins among clinical isolates of methicillin-susceptible Staphylococcus aureus. Antimicrob Agents Chemother 2010 May;54(5):2206-2208.

(112) Paul M et al. Are all beta-lactams similarly effective in the treatment of methicillin-sensitive Staphylococcus aureus bacteraemia? Clin Microbiol Infect 2011 Oct;17(10): 1581–1586.

(113) Lee S et al. Is cefazolin inferior to nafcillin for treatment of methicillin-susceptible Staphylococcus aureus bacteremia? Antimicrob Agents Chemother 2011 Nov;55(11):5122-5126.

(114) Bryant R and Alford R. Unsuccessful treatment of Staphylococcal endocarditis with cefazolin. JAMA. 1977 Feb;237(6):569-570.

(115) Fernandez-Guerrero M and de Gorgolas M. Cefazolin therapy for Staphylococcus bacteremia. Clin Infect Dis 2005 Jul 1;41(1):127.

(116) Nannini EC, Singh KV and Murray BE. Relapse of type A beta-lactamase-producing Staphylococcus aureus native valve endocarditis during cefazolin therapy: revisiting the issue. Clin Infect Dis 2003 Nov 1;37(9):1194-1198.

(117) Quinn EL et al. Clinical experience with cefazolin and other cephalosporins in bacterial endocarditis. J Infect Dis 1973 Oct;128:Suppl:S386-391.

(118) Canadian Antimicrobial Resistance Alliance (CARA). 2012 NATIONAL Antimicrobial Susceptibility Testing Results: Staphylococcus aureus, MSSA [Internet]. Winnipeg (MB): CARA. C2007 – [cited 2014 Jun 14]. Available from: http://www.can-r.com/study.php?study=canw 2012.

(119) Wynn M et al. Evaluation of the efficacy and safety of outpatient parenteral antimicrobial therapy for infections with methicillin-sensitive Staphylococcus aureus. South Med J 2005 Jun;98(6):590-595.

(120) Winans SA, Luce AM and Hasbun R. Outpatient parenteral antimicrobial therapy for the treatment of methicillin-susceptible Staphylococcus aureus: a comparison of cefazolin and ceftriaxone. Infection 2013 Aug; 41: 769-774.

(121) Guglielmo BJ et al. Ceftriaxone therapy for staphylococcal osteomyelitis: a review. Clin Infect Dis 2000 Jan;30(1):205–207.

(122) Wieland BW et al. A retrospective comparison of ceftriaxone versus oxacillin for osteoarticular infections due to methicillin-susceptible Staphylococcus aureus. Clin Infect Dis 2012 Mar 1;54(5):585–590.

(123) Van Bambeke et al. Glycopeptide antibiotics: from conventional molecules to new derivatives. Drugs 2004;64(9):913-936.

(124) Pantosti A, Sanchini A and Monaco M. Mechanisms of antibiotic resistance in Staphylococcus aureus. Futur Microbiol 2007 Jun; 2(3):323-334.

(125) Small PM and Chambers HF. Vancomycin for Staphylococcus aureus endocarditis in intravenous drug users. Antimicrob Agents Chemother 1990 Jun;34(6):1227-1231.

(126) Fernandez Guerrero ML and de Gorgolas M. Comparative activity of cloxacillin and vancomycin against methicillin-susceptible Staphylococcus aureus experimental endocarditis. J Antimicrob Chemother 2006 Nov;58(5):1066-1069.

(127) Stryjewski ME et al. Use of vancomycin or first-generation cephalosporins for the treatment of hemodialysis-dependent patients with methicillin-susceptible Staphylococcus aureus bacteremia. Medicine (Baltimore) 2007 Jan 15;44(2):190-196.

(128) Kim S et al. Outcome of vancomycin in treatment in patients with methicillin-susceptible Staphylococcus aureus bacteremia. Antimicrob Agents Chemother 2008 Jan;52(1):192-197.

(129) Schweizer ML et al. Comparative effectiveness of nafcillin or cefazolin versus vancomycin in methicillin-susceptible Staphylococcus aureus bacteremia. BMC Infect Dis 2011 Oct 19;11:279-285.

(130) Centers for Disease Control and Prevention (CDC). Antibiotic Resistance Threats in the United States 2013. http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf. Retrieved on February 2, 2014.

(131) Fowler VG Jr et al. Daptomycin versus standard therapy for bacteremia and endocarditis caused by Staphylococcus aureus. N Engl J Med 2006 Aug 17;355(7):653-665.

(132) Moore CL et al. Daptomycin versus vancomycin for bloodstream infections due to methicillin-resistant Staphylococcus aureus with a high vancomycin minimum inhibitory concentration: a case-control study. Clin Infect Dis 2012 Jan 1;54(1):51-58.

(133) Murray KP et al. Early use of daptomycin versus vancomycin for methicillin-resistant Staphylococcus aureus bacteremia with vancomycin minimum inhibitory concentration >1 mg/L: a matched cohort study. Clin Infect Dis 2013 Jun;56(11):1562-1569.

(134) Wilcox MH et al. Complicated skin and skin-structure infections and catheter-related bloodstream infections: noninferiority of linezolid in a phase 3 study. Clin Infect Dis 2009 Jan 15;48(2):203-212.

(135) Markowitz N, Quinn EL and Saravolatz LD. Trimethoprim-sulfamethoxazole compared with vancomycin for the treatment of Staphylococcus aureus infection. Ann Intern Med 1992 Sept 1;117(5):390-398.

(136) Procter RA. Role of folate antagonists in the treatment of methicillin-resistant Staphylococcus aureus infection. Clin Infect Dis 2008 Feb 15;46(4):584-593.

(137) Levine DP, Fromm BS and Reddy BR. Slow response to vancomycin or vancomycin plus rifampin in methicillin-resistant Staphylococcus aureus endocarditis. Ann Intern Med 1991 Nov 1;115(9):674-680.

(138) Riedel DJ, Weekes E and Forrest GN. Addition of rifampin to standard therapy for treatment of native valve infective endocarditis caused by Staphylococcus aureus. Antimicrob Agents Chemother 2008 Jul;52(7):2463-2467.

(139) Madrigal AG, Basuino L and Chambers HF. Efficacy of telavancin in a rabbit model of aortic valve endocarditis due to methicillin-resistant Staphylococcus aureus or vancomycin-intermediate Staphylococcus aureus. Antimicrob Agents Chemother 2005 Aug;49(8):3163-3165.

(140) Nace H and Lorber B. Successful treatment of methicillin-resistant Staphylococcus aureus endocarditis with telavancin. J Antimicrob Chemother 2010 Jun;65(6):1315-1316.

(141) Jacqueline C et al. In vivo efficacy of ceftaroline (PPI-0903), a new broad-spectrum cephalosporin, compared with linezolid and vancomycin against methicillin-resistant and vancomycin-intermediate Staphylococcus aureus in a rabbit endocarditis model. Antimicrob Agents Chemother 2007 Sept;51(9):3397-3400.

(142) Rubinstein E et al. Linezolid (PNU-100766) versus vancomycin in the treatment of hospitalized patients with nosocomial pneumonia: a randomized, double-blind, multicenter study. Clin Infect Dis 2001 Feb 1;32(3):402-412.

143) Stevens DL et al. Linezolid versus vancomycin for the treatment of methicillin-resistant Staphylococcus aureus infections. Clin Infect Dis 2002 Jun 1;34(11):1481-1490.

(144) Huang YT et al. Comparative bactericidal activities of daptomycin, glycopeptides, linezolid and tigecycline against blood isolates of Gram-positive bacteria in Taiwan. Clin Microbiol Infect 2008 Feb;14(2):124-129.

(145) Dailey CF et al. Efficacy of linezolid in treatment of experimental endocarditis caused by methicillin-resistant Staphylococcus aureus. Antimicrob Agents and Chemother 2001 Aug;45(8):2304-2308.

(146) Ruiz ME, Guerrero IC and Tuazon CU. Endocarditis caused by methicillin-resistant Staphylococcus aureus: treatment failure with linezolid. Clin Infect Dis 2002 Oct 15;35(8):1018-1020.

(147) Sperber SJ, Levine JF and Gross PA. Persistent MRSA bacteremia in a patient with low linezolid levels. Clin Infect Dis 2003 Mar 1;36(5):675-676.

(148) Muñoz P et al. Linezolid therapy for infective endocarditis. Clin Microbiol Infect 2007 Feb;13(2):211-215.

(149) Jang HC et al. Salvage treatment for persistent methicillin-resistant Staphylococcus aureus bacteremia: efficacy of linezolid with or without carbapenem. Clin Infect Dis 2009 Aug 1;49(3):395-401.

(150) Marco F et al. Daptomycin is effective in treatment of experimental endocarditis due to methicillin-resistant and glycopeptide-intermediate Staphylococcus aureus. Antimicrob Agents Chemother 2008 Jul;52(7):2538-2543.

(151) Levison ME and Levison JH. Pharmacokinetics and pharmacodynamics of antibacterial agents. Infect Dis Clin North Am 2009 Dec;23(4):791-815.

(152) German Research Foundation; University of Cologne. Early oral switch therapy in low-risk Staphylococcus aureus bloodstream infection. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2014 Jun 27]. http://clinicaltrials.gov/show/NCT01792804 NLM Identifier: NCT01792804.

(153) Ariano RE et l. Pharmacokinetics and pharmacodynamics of meropenem in febrile neutropenic patients with bacteremia. Ann Pharmacother 2005 Jan;39(1):32-38.

(154) McKinnon P et al. Evaluation of area under the inhibitory curve (AUIC) and time above the minimum inhibitory concentration (T>MIC) as predictors of outcome for cefepime and ceftazidime in serious bacterial infections. International Journal of Antimicrobial Agents. 2008; 31(4): 345-351.

(155) Jensen AG et al. Treatment and outcome of Staphylococcus aureus bacteremia: a prospective study of 278 cases. Arch Intern Med 2002 Jan 14;162(1):25-32.

(156) Woodnut G and Berry V. Two pharmacodynamic models for assessing the efficacy of amoxicillin-clavulanate against experimental respiratory tract infections caused by strains of Streptococcus pneumoniae. Antimicrob Agents Chemother 1999 Jan;43(1):29–34.

(157) Li C et al. Clinical pharmacodynamics of meropenem in patients with lower respiratory tract infections. Antimicrob Agents Chemother 2007 May;51(5):1725-1730.

(158) Roberts JA and Lipman J. Pharmacokinetic issues for antibiotics in the critically ill patient. Crit Care Med 2009 Mar;37(3):840-851.

(159) Moise-Broder PA et al. Pharmacodynamics of vancomycin and other antimicrobials in patients with Staphylococcus aureus lower respiratory tract infections. Clin Pharmacokinet 2004;43(13):925–942.

(160) Kullar R et al. Impact of vancomycin exposure on outcomes in patients with methicillin-resistant Staphylococcus aureus bacteremia: support for consensus guidelines suggested targets. Clin Infect Dis 2011 Apr 15;52(8):975–981.

(161) Rybak M et al. Therapeutic monitoring of vancomycin in adult patients: A consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Am J Health-Syst Pharm. 2009; 66: 82-98.

(162) MacGowan AP. Pharmacokinetic and pharmacodynamic profile of linezolid in healthy volunteers and patients with Gram-positive infections. J Antimicrob Chemother 2003 May;51 Suppl2:ii17-25.

(163) Rayner CR et al. Clinical pharmacodynamics of linezolid in seriously ill patients treated in a compassionate use programme. Clin Pharmacokinet 2003;42(15):1411-1423.

(164) Louie A et al. Pharmacodynamics of daptomycin in a murine thigh model of Staphylococcus aureus infection. Antimicrob Agents Chemother 2001 Mar;45(3):845-851.

(165) Safdar N, Andes D and Craig WA. In vivo pharmacodynamics activity of daptomycin. Antimicrob Agents Chemother 2004 Jan;48(1):63-68.

(166) Dandekar PK et al. Pharmacodynamic profile of daptomycin against Enterococcus species and methicillin-resistant Staphylococcus aureus in a murine thigh infection model. J Antimicrob Chemother 2003 Sept;52(3):405-411.

(167) e-CPS [Internet]. Ottawa (ON): Canadian Pharmacists Association; 2005 Nov [updated 2009 Sept; cited 2014 Jul 15]. Cefazolin [product monograph]. https://www-e-therapeutics-ca.proxy2.lib.umanitoba.ca/cps.showMonograph.action?newSearch=true&simpleIndex=brand_generic&simpleQuery=cefazolin&brandExactMatch=false#. Also available in paper copy from the publisher.

(168) e-CPS [Internet]. Ottawa (ON): Canadian Pharmacists Association; [updated 2012 Oct; cited 2014 Jul 15]. Ceftriaxone [product monograph]. https://www-e-therapeutics-ca.proxy2.lib.umanitoba.ca/cps.showMonograph.action?newSearch=true&simpleIndex=brand_generic&simpleQuery=ceftriaxone&brandExactMatch=false#. Also available in paper copy from the publisher.

(169) e-CPS [Internet]. Ottawa (ON): Canadian Pharmacists Association; [cited 2014 Jul 15]. Piperacillin/tazobactam [product monograph]. https://www-e-therapeutics-ca.proxy2.lib.umanitoba.ca/cps.showMonograph.action?simpleQuery=Piperacillin%20Sodium/Tazobactam%20Sodium%20Powder%20for%20Injection%20(Sandoz)&simpleIndex=brand_generic&simpleMonographId=m701788&simpleMonographDin=02299623&simpleMonographNpn=&simpleMonographCphaId=&simpleMonographManufacturer=Sandoz&brandExactMatch=true&

newSearch=true. Also available in paper copy from the publisher.

(170) e-CPS [Internet]. Ottawa (ON): Canadian Pharmacists Association; 2012 Jan 24 [cited 2014 Jul 15]. Meropenem [product monograph]. https://www-e-therapeutics-ca.proxy2.lib.umanitoba.ca/cps.showMonograph.action?newSearch=true&simpleIndex=brand_generic&simpleQuery=Meropenem&brandExactMatch=false#. Also available in paper copy from the publisher.

(171) e-CPS [Internet]. Ottawa (ON): Canadian Pharmacists Association; [updated 2013 Sept; cited 2014 Jul 15]. Vancomycin [product monograph]. https://www-e-therapeutics-ca.proxy2.lib.umanitoba.ca/cps.showMonograph.action?newSearch=true&simpleIndex=brand_generic&simpleQuery=vancomycin&brandExactMatch=false#. Also available in paper copy from the publisher.

(172) http://www.sunovion.ca/monographs/cubicin.pdf. Cubist Pharmaceuticals. Cubicin (daptomycin for injection) Product Monograph. Lexington, MA; 2003 Sept.

(173) http://www.pfizer.ca/en/our_products/products/monograph/143. Pfizer Canada. Zyvoxam (linezolid injection) Product Monograph. Kirkland, QC; 2013 Dec.

(174) Kalman D and Barriere SL. Review of the pharmacology, pharmacokinetics, and clinical use of cephalosporins. Tex Heart Inst J 1990;17(3):203-215.

(175) Solomkin JS et al. Ertapenem versus piperacillin/tazobactam in the treatment of complicated intraabdominal infections: results of a double-blind, randomized comparative phase III trial. Ann Surg 2003 Feb;237(2):235-245.

(176) Schmitt DV et al. Piperacillin/tazobactam vs imipenem/cilastatin in the treatment of nosocomial pneumonia--a double blind prospective multicentre study. Infection 2006 Jun;34(3):127-134.

(177) Bow EJ et al. A randomized, open-label, multicenter comparative study of the efficacy and safety of piperacillin-tazobactam and cefepime for the empirical treatment of febrile neutropenic episodes in patients with hematologic malignancies. Clin Infect Dis 2006 Aug 15;43(4):447-459.

(178) Lipsky BA et al. Ertapenem versus piperacillin/tazobactam for diabetic foot infections (SIDESTEP): prospective, randomised, controlled, double-blinded, multicentre trial. Lancet 2005 Noc 12;366(9498):1695-1703.

(179) Bryson HM and Brogden RN. Piperacillin/tazobactam. A review of its antibacterial activity, pharmacokinetic properties and therapeutic potential. Drugs 1994 Mar;47(3):506-535.

(180) Mouton JW and Michel MF. Pharmacokinetics of meropenem in serum and suction blister fluid during continuous and intermittent infusion. J Antimicrob Chemother 1991 Dec;28(6):911-918.

(181) Mouton JW and van den Anker JN. Meropenem clinical pharmacokinetics. Clin Pharmacokinet 1995 Apr;28(4):275-286.

(182) Drusano GL and Hutchison M. The pharmacokinetics of meropenem. Scand J Infect Dis Suppl 1995;96:11-16.

(183) James JK et al. Comparison of conventional dosing versus continuous-infusion vancomycin therapy for patients with suspected or documented gram-positive infections. Antimicrob Agents Chemother 1996 Mar;40(3):696-700.

(184) Wysocki M et al. Continuous versus intermittent infusion of vancomycin in severe Staphylococcal infections: prospective multicenter randomized study. Antimicrob Agents Chemother 2001 Sept;45(9):2460-2467.

(185) Finch RG et al. Antibiotic and Chemotherapy: Anti-Infective Agents and Their Use in Therapy (8th ed). 2003, Edinburgh: Churchill Livingstone.

(186) Benvenuto M et al. Pharmacokinetics and tolerability of daptomycin at doses up to 12 milligrams per kilogram of body weight once daily in healthy volunteers. Antimicrob Agents Chemother 2006 Oct;50(10):3245-3249.

(187) Figueroa DA et al. Safety of high-dose intravenous daptomycin treatment: three-year cumulative experience in a clinical program. Clin Infect Dis 2009 Jul 15;49(2):177-180.

(188) Mermel LA et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. Clin Infect Dis 2009 Jul 1;49(1):1-45.

(189) Chong YP et al. Treatment duration for uncomplicated Staphylococcus aureus bacteremia to prevent relapse: analysis of a prospective observational cohort study. Antimicrob Agents Chemother 2013 Mar;57(3):1150-1156.

(190) Durack DT and Beeson PB. Experimental bacterial endocarditis. II. Survival of a bacteria in endocardial vegetations. Br J Exp Pathol 1972 Feb;53(1):50-53.

(191) Karchmer AW et al. Single-antibiotic therapy for streptococcal endocarditis. JAMA 1979 Apr;241(17):1801-1806.

(192) Hamburger M and Stein L. Streptococcus viridans subacute bacterial endocarditis; two week treatment schedule with penicillin. J Am Med Assoc 1952 Jun 7;149(6):542-545.

(193) Dimar JR et al. Treatment of pyogenic vertebral osteomyelitis with anterior debridement and fusion followed by delayed posterior spinal fusion. Spine. 2004 Feb 1;29(3):326-332.

(194) Falcone M et al. Considerations for higher doses of daptomycin in critically ill patients with methicillin-resistant Staphylococcus aureus bacteremia. Clin Infect Dis 2013 Dec;57(11):1568-1576.

(195) Fowler VG Jr et al. Outcome of Staphylococcus aureus bacteremia according to recommendations of infectious diseases specialists: experience with 244 patients. Clin Infect Dis 1998 Sep;27(3):478-486.

(196) Lalani T et al. Analysis of the impact of early surgery on in-hospital mortality of native valve endocarditis: use of propensity score and instrumental variable methods to adjust for treatment-selection bias. Circulation 2010 Mar 2;121(8):1005-1013.

(197) Kim SH et al. Outcome of Staphylococcus aureus bacteremia in patients with eradicable foci versus noneradicable foci. Clin Infect Dis 2003 Sep 15;37(6):794-799.

(198) Thwaites GE et al. Clinical management of Staphylococcus aureus bacteraemia. Lancet Infect Dis 2011 Mar;11(3):208-222.

(199) Conterno LO, Wey SB and Castelo A. Risk factors for mortality in Staphylococcus aureus bacteremia. Infect Control Hosp Epidemiol 1998 Jan;19(1):32-37.

(200) Kim SH et al. Outcome of inappropriate initial antimicrobial treatment in patients with methicillin-resistant Staphylococcus aureus bacteremia. J Antimicrob Chemother 2004 Aug;54(2):489-497.

(201) Fang CT et al. Early empirical glycopeptide therapy for patients with methicillin-resistant Staphylococcus aureus bacteremia: impact on the outcome. J Antimicrob Chemother 2006 Mar;57(3):511-519.

(202) Khatib R et al. Impact of initial antibiotic choice and delayed appropriate treatment on the outcome of Staphylococcus aureus bacteremia. Eur J Clin Microbiol Infect Dis 2006 Mar;25(3):181-185.

(203) Nevrekar S et al. Evaluation of treatment outcomes of cefazolin (CEZ) versus oxacillin (OXA) for methicillin-sensitive Staphylococcus aureus (MSSA) bloodstream infections (BSI): a multicenter observational study. Presented at: 54th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); 2014 Sept 5-9; Washington, DC, USA.

(204) Miller M et al. Comparison of treatment outcomes and safety with nafcillin or cefazolin for the management of methicillin-sensitive Staphylococcus aureus bacteremia. Presented at: 54th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); 2014 Sept 5-9; Washington, DC, USA.

(205) Joo J et al. Early response assessment to guide management of methicillin-resistant Staphylococcus aureus bloodstream infections with vancomycin therapy. Clin Ther 2013 July;35(7):995-1004.

(206) Vandenbroucke JP et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. PLoS Med 2007 Oct 16;4(10):e297.

(207) D'Angio R, Platt DR and Gannon R. Creatinine clearance: corrected versus uncorrected. DICP. 1988;22:32–33.

(208) Gore E. Comorbidity Scoring for the Charlson Comorbidity Index [Internet]. Milwaukee (WI): Zablocki VA Medical Center, Department of Radiation Oncology; [cited 2014 Apr 12]. Available from: http://www.rtog.org/LinkClick.aspx?fileticket=5k5W WASsxuw%3D&tabid=276.

(209) Charlson ME et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40(5):373-383.

(210) Hill PC et al. Prospective study of 424 cases of Staphylococcus aureus bacteraemia: determination of factors affecting incidence and mortality. Intern Med J 2001 Mar;31(2)97-103.

(211) Hall RG 2nd et al. Empiric guideline-recommended weight-based vancomycin dosing and mortality in methicillin resistant Staphylococcus aureus bacteremia: a retrospective cohort study. BMC Infect Dis 2012 Apr 27;12:104

(212) Lautenbach E et al. The role of chloramphenicol in the treatment of bloodstream infection due to vancomycin-resistant Enterococcus. Clin Infect Dis 1998 Nov;27(5):1259-1265.

(213) Kim J et al. Impact of a computerized alert system for bacteremia notification on the appropriate antibiotic treatment of Staphylococcus aureus bloodstream infections. Eur J Clin Microbiol Infect Dis 2013 Jul;32(7):937-945.

(214) Big C and Malani PN. Staphylococcus aureus bloodstream infections in older adults: clinical outcomes and risk factors for in-hospital mortality. J Am Geriatr Soc 2010 Feb;58(2):300-305.

(215) Van Hal SJ et al. Vancomycin heteroresistance is associated with reduced mortality in ST239 methicillin-resistant Staphylococcus aureus blood stream infections. PLoS One 2011;6(6):e21217.

(216) Collignon P et al. Staphylococcus aureus bacteremia, Australia. Emerg Infect Dis 2005 Apr;11(4):554-561.

(217) Lodise TP et al. Relationship between vancomycin MIC and failure among patients with methicillin-resistant Staphylococcus aureus bacteremia treated with vancomycin. Antimicrob Agents Chemother 2008 Sept;52(9):3315-3320.

(218) Li J et al. Comparison of cefazolin versus oxacillin for treatment of complicated bacteremia caused by methicillin-susceptible Staphylococcus aureus. Antimicrob Agents Chemother 2014 Sept;58(9):5117-5124.

(219) Rehm SJ et al. Daptomycin versus vancomycin plus gentamicin for treatment of bacteraemia and endocarditis due to Staphylococcus aureus: subset analysis of patients infected with methicillin-resistant isolates. J Antrimicrob Chemother 2008 Dec;62(6):1413-1421.

(220) Loonen AJ et al. Developments for improved diagnosis of bacterial bloodstream infections. Eur J Clin Microbiol Infect Dis 2014 Oct;33(10):1687-1702.

(221) Ligthelm RJ et al. Importance of observational studies in clinical practice. Clin Ther 2007 Jun;29(6 Pt 1):1284-1292.

(222) Fatkenheuer G and Kaasch AJ. How deadly is meticillin-resistant Staphylococcus aureus? Lancet Infect Dis 2014 Oct;14(10):905-907.

(223) Vikram HR et al. Clinical progression of methicillin-resistant Staphylococcus aureus vertebral osteomyelitis associated with reduced susceptibility to daptomycin. J Clin Microbiol 2005 Oct;43(10):5384-5487.

(224) Marty FM et al. Emergence of a clinical daptomycin-resistant Staphylococcus aureus isolate during treatment of methicillin-resistant Staphylococcus aureus bacteremia and osteomyelitis. J Clin Microbiol 2006 Feb;44(2):595-597.

(225) Watkins RR et al. Current concepts on the virulence mechanisms of meticillin-resistant Staphylococcus aureus. J Med Microbiol 2012 Sept;61(Pt 9):1179-1193.

Table 1. Pharmacokinetics data [109,167-85]

	Vd (L/kg)	$T_{1/2}$ (h)	% Protein bound	% Renal excretion
Cloxacillin	0.15	0.4-0.8	>90	75
Cefazolin	0.074	2	74-86	95
Ceftriaxone	0.10-0.13	6-9	83-96	33-67
Piperacillin/tazobactam	0.25	1	16-22	70
Meropenem	0.25-0.36	1	2	70
Vancomycin	0.4-1.0	6-12	50-55	80-90
Linezolid	0.57-0.71	4.3-5.4	31	30
Daptomycin	0.1	7.7-8.1	90-93	78

Table 2. Parenteral dosing in patients with normal renal function and renal impairment [109, 167-73]

	Usual dose based on normal renal function	Creatinine clearance (CrCl) in mL/min/1.73m^2 (suggested dose adjustment based on normal dose)			
Cloxacillin	2g q4-6h	none			
Cefazolin	1-2g q8h	> 50 (q8h)	10-50 (q12h)	< 10 (q24h)	
Ceftriaxone	1-2g q24h	none			
Piperacillin/tazobactam	3.375g q6h	> 40 (3.375g q6h)	20-40 (2.25g q6h)	< 20 (2.25g q8h)	
Meropenem	1g q8h	> 50 (q8h)	26-50 (q12h)	10-25 (500mg q12h)	< 10 (500mg q24h)
Vancomycin	15-20mg/kg q8-12h	> 50 (q8-12h)	10-49 (q24h)	< 10 (q4-7days)	
Linezolid	600mg q12h	none			
Daptomycin[1]	6-10mg/kg q24h	$\geq$ 30 (q24h)		< 30 (q48h)	

[1] Monograph recommends 6mg/kg but higher dose of 8-10 mg/kg have been suggested, especially in the critically ill [66, 186, 187, 194]

Table 3. Susceptibility breakpoints set by the Clinical and Laboratory Standards Institute [6, 49]

	MIC Interpretive Criteria μg/mL		
	Susceptible (S)	Intermediate (I)	Resistant (R)
Oxacillin	≤ 2 (oxacillin)	-	≥ 4 (oxacillin)
	≤ 4 (cefoxitin)	-	≥ 8 (cefoxitin) [1]
Clindamycin	≤ 0.5	1-2	≥ 4
Erythromycin	≤ 0.5	1-4	≥ 8
Linezolid	≤ 4	-	≥ 8
TMP/SMX	≤ 2/38	-	≥ 4/76
Tetracycline	≤ 4	8	≥ 16
Vancomycin	≤ 2	4-8	≥ 16

[1]Vitek AST-GP067 card reports R with cefoxitin concentrations ≥ 6 μg/mL

Table 4. Patient demographics (n = 108 cases of SABSI unless otherwise stated)

Female	37 (34.3%)
Age (y)	66.0 ± 19.0
>65 y	63 (58.3%)
Height (m) (n = 97)	1.7 ± 0.1
Weight (kg) (n = 105)	83.6 ± 29.8
BMI (kg/m^2) (n = 97)	29.2 ± 8.9
Obese (BMI ≥30 kg/m^2)	30 (30.9%)
Clcr (mL/min/1.73m^2)	62.0 ± 38.0
Smoker	23 (21.3%)
Alcohol use	40 (37.0%)
IV drug use	4 (3.7%)

*Data reported as percentage or mean ± standard deviation.

Table 5. Patient co-morbidities (n = 108 cases of SABSI)

Hypertension	78 (72.2%)
Congestive heart failure	40 (37.0%)
Ischemic heart disease	41 (38.0%)
Myocardial infarction	18 (16.7%)
Diabetes mellitus	43 (39.8%)
with end organ damage	30 (27.8%)
Cancer	21 (19.5%)
solid tumor (non-metastatic and metastatic)	17 (15.7%)
lymphoma	3 (2.8%)
leukeumia	1 (0.9%)
Chronic pulmonary disease	20 (18.5%)
Cerebral vascular disease	20 (18.5%)
Peripheral vascular disease	14 (13.0%)
Autoimmune disease	12 (11.1%)
Dementia	10 (9.3%)
Liver disease	6 (5.6%)
Hemiplegia	4 (3.7%)
Chronic renal failure	3 (2.8%)
Peptic ulcer disease	2 (1.9%)
Connective tissue disease	1 (0.9%)

Table 6. *S. aureus* blood culture characteristics (n = 108 cases of SABSI unless otherwise stated)

Index blood culture (day of hospitalization)	2.0 [IQR, 1.0, 6.0]
Healthcare–associated	40 (37.0%)
Time to Gram stain report since index blood culture draw (hours)	21.5 [IQR, 18.0, 27.0]
Time to susceptibility report since index blood culture draw (hours)	60.0 [IQR, 47.9, 71.8]
Susceptible to	
oxacillin	92 (85.2%)
vancomycin (n = 16)	16 (100.0%)
linezolid (n = 17)	17 (100.0%)
tetracycline	104 (96.3%)
TMP/SMX	103 (95.4%)
clindamycin	82 (75.9%)
erythromycin	75 (69.4%)

*Data reported as percentage or median and interquartile range.

Table 7. Concurrent *S. aureus* infections (n = 126 in 98 cases of SABSI)

Total concurrent infections	126
cases with one concurrent infection	74 (68.5%)
cases with two concurrent infections	20 (18.5%)
cases with three concurrent infections	4 (3.7%)
Skin and skin structure	34 (27.0%)
Endocarditis	19 (15.1%)
Intravenous catheter	18 (14.3%)
Urinary tract	17 (13.5%)
Bone or joint	15 (11.9%)
Pneumonia	12 (9.5%)
Central nervous system	6 (4.7%)
Device-related	5 (4.0%)

Table 8. Clinical presentation on day of index blood culture (n = 108 cases of SABSI)

Heart rate (beats/min)	106 ± 22
tachycardic (>90 beats/min)	84 (77.8%)
Respiratory rate (breaths/min)	24 ± 6
tachypneic (>20 breaths/min)	64 (59.2%)
White blood cell count (cells/μL)	16,100 ± 7000
leukocytosis (>11,000 cells/μL)	81 (75.0%)
Percent neutrophils (%)	86.4 ± 6.6
neutrophilia (≥80%)	95 (88.0%)
Maximum temperature (°C)	38.5 ± 1.0
febrile (>37.8°C)	82 (75.9%)
Antipyretics	67 (62.0%)

* Data reported as percentage or mean ± standard deviation.

Table 9. End-of-treatment outcome analysis of SABSI (n=108)

Variable		Clinical Cure (n=76)	Treatment Failure (n=32)	*P*-value
Patient demographics and infection characteristics				
Age (years)		**62.0 ± 18.3**	**75.3 ± 18.2**	**p < 0.001**
Charlson Comorbidity Index		**2.4 ± 2.0**	**3.4 ± 1.9**	**p = 0.01**
Healthcare-associated infection		**20 (26.3)**	**20 (62.5)**	**p < 0.001**
Complicated infection		**54 (71.1)**	**30 (93.8)**	**p = 0.01**
Pitt score		**1.5 ± 1.6**	**2.4 ± 2.2**	**p = 0.02**
Endocarditis		11 (14.5)	8 (25.0)	p = 0.19
ICU admission		11 (14.5)	9 (28.1)	p = 0.10
Any antibiotic selection during treatment				
Optimal targeted antibiotic		**68 (89.5)**	**22 (68.8)**	**p = 0.008**
Optimal broad antibiotic		25 (32.9)	9 (28.1)	p = 0.63
Optimal (targeted or broad) antibiotic		**71 (93.4)**	**24 (75.0)**	**p = 0.02**
Time to initiation				
Optimal targeted antibiotic (n=90)		64.1 ± 46.5	63.4 ± 40.6	p = 0.95
Optimal broad antibiotic (n=34)		7.1 ± 10.7	6.2 ± 7.6	p = 0.81
Earliest optimal (targeted or broad) antibiotic (n=95)		42.3 ± 48.6	41.5 ± 45.1	p = 0.95
Earliest optimal or adequate antibiotic (n=106)		20.8 ± 27.7	23.5 ± 34.0	p = 0.87
Early antibiotic selection within 3 days				
0-23.9 hours	Optimal targeted therapy	13 (17.1)	3 (9.4)	p = 0.78
	Optimal broad therapy	22 (28.9)	8 (25.0)	
	Adequate therapy	20 (26.3)	8 (25.0)	
	Inadequate therapy	10 (13.2)	8 (25.0)	
	No therapy	11 (14.5)	5 (15.6)	
24-47.9 hours	Optimal targeted therapy	22 (28.9)	9 (28.1)	p = 0.76
	Optimal broad therapy	18 (23.7)	7 (21.9)	
	Adequate therapy	23 (30.3)	10 (31.3)	
	Inadequate therapy	5 (6.6)	5 (15.6)	
	No therapy	8 (10.5)	1 (3.1)	
48-72 hours	**Optimal targeted therapy**	**42 (55.3)**	**11 (34.3)**	**p = 0.047**[1]
	Optimal broad therapy	8 (10.5)	6 (18.8)	
	Adequate therapy	21 (27.6)	7 (21.9)	
	Inadequate therapy	1 (1.3)	6 (18.8)	
	No therapy	4 (5.3)	2 (6.3)	
Antibiotic duration within 7 days				
Optimal targeted therapy		3.8 ± 2.1	2.9 ± 2.3	p = 0.05
Optimal broad therapy		0.8 ± 1.6	1.0 ± 2.0	p = 0.60
Total optimal (targeted or broad) therapy		4.6 ± 2.2	3.7 ± 2.7	p = 0.09
Total optimal or adequate therapy		5.7 ± 1.4	5.0 ± 2.2	p = 0.06

Table 9. (continued)

Antibiotic exposure within 7 days			
TSE score	16.6 ± 3.9	15.5 ± 4.7	p = 0.20
≥15.2	53 (69.7)	18 (56.3)	p = 0.18

[1] Selection of optimal targeted therapy against optimal broad, adequate, inadequate and no therapy

Table 10. End-of-treatment outcome analysis of complicated MSSA BSI (n=71)

Variable		Clinical Cure (n = 45)	Treatment Failure (n=26)	*P*-value
Patient demographics and infection characteristics				
Age (years)		**62.4 ± 20.3**	**73.7 ± 19.5**	**p = 0.03**
Charlson Comorbidity Index		**2.0 ± 1.8**	**3.3 ± 2.1**	**p = 0.007**
Healthcare-associated infection		**11 (24.4)**	**15 (57.7)**	**p = 0.005**
Pitt score		1.6 ± 1.7	2.5 ± 2.4	p = 0.07
Endocarditis		10 (22.2)	7 (26.9)	p = 0.65
ICU admission		7 (15.6)	8 (30.8)	p = 0.13
Any antibiotic selection during treatment				
Optimal targeted antibiotic		**41 (91.1)**	**17 (65.4)**	**p = 0.007**
Optimal broad antibiotic		17 (37.8)	9 (34.6)	p = 0.79
Optimal (targeted or broad) antibiotic		**42 (93.3)**	**19 (73.1)**	**p = 0.02**
Time to initiation				
Optimal targeted antibiotic (n=58)		66.4 ± 44.4	66.1 + 40.1	p = 0.98
Optimal broad antibiotic (n=26)		6.3 ± 7.3	6.2 ± 7.6	p = 0.97
Earliest optimal (targeted or broad) antibiotic (n=61)		41.9 ± 50.2	38.2 ± 45.7	p = 0.79
Earliest optimal or adequate antibiotic (n=69)		14.7 ± 18.7	18.0 ± 28.9	p = 0.53
Early antibiotic selection within 3 days				
0-23.9 hours	Optimal targeted therapy	4 (8.9)	2 (7.7)	p = 0.41
	Optimal broad therapy	16 (35.6)	8 (30.8)	
	Adequate therapy	17 (37.8)	7 (26.9)	
	Inadequate therapy	4 (8.9)	8 (30.7)	
	No therapy	4 (8.9)	1 (3.8)	
24-47.9 hours	Optimal targeted therapy	12 (26.7)	6 (23.1)	p = 0.95
	Optimal broad therapy	12 (26.7)	7 (26.9)	
	Adequate therapy	16 (35.6)	9 (34.6)	
	Inadequate therapy	3 (6.7)	4 (15.4)	
	No therapy	2 (4.4)	0 (0.0)	
48-72 hours	**Optimal targeted therapy**	**27 (60.0)**	**9 (34.6)**	**p = 0.04**[1]
	Optimal broad therapy	3 (6.7)	6 (23.1)	
	Adequate therapy	15 (33.3)	6 (23.1)	
	Inadequate therapy	0 (0.0)	5 (19.2)	
	No therapy	0 (0.0)	0 (0.0)	
Antibiotic duration within 7 days				
Optimal targeted therapy		**3.9 ± 1.9**	**2.6 ± 2.3**	**p = 0.02**
≥3.9 days		**29 (64.4)**	**10 (38.5)**	**p = 0.03**
Optimal broad therapy		0.7 ± 1.2	1.2 ± 2.1	p = 0.19
Optimal (targeted or broad) therapy		4.6 ± 2.1	3.7 ± 2.8	p = 0.14
Optimal or adequate therapy		**6.1 ± 1.2**	**5.0 ± 2.3**	**p = 0.02**
≥6 days		**33 (73.3)**	**13 (50.0)**	**p = 0.047**

Table 10. (continued)

Antibiotic exposure within 7 days			
TSE score	17.2 ± 3.3	15.3 ± 5.0	p = 0.05
≥15.2	**36 (80.0)**	**14 (53.8)**	**p = 0.02**

[1] Selection of optimal targeted therapy against optimal broad, adequate, inadequate and no therapy

Table 11. Patient, infection and treatment variables of complicated MSSA BSI utilized in multivariate end-of-treatment outcome analysis (n=71)

Variable	Clinical Cure (n = 45)	Treatment Failure (n=26)	*P*-value
Patient demographics and infection characteristics			
Age (years)	62.4 ± 20.3	73.7 ± 19.5	p = 0.03
Charlson Comorbidity Index	2.0 ± 1.8	3.3 ± 2.1	p = 0.007
Healthcare-associated infection	11 (24.4)	15 (57.7)	p = 0.005
Antibiotic duration within 7 days			
Optimal targeted therapy	3.9 ± 1.9	2.6 ± 2.3	p = 0.02
Optimal or adequate therapy	6.1 ± 1.2	5.0 ± 2.3	p = 0.02
Antibiotic exposure within 7 days			
TSE score	17.2 ± 3.3	15.3 ± 5.0	p = 0.05

Table 12. Multivariate end-of-treatment outcome analysis (n=71)

Variable	**Model 1 (*P*-value)**	**Model 2 (*P*-value)**	**Model 3 (*P*-value)**
Charlson Comorbidity Index	0.03	0.015	0.013
Healthcare-associated	0.024	0.014	0.018
Antibiotic therapy	---	---	---
Duration of optimal targeted	0.025		
Duration of optimal or adequate		0.023	
TSE score			0.03

Figure 1. Case selection

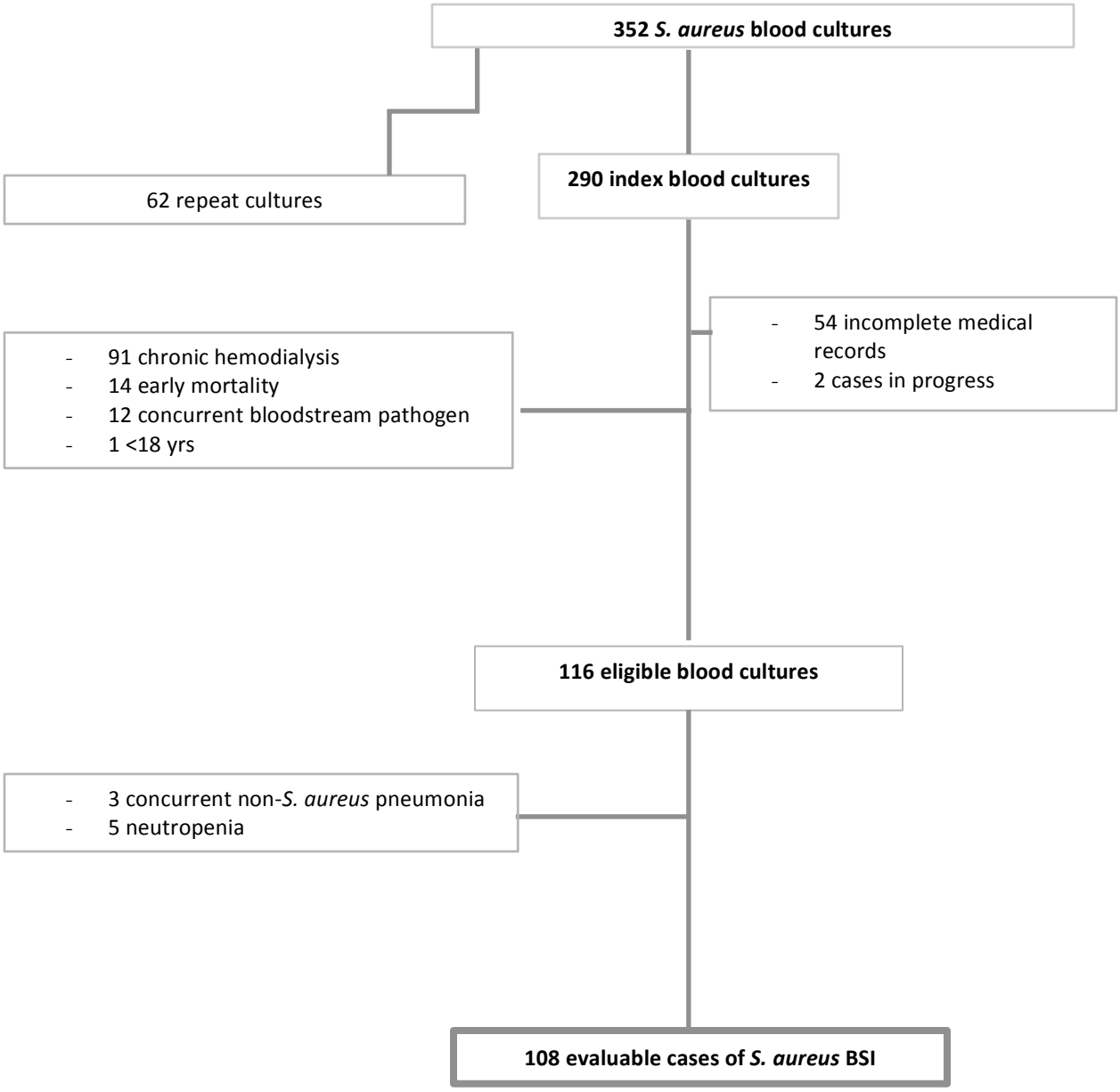


Figure 2. Complicated *S. aureus* bloodstream infection (n=84)

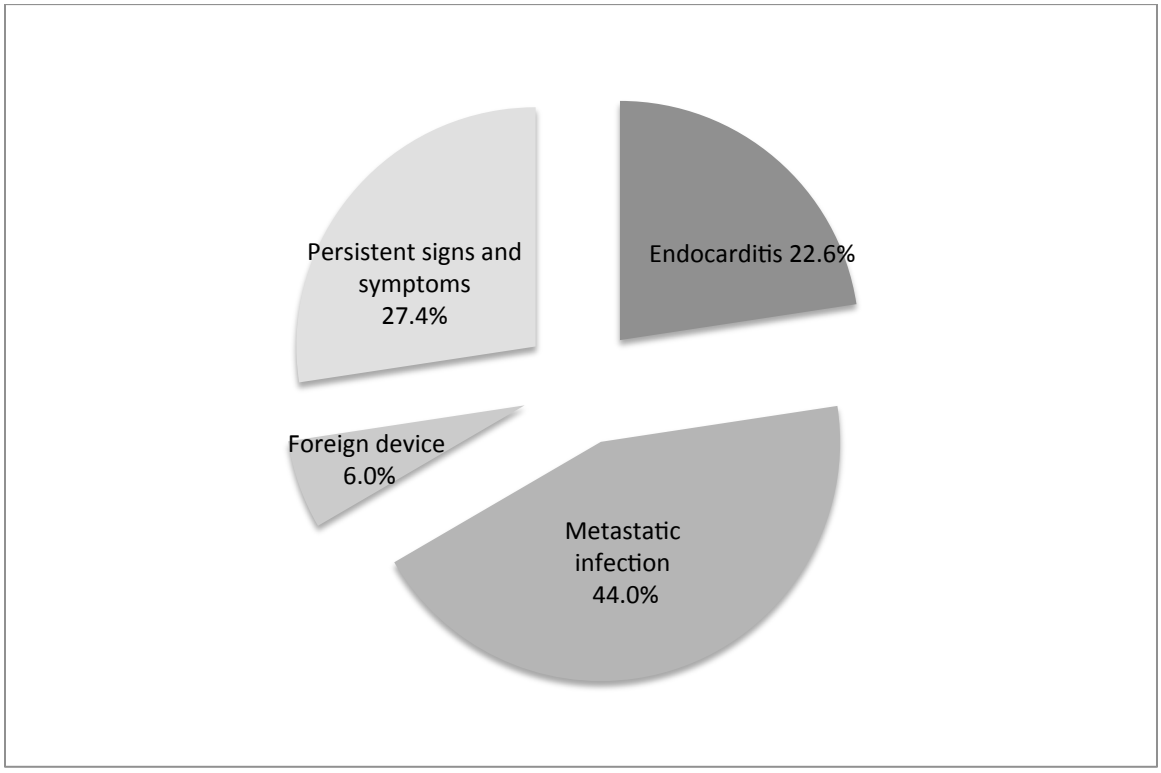


Figure 3. Any antibiotic selected during treatment

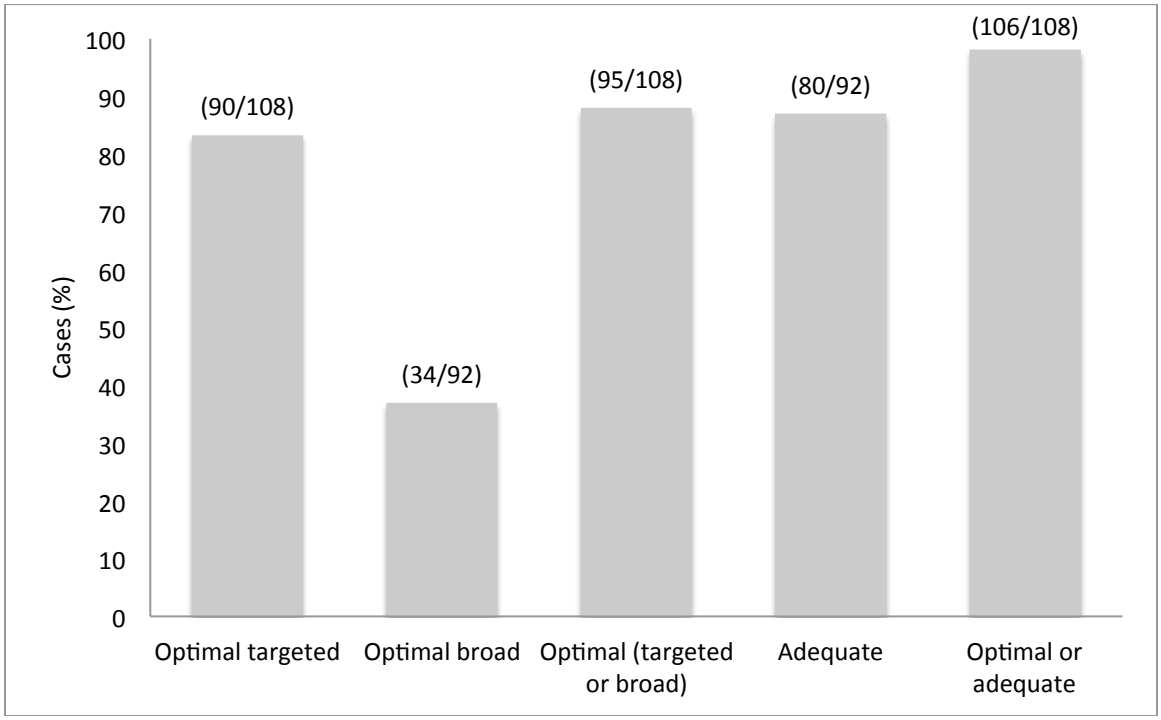


Figure 4. Time to initiation of any optimal targeted antibiotic (n = 90)

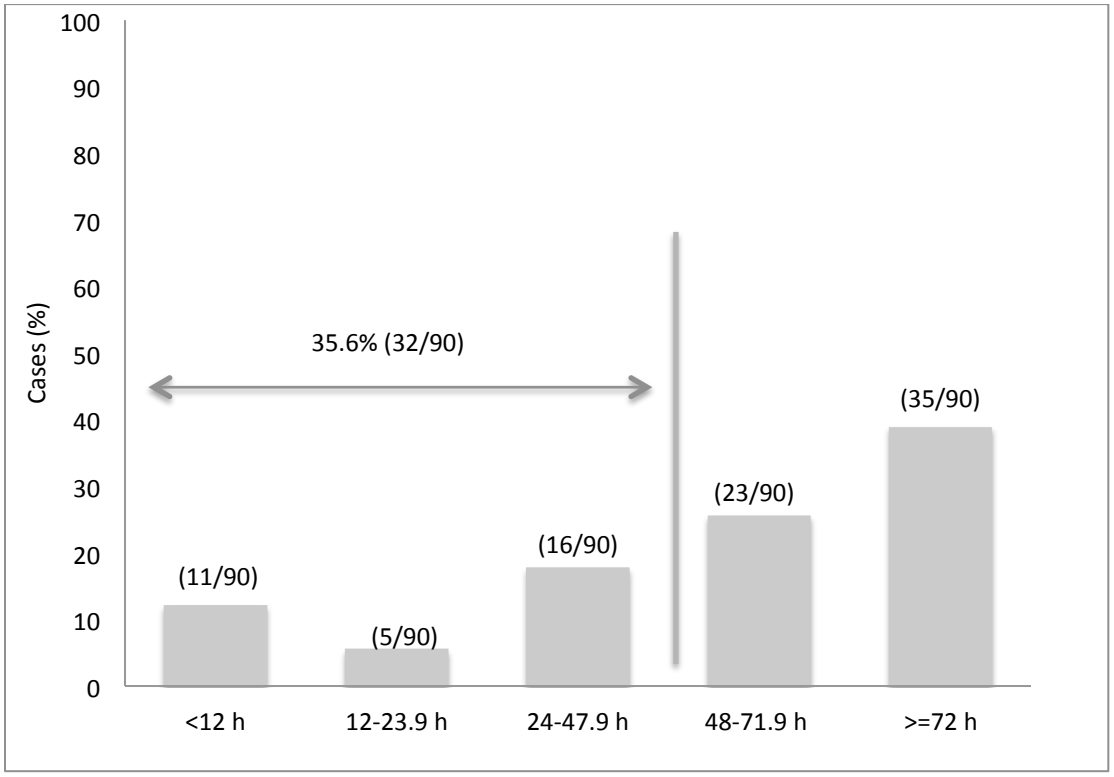


Figure 5. Time to initiation of any optimal broad antibiotic (n = 34)

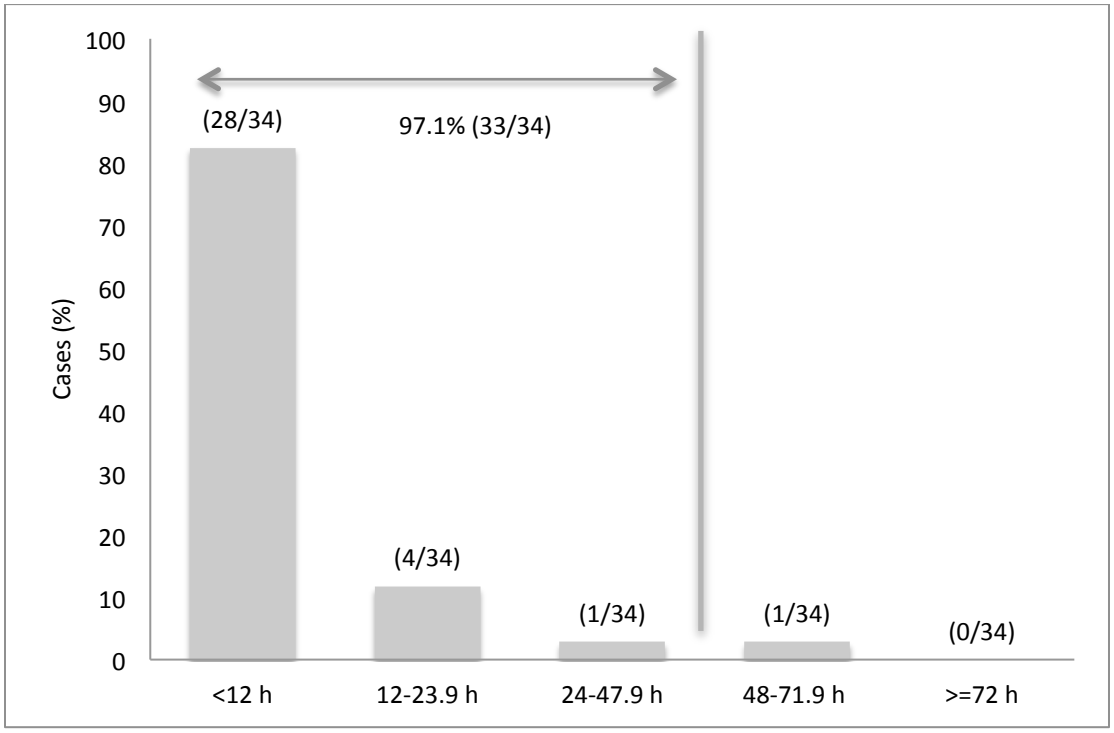


Figure 6. Earliest time to initiation of any optimal (targeted or broad) antibiotic (n = 95)

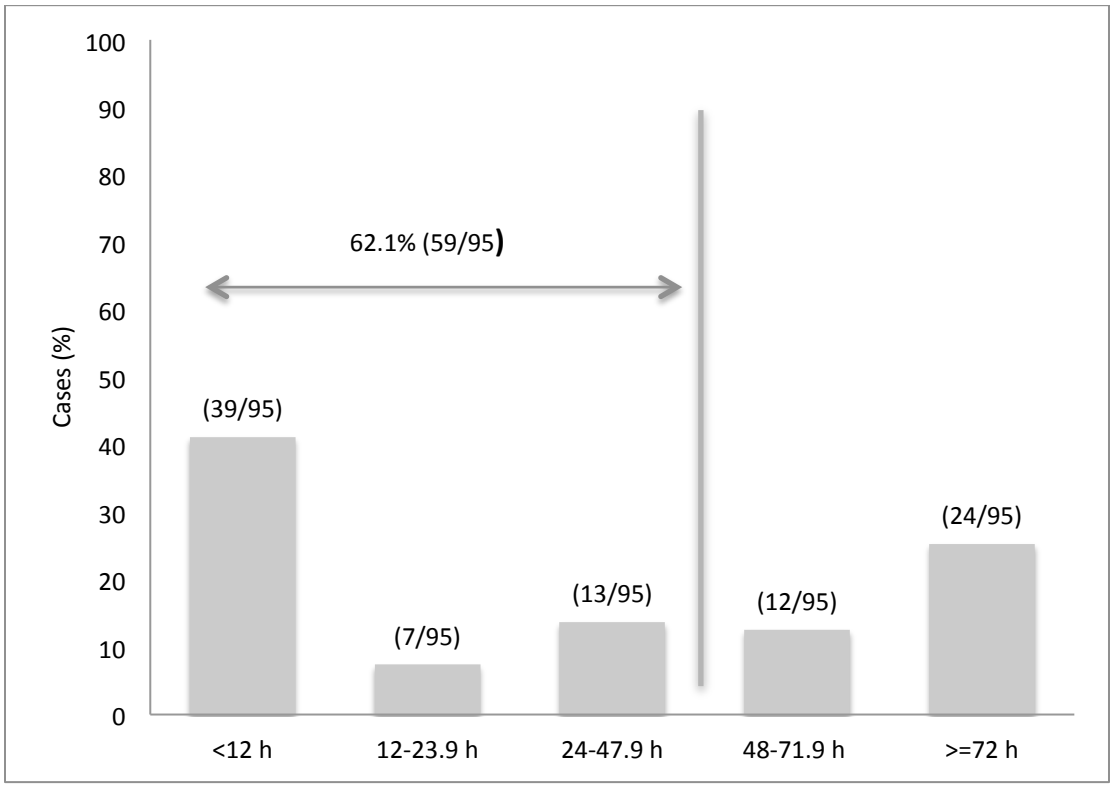


Figure 7. Earliest time to initiation of any optimal or adequate antibiotic (n = 106)

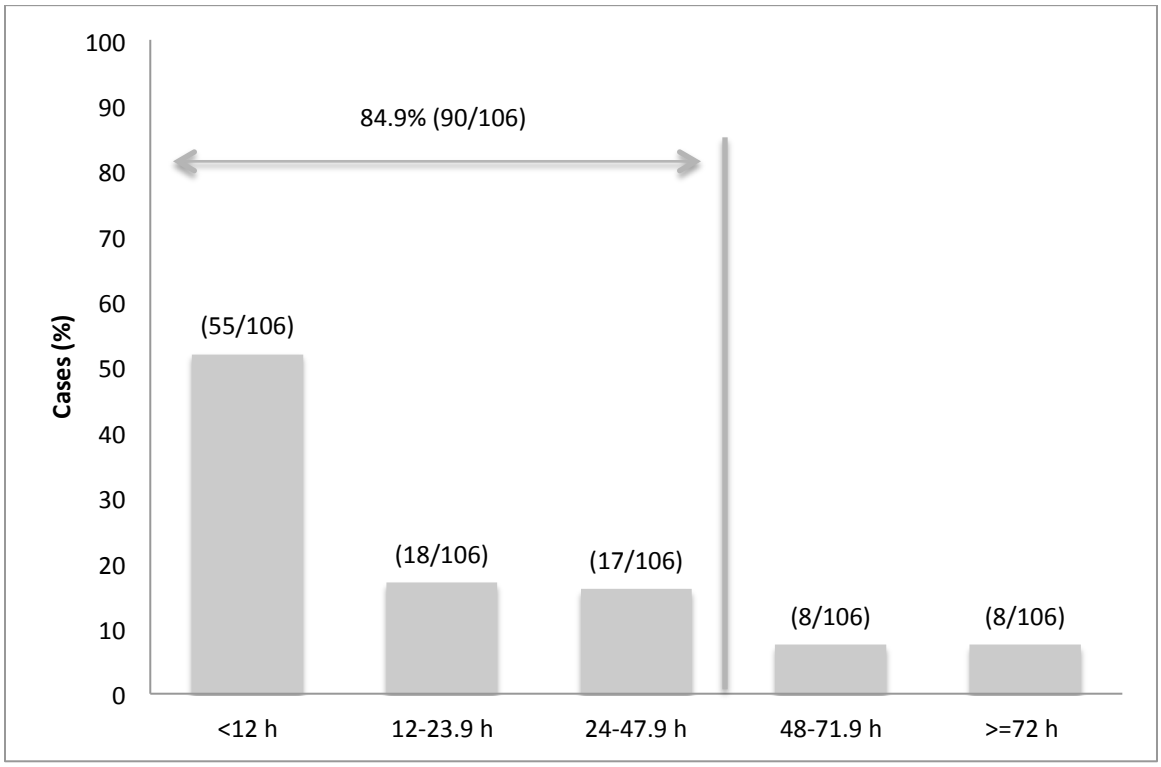


Figure 8. Early antibiotic selection within 3 days following the index blood culture (n = 108 cases of SABSI)

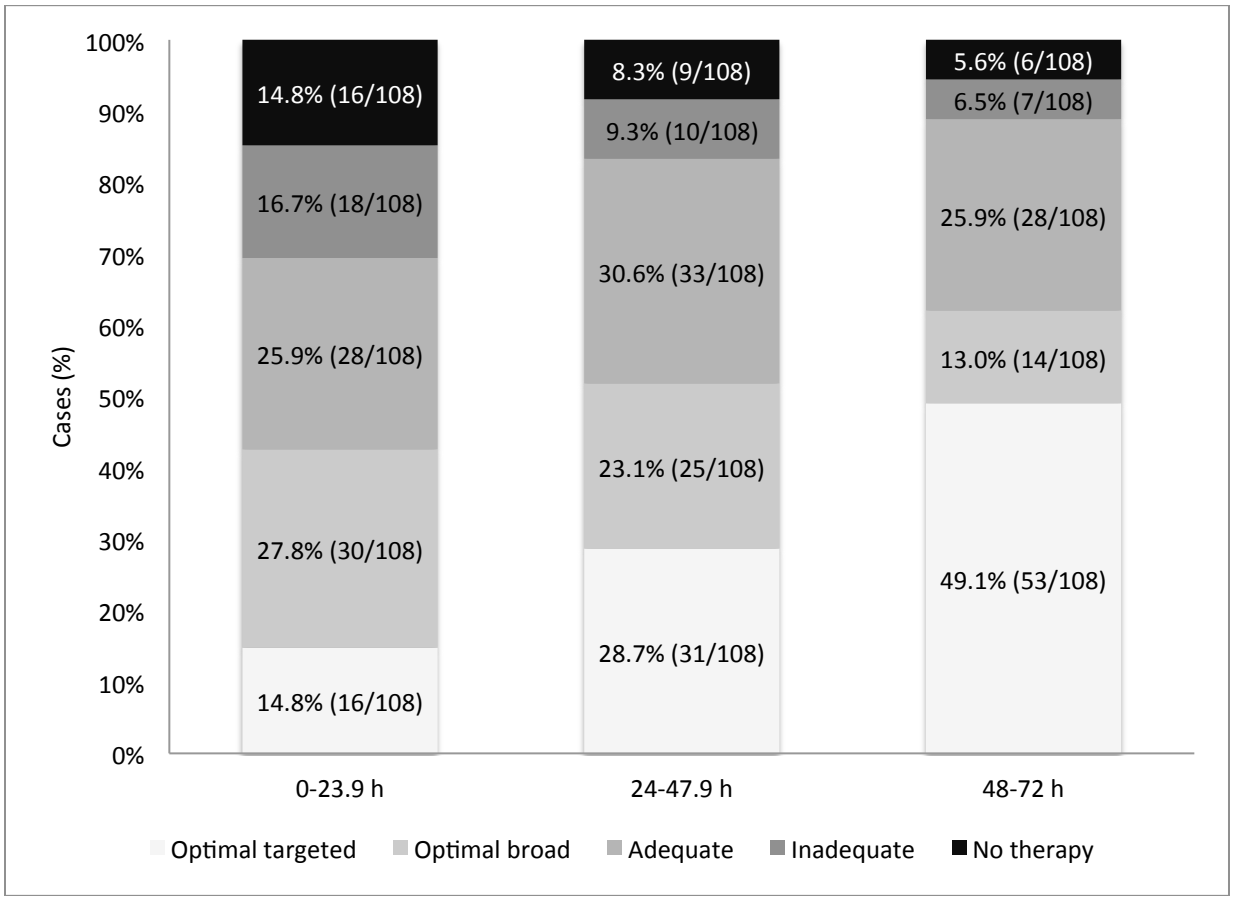


Figure 9. Antibiotic duration within 7 days following the index blood culture (n = 108 cases of SABSI including 92 cases of MSSA)

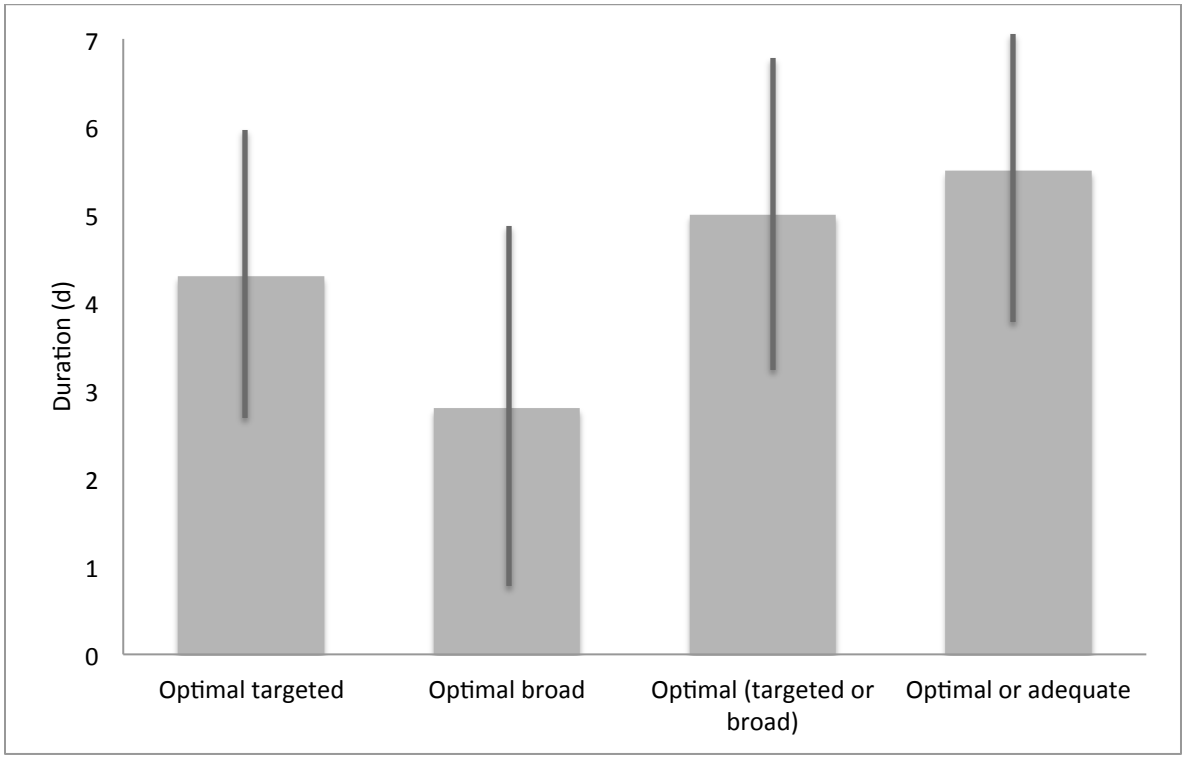


Figure 10. TSE score for antibiotic exposure within 7 days following the index blood culture (n = 108 cases of SABSI)

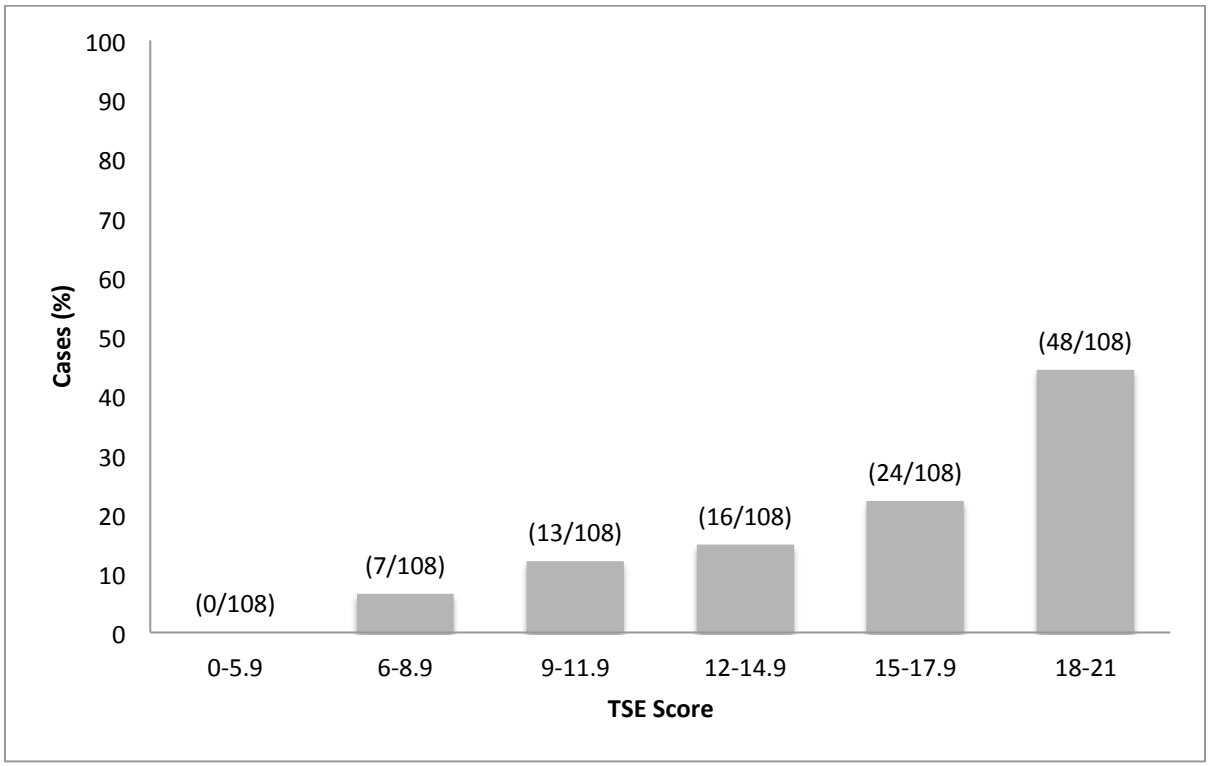


Figure 11. Vancomycin trough concentrations within 3 days of therapy

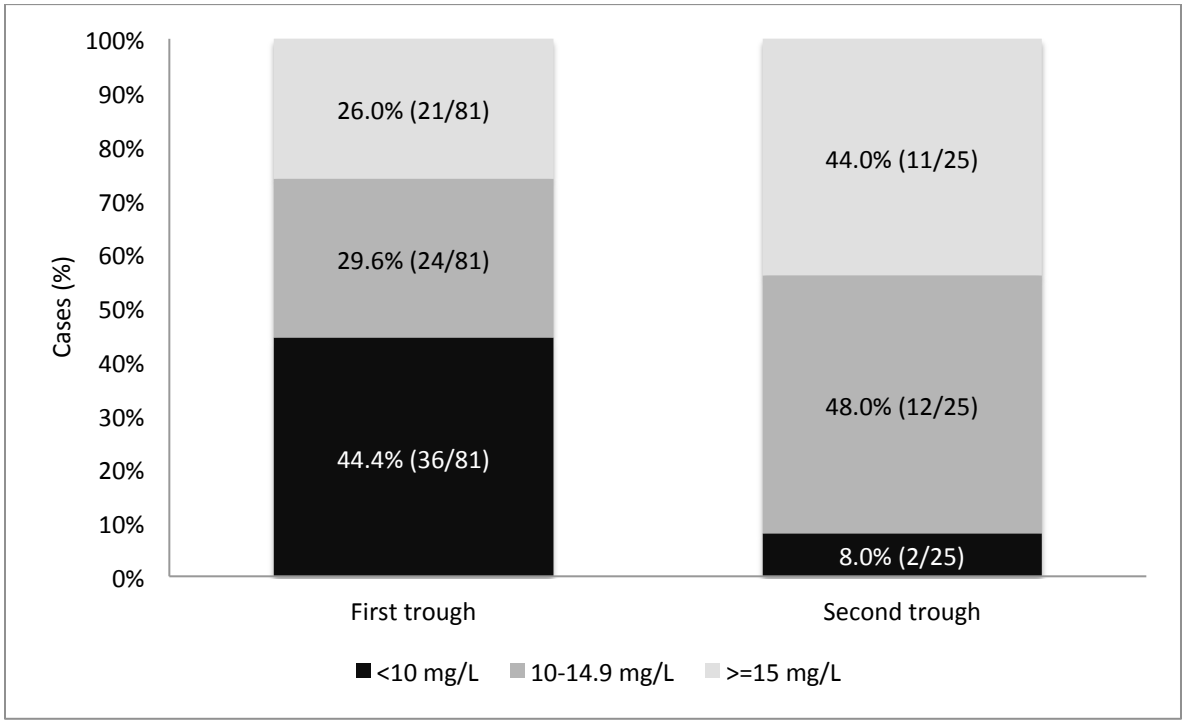


Figure 12. Clinical response on days 3, 5 and 7 following the index blood culture (n = 108 cases of SABSI)

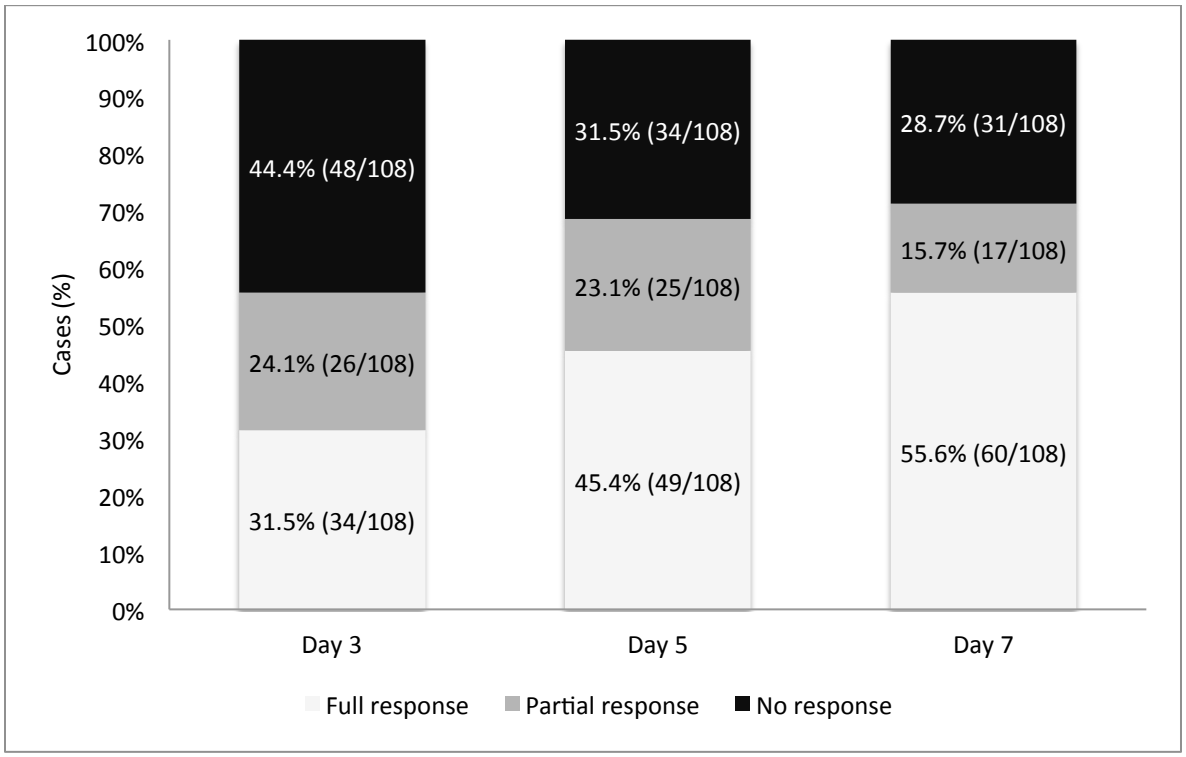


Figure 13. End-of-treatment failure amongst 108 cases of SABSI (n=32)

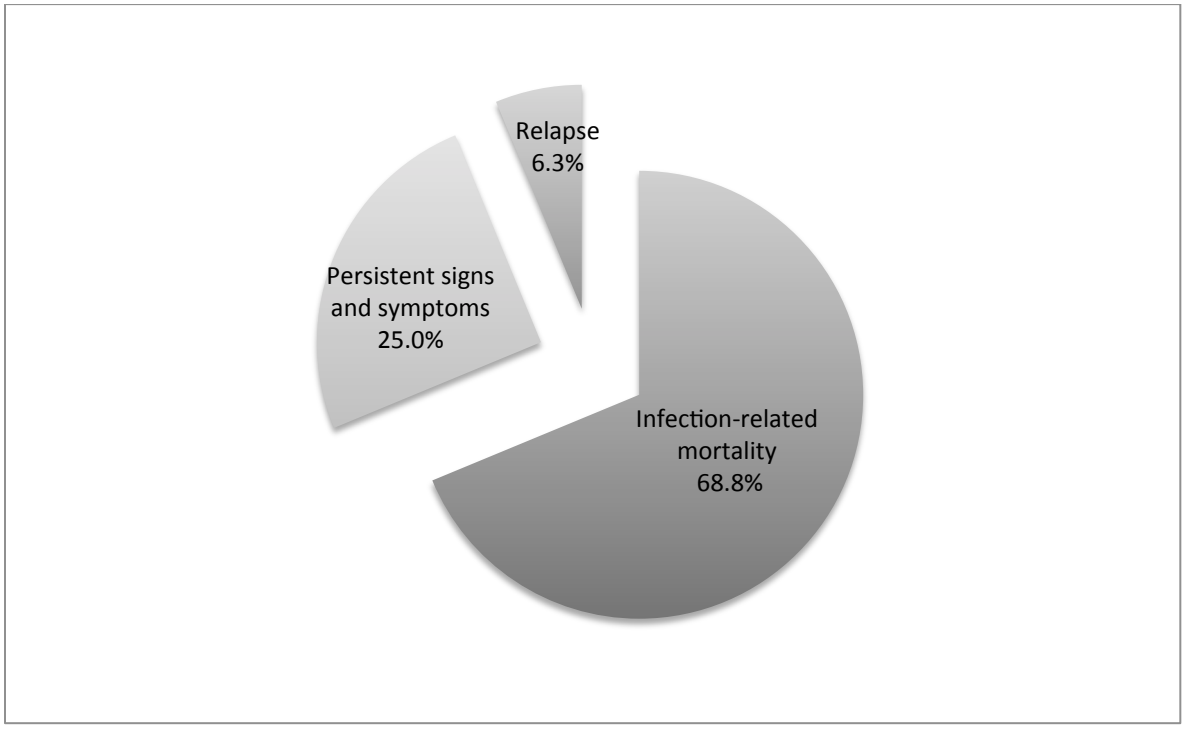
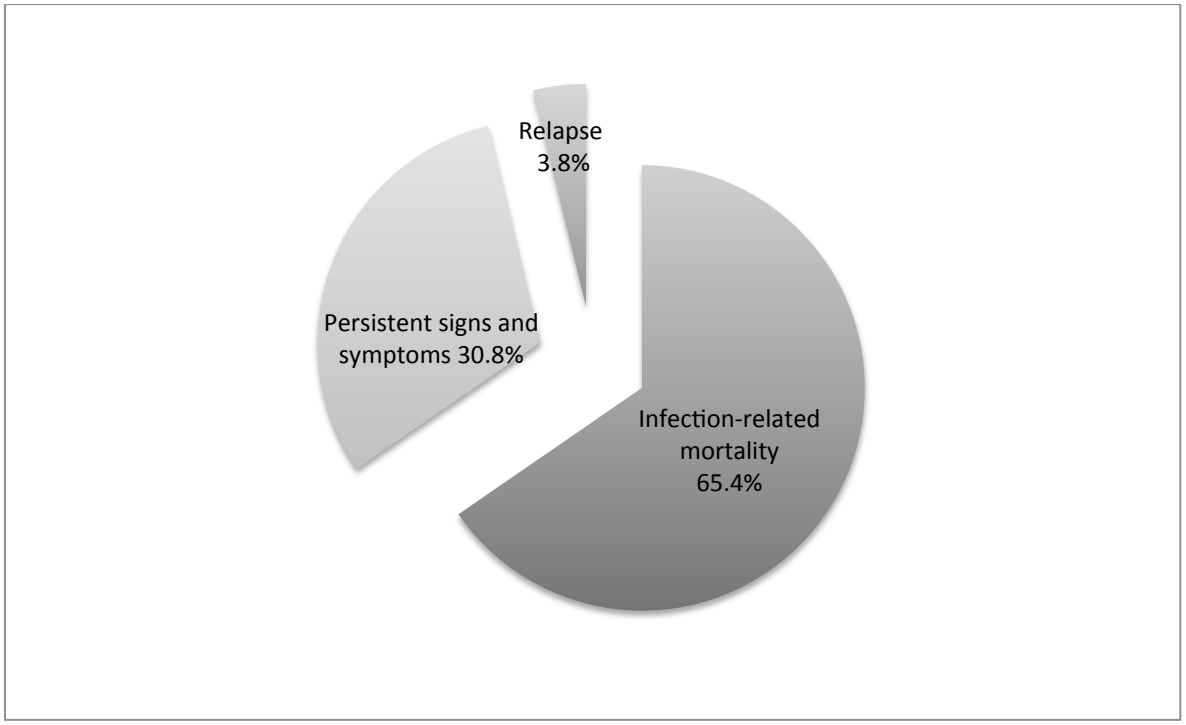


Figure 14. End-of-treatment failure amongst 71 cases of complicated MSSA BSI (n=26)



Appendix 1

DATA COLLECTION – *Staphylococcus aureus* bloodstream infection (BSI) **Study Number_____**
Ward(s)_____

HOSPITALIZATION

date admitted____/____/____ (m/d/y) date □ disch'd □ died____/____/____ LOS ____d

admitting diagnosis_____

secondary complications_____

prior hosp admission / institutional residence (within 6 m) _____

Additional notes _____

DEMOGRAPHICS

male □ female □ year of birth ____ age ____y height____ cm weight____kg BMI_____kg/m^2

Vitals	***Paramedic Services (t)**	***Emergency Triage (t)**	***Emergency Triage (t)**
Temp			
Hr			
RR			
BP			
O2 % Sat			

* If applicable

BLOODSTREAM INFECTION (BSI)

Associated with

□ respiratory (□ ventilator associated pneumonia)
□ intravenous catheter
□ skin / soft tissue (□ surgical wound)
□ urinary (□ urinary catheter)
□ bone / joint _____
□ foreign / prosthetic device _____
□ endocarditis
□ other _____
□ none evident (primary)

Pitt Bacteremia Score (Worst of Day of Positive Blood Culture and 48 hours prior) **Total:**

Criterion			
Fever	<35 or >40 35.1-36.0 or 39.0-39.9 36.1-38.9	2 1 0	
Hypotension	SBP >30mmHg and DBP > 20 mmHg or IV Vasopressor agents or SBP < 90 mmHg	2	
Mechanical Ventilation		2	
Cardiac Arrest		4	
Mental status	Alert Disoriented Stuporous Comatose	0 1 2 4	

Blood Culture Data

# of blood samples (sets) _____# of positive blood cultures _____

BSI *S. aureus* isolate # ___ Date/Time Ordered/Collected _____Day of admission_____

____ of ____ bottles Site drawn_____

Growth ____ No Growth (after 5 incubation days)_____

□ community (day 1 or 2 of admission) □ health-care associated (> day 3, or other _____)

Antimicrobials	Sensitivities
Clindamycin	
Erythromycin	
Oxacillin	
Tetracycline	
TMP/SMX	

Date/Time Results Reported by Clinical Micro to Clinician_____

BSI *S. aureus* isolate # ____ Date/Time Ordered/Collected _____Day of admission _____

____ of ____ bottles Site drawn_____

Growth ____ No Growth (after 5 incubation days)_____

□ community (day 1 or 2 of admission) □ health-care associated (> day 3, or other _____)

Antimicrobials	Sensitivities
Clindamycin	
Erythromycin	
Oxacillin	
Tetracycline	
TMP/SMX	

Date/Time Results Reported by Clinical Micro to Clinician_____

Concurrent Infections

Date/Time Ordered ____________________

Date/Time Results Reported

____

Source _______________________________

Growth_____ No Growth ______

Organism/Load_______________________

Antimicrobials	Sensitivities

Date/Time Ordered ____________________

Date/Time Results Reported

____

Source _______________________________

Growth_____ No Growth ______

Organism/Load_______________________

Antimicrobials	Sensitivities

Date/Time Ordered ____________________

Date/Time Results Reported

____

Source _______________________________

Growth_____ No Growth ______

Organism/Load_______________________

Antimicrobials	Sensitivities

Date/Time Ordered ____________________

Date/Time Results Reported

____

Source _______________________________

Growth_____ No Growth ______

Organism/Load_______________________

Antimicrobials	Sensitivities

MEDICAL HISTORY

social (smoking, alcohol, iv drug use)_____

medications on admission

antibiotics within 6 m

- ☐ yes _____
  _____
  _____
- ☐ no
- ☐ unknown

drug allergies _____
_____
_____

comorbidities

- ☐ COPD_____
- ☐ ischemic heart disease
- ☐ peripheral vascular disease
- ☐ congestive heart failure
- ☐ hypertension
- ☐ cerebrovascular disease_____
- ☐ chronic renal disease ☐ hemodialysis
- ☐ liver failure (cirrhosis)
- ☐ diabetes mellitus ☐ medication controlled ☐ insulin dependent
- ☐ autoimmune disease_____
- ☐ neutropenia (ANC < 500/ul)
- ☐ HIV/AIDS_____
- ☐ malignancy ☐ solid tumor ☐ lymphoma ☐ leukemia ☐ multiple myeloma
- ☐ chemotherapy_____
- ☐ chronic steroids_____

- ☐ foreign device (valve, joint)_____
- ☐ indwelling catheter / drain/ foreign devices/joints _____
- ☐ surgery within 30 d – elective_____
- ☐ surgery within 30 d – emergency_____

Additional relevant information

Discharge diagnosis:

 Charlson Index of comorbidity _____

Assigned Weight for Disease	Condition	Points
1	Myocardial infarct Congestive heart failure Peripheral vascular disease Cerebrovascular disease Dementia COPD Connective tissue disease Ulcer disease Mild liver disease Diabetes	
2	Hemiplegia Moderate or severe renal disease Diabetes with end organ damage Any tumor Leukemia Lymphoma	
3	Moderate or severe liver disease	
6	Metastatic solid tumor AIDS	

CLINICAL VARIABLES (days following first positive blood culture)

 Pitt bacteremia score_____

 ICU admission LOS ____d
 APACHE II score_____ (available only through ICMS records)
 septic shock

Clinical and Laboratory Data

Date											
Temp (lowest)											
Temp (highest)											
HR (highest)											
RR (highest)											
BP (lowest)											
WBC											
%Neutro											
ANC											
Albumin											
Urea											
Creatinine											
Urea/Cr											
Urine pH											
Protein											
Glucose											
Ketones											
Hb											
LE											

ANTIBIOTIC THERAPY (days following first positive blood culture)

On day of first blood culture:

 on antibiotics for prior indication

 started on empiric antibiotics for current signs and symptoms of infection

Antimicrobial therapy in response to first positive blood culture (detail first 3 d)

Antimicrobial	Regimen	start d, time / stop d, time (first dose) (last dose)	Clcr on start d	First 3 days of new dose (time)					
		/							
		/							
		/							
		/							
		/							
		/							
		/							
		/							
		/							
		/							
Acetaminophen Usage									

Vancomycin levels

level (mg/L)	d of therapy	peak / trough	Prior dose (dose #,mg, h prior to level)	Next scheduled dose (mg, h following level)	time/date collected

OTHER TREATMENTS (days following first positive blood culture)

- ☐ fluids (d ___ to d___)_____
- ☐ vasopressors (d ___ to d___)_____
- ☐ inotropes (d ___ to d___)_____
- ☐ sedation (d ___ to d___)_____
- ☐ HD (d ___ to d___)_____
- ☐ CRRT (d ___ to d___)_____
- ☐ mechanical ventilation (d ___ to d___)_____

- ☐ source control
  - ☐ catheter removal / replacement (d ___ to d___)_____
  - ☐ surgery (d ___ to d___)_____
  - ☐ debridement (d ___ to d___)_____
  - ☐ drainage (d ___ to d___)_____

CLINICAL OUTCOMES

d3 of ☐ antimicrobial therapy or ☐ source control
- ☐ clinical cure ☐ negative blood culture (d____)
- ☐ clinical failure
  - ☐ febrile
  - ☐ repeat positive blood culture (d____)
  - ☐ other signs and symptoms_____

d7 of ☐ antimicrobial therapy or ☐ source control
- ☐ clinical cure ☐ negative blood culture (d____)
- ☐ clinical failure
  - ☐ febrile
  - ☐ repeat positive blood culture (d____)
  - ☐ other signs and symptoms_____

end of antimicrobial therapy
- ☐ clinical cure ☐ negative blood culture (d____)
- ☐ clinical failure
  - ☐ febrile
  - ☐ repeat positive blood culture (d____)
    - ☐ other signs and symptoms_____

☐ died (d____ following first positive blood culture; d____ of antimicrobial therapy)
- ☐ infection-related
- ☐ not infection-related_____
- ☐ unknown