CMAJ
Medical knowledge that matters

Risk factors for mortality among Canadian patients with Staphylococcus aureus bacteremia: a retrospective cohort study

Journal:	*CMAJ*
Manuscript ID:	CMAJ-14-0153
Manuscript Type:	Research - Cohort study (retrospective)
Date Submitted by the Author:	07-Feb-2014
Complete List of Authors:	Anantha, Ram; Western University, Division of General Surgery Jegatheswaran, Januvi; Western University, Schulich School of Medicine and Dentistry Pepe, Daniel; Western University, Schulich School of Medicine and Dentistry Priestap, Fran; Western University, Division of Critical Care Medicine, Department of Medicine, Schulich School of Medicine and Dentistry Delport, Johan; Western University, Department of Pathology, Schulich School of Medicine and Dentistry Haeryfar, S.M. Mansour; Western University, Department of Microbiology and Immunology, Schulich School of Medicine and Dentistry McCormick, John; Western University, Department of Microbiology and Immunology, Schulich School of Medicine and Dentistry Mele, Tina; Western University, Division of General Surgery, Department of Surgery, Schulich School of Medicine and Dentistry
Keywords:	Infectious Diseases, Microbiology, Statistics and Research Methods
More Detailed Keywords:	Staphylococcus aureus, bacteremia, MRSA, health outcomes research
Abstract:	Introduction: Staphylococcus aureus bacteremia (SAB) is a persistent and challenging disease, with few recent studies assessing its scope and burden in a Canadian population. We evaluated the magnitude of SAB in a large cohort of patients, and identified risk factors associated with increased mortality. Methods: We retrospectively reviewed adult (>18 years old) patients admitted with SAB between 2008 and 2012 at a regional tertiary-care centre in Southwestern Ontario. Hospital records were used to identify comorbidities, complications of SAB such as sepsis and need for mechanical ventilation (MV), and mortality. Multivariable logistic regression was performed to determine predictors of overall, in-hospital, and post-discharge mortality. Results: We identified 1114 patients in our study. The proportion of methicillin-resistant S. aureus (MRSA) strains rose significantly during the study period (p= 0.045), while in-hospital mortality declined significantly (29% in 2008 to 11% in 2012, p< 0.0001). Age, MRSA, sepsis, admission to the intensive care unit, hepatic failure, prolonged (> 21 days) MV,

	chronic obstructive pulmonary disease (COPD), and malignancy (primary and metastatic) were associated with overall mortality and— with the exception of COPD and primary malignancy— in-hospital mortality. In contrast, peripheral vascular and cerebrovascular disease, COPD, diabetes, and malignancy (solid and hematogenous) were associated with increased post-discharge mortality. Interpretation: This study features one of the largest retrospective cohort studies of SAB in Canada, and identifies key factors associated with in-hospital and post-discharge mortality. Identification of these predictors may guide empiric therapy and provide prognostic clarity for patients with SAB during and after their hospital admission.

Risk factors for mortality among Canadian patients with *Staphylococcus aureus* bacteremia: a retrospective cohort study

Running Title: *Staphylococcus aureus* bacteremia in a Canadian population

Ram Venkatesh Anantha[1,4], Januvi Jegatheswaran[2,*], Daniel Luke Pepe[2,*], Fran Priestap[5], Johan Delport[3], S.M. Mansour Haeryfar[4], John K. McCormick[4], Tina Mele[1,4,5]

[1]Division of General Surgery, Department of Surgery, Schulich School of Medicine and Dentistry, Western University, London, ON, Canada

[2]Schulich School of Medicine and Dentistry, Western University, London, ON, Canada

[3]Department of Pathology, Schulich School of Medicine and Dentistry, Western University, London, ON, Canada

[4]Department of Microbiology and Immunology, Schulich School of Medicine and Dentistry, Western University, London, ON, Canada

[5]Division of Critical Care Medicine, Department of Medicine, Schulich School of Medicine and Dentistry, Western University, London, ON, Canada

[*]Both authors contributed equally to this work.

Corresponding authors:

Dr. Tina Mele, MD PhD FRCSC; Room A8-124, Division of General Surgery and Critical Care, Western University, 339 Windermere Road, London, ON, N6A 5A5 (Phone: 519-663-3970; Fax: 519-663-3459; Email: tina.mele@lhsc.on.ca) **OR** Dr. John K. McCormick PhD; Siebens-Drake Research Institute Rm. 133; Department of Microbiology and Immunology, Schulich School of Medicine and Dentistry, Western University, 1200 Richmond Road, London, ON, Canada, N6A5A5 (Phone: Fax: Email: john.mccormick@schulich.uwo.ca)

Abstract

Introduction: *Staphylococcus aureus* bacteremia (SAB) is a persistent and challenging disease, with few recent studies assessing its scope and burden in a Canadian population. We evaluated the magnitude of SAB in a large cohort of patients, and identified risk factors associated with increased mortality.

Methods: We retrospectively reviewed adult (>18 years old) patients admitted with SAB between 2008 and 2012 at a regional tertiary-care centre in Southwestern Ontario. Hospital records were used to identify comorbidities, complications of SAB such as sepsis and need for mechanical ventilation (MV), and mortality. Multivariable logistic regression was performed to determine predictors of overall, in-hospital, and post-discharge mortality.

Results: We identified 1114 patients in our study. The proportion of methicillin-resistant *S. aureus* (MRSA) strains rose significantly during the study period (p= 0.045), while in-hospital mortality declined significantly (29% in 2008 to 11% in 2012, p< 0.0001). Age, MRSA, sepsis, admission to the intensive care unit, hepatic failure, prolonged (> 21 days) MV, chronic obstructive pulmonary disease (COPD), and malignancy (primary and metastatic) were associated with overall mortality and— with the exception of COPD and primary malignancy— in-hospital mortality. In contrast, peripheral vascular and cerebrovascular disease, COPD, diabetes, and malignancy (solid and hematogenous) were associated with increased post-discharge mortality.

Interpretation: This study features one of the largest retrospective cohort studies of SAB in Canada, and identifies key factors associated with in-hospital and post-discharge mortality.

Identification of these predictors may guide empiric therapy and provide prognostic clarity for patients with SAB during and after their hospital admission.

Keywords: *Staphylococcus aureus*, bacteremia, MRSA, health outcomes research

Introduction

Staphylococcus aureus is a versatile and virulent pathogen with the ability to cause a multitude of life-threatening illnesses, including necrotizing soft-tissue infections,[1] infective endocarditis (IE)[2,3] and sepsis.[4] *S. aureus* is also one of the leading causes of healthcare-associated and hospital-acquired infections,[1,5,6] and the rates of infections are increasing steadily, particularly in North America and Europe.[5-8]

S. aureus bacteremia (SAB) is particularly associated with significant morbidity and mortality,[9] and demands rigorous management in order to prevent further infectious complications such as IE,[2,3] vertebral osteomyelitis,[10] embolic stroke,[9] recurrent infection, and metastatic disease. Despite the availability of treatment guidelines,[11,12] and scoring systems to estimate the likelihood of developing complications,[9] mortality from SAB remains approximately 20%.[1,9,12] Many studies from the previous decade[6,8,13-16] have also demonstrated the increasing prevalence of methicillin-resistant *S. aureus* (MRSA) strains within the community and in the hospital, leading to changes in the empiric treatment of SAB.[11] The objectives of our current retrospective cohort study, therefore, were to describe the contemporary scope of SAB and its complications, and to elucidate the risk factors associated with increased overall, in-hospital, and post-discharge mortality.

Methods

Setting

The present study was approved by the Western University Research Ethics Board (London, Ontario, Canada) and the Lawson Health Research Institute (approval number R-13-350). This study was conducted at the London Health Sciences Centre (LHSC), a tertiary-care

hospital system with two academic hospitals in Southwestern Ontario that serve a metropolitan population of approximately 435,000.[17] In addition to serving the local population, LHSC also receives referrals from 33 rural hospitals in 7 counties, covering a catchment area that spans 21,000 square kilometres and a population of 2 million.[17]

Patients

All adult patients who developed *S. aureus* bacteremia between January 1, 2008 and December 31, 2012 were initially included in the study. Reasons for excluding patients from the study are indicated in Figure 1 and included polymicrobial infection (blood culture result positive for more than 1 pathogen), age younger than 18 years, death prior to the return of a positive culture result (to avoid confounding the analysis for mortality), patients who were not admitted or left against medical advice, and incomplete hospital records.

Definitions

SAB was defined as occurring in a patient with at least one blood culture positive for *S. aureus*. Comorbidity was defined as a disease or therapy that could predispose patients to infection, alter defense mechanisms, or cause functional impairment, such as the following: coronary artery disease; severe cardiac disease with symptomatic heart failure; peripheral vascular disease; cerebrovascular disease; dementia; severe chronic obstructive pulmonary disease (COPD); connective tissue disease; peptic ulcer disease; liver disease; diabetes; renal disease; active neoplastic disease; and HIV infection.

Patients with complicated SAB infections had a site of infection remote from the primary focus caused by hematogenous seeding (e.g. endocarditis or vertebral osteomyelitis) or extension of infection beyond the primary focus (e.g. septic thrombophlebitis or abscess). All cases of

complicated infection were independently defined by radiologic imaging, culture of *S. aureus* from an otherwise normally sterile site, or the use of validated diagnostic criteria.[9,11,12] Septic shock, soft tissue source, and intravascular catheter source were defined according to standard methods.[12,18,19] Patients with uncomplicated SAB exhibited no evidence of complicated or recurrent SAB infection, which was defined as a positive culture result obtained from the same case within twelve weeks from the initial culture.

Operative intervention was defined as a procedure requiring general anaesthesia, and/or performed by a surgeon or interventional radiologist in the operating room or angiography suite. Bedside procedures such as upper and lower endoscopy, percutaneous tracheostomy, and abscess drains were not considered operations for this study.

Study design and outcomes

This was a retrospective cohort study. Our primary outcome was overall mortality which was identified from the patient record. Secondary outcomes included attributable in-hospital mortality,[9] defined as patients who died with persistent signs or symptoms of systemic infection, positive blood culture results, or a persistent focus of infection in the absence of another explanation for death during their hospital admission for SAB, requirement for prolonged (>21 days) mechanical ventilation, length of hospital stay, development of complicated SAB infections, and post-discharge mortality.

Statistical analysis

Descriptive statistics of patient variables were calculated for all patients with SAB. Continuous data were expressed as median (interquartile range; IQR; 25-75 percentile), and categorical variables were reported as frequencies and percentages. The significance of trends in

methicillin-resistant *S. aureus* (MRSA) infections, proportion of intravenous drug users, and in-hospital mortality was assessed with the Cochran-Armitage chi-square test for trend.

Univariable logistic regression was used to evaluate the association between mortality (overall, in-hospital, and post-discharge) and each individual patient characteristic or clinical factor. Clinically-relevant variables (based on published studies[18,20-23]), as well as variables showing a significant association ($p< 0.1$) with overall mortality, in-hospital mortality, or post-discharge mortality, were included in three multivariable logistic regression models obtained using stepwise regression. The significance levels for variables entering into and remaining in the models were set at 0.05 and 0.10 respectively. For recurrent cases of SAB, only the first admission was used in the univariable and multivariable analyses. Odds ratios (ORs) and Wald 95% confidence intervals (CIs) were computed. Calibration of each multivariable model was assessed using the Hosmer-Lemeshow goodness-of-fit test[24] to evaluate whether significant discrepancies existed between the observed and expected mortality. All tests were two-tailed, and a p value of less than 0.05 was considered to be statistically significant. Statistical analysis was performed using SAS, Version 9.3 (SAS Institute, Inc., Cary, NC).

Results

We identified 1114 patients who met our inclusion criteria and were admitted to LHSC for SAB during the study period (Figure 1); their demographics are presented in Table 1. Sixty-three percent of patients were male and 19% were intravenous drug users (IVDU). The overall incidence of MRSA was 43% in our study, while the incidence of sepsis was 70%. In our study, 126 patients (11%) had pneumonia, while 20% had a soft-tissue infection, and a further 6.9% had an intravascular catheter as a source of their infection.

In this study, 499 patients (45%) developed a complicated SAB infection (Table 2). Amongst all cases, 205 patients (18%) developed recurrent invasive infections, and 122 patients (11%) were diagnosed with IE. A smaller proportion of patients developed vertebral osteomyelitis (2.2%), deep tissue infections (5%), epidural and psoas abscesses (2% and 1.1% respectively), and embolic strokes (0.72%). Complications sustained during the course of the hospital stay included renal failure requiring dialysis (9.5%), prolonged mechanical ventilation lasting more than 21 days (5.6%) and hepatic failure (2.2%). A further 39 patients (3.5%) developed *C. difficile* enterocolitis or ischemic colitis. A total of 263 patients (24%) were admitted to the intensive care unit during their admission, while 251 (23%) patients died in-hospital; a further 212 (19%) patients died post-discharge. Among the latter group, 60 patients (28% of post-discharge mortalities) died within 90 days of discharge.

We examined the trends in proportions of MRSA, IVDUs, and in-hospital mortality throughout the study period. The proportion of MRSA strains isolated from SAB patients increased significantly from 40% in 2008 to 51% in 2012 (Figure 2; $p = 0.045$). The proportion of IVDUs in our study population also rose significantly during the study period (14% in 2008 to 22% of patients in 2012, $p = 0.0034$). In-hospital mortality, however, declined significantly from 29% in 2008 to 11% in 2012 ($p < 0.0001$; Figure 2).

When we performed multivariable logistic regression analyses on overall mortality (Table 3), age (in decades), methicillin resistance, diagnosis of sepsis, admission to the ICU, development of hepatic failure, requirement for prolonged mechanical ventilation, COPD, presence of solid malignancy or leukemia, and metastatic cancer, were all independently associated with increased mortality. Operative intervention was associated with a reduced risk of overall mortality. These factors, with the exception of COPD and the presence of solid

malignancy or leukemia, were also independently associated with increased in-hospital mortality (Table 4). The presence of skin and soft tissue infection as a source of SAB was associated with reduced in-hospital mortality. The clinical variables independently associated with increased post-discharge mortality (Table 4) were the presence of peripheral vascular and cerebrovascular disease, COPD, diabetes, and primary solid or hematogenous malignancy. As with overall mortality, operative intervention was independently associated with a reduced risk of post-discharge mortality.

Interpretation

Information about the magnitude and burden of SAB, as well as associated risk factors for mortality, is critical for the management of this disease. Our study features one of the largest retrospective cohort studies of SAB in Canada, wherein we describe the incidence and distribution of SAB and its complications, and identify predictors of overall, in-hospital, and post-discharge mortality.

Although the overall mortality rate in our cohort was 23%, the in-hospital mortality rate declined significantly during the study period. This observation may be explained by two priorities that were initiated at our institution in 2008 to reduce *S. aureus* infections: the implementation of infection control strategies to specifically prevent the spread of *S. aureus*; and the development of algorithms to rapidly identify and treat patients with severe infections.[25] The adoption of similar measures is also felt to have contributed to a comparable observation made by Benfield *et al* in a Danish study,[26] where case-mortality associated with hospital- and community-acquired SAB declined by 43% and 23% respectively over a 19-year period.

Factors that were previously shown to be predictive of in-hospital mortality correlated with the variables identified in our study, including age,[27] sepsis,[27,28] methicillin resistance,[14,29] ICU admission,[30] hepatic failure,[27] mechanical ventilation,[31] COPD, and primary and metastatic malignancy (both solid and haematological).[31,32] The large sample size allowed us to investigate the association between specific patient characteristics and outcomes, rather than aggregating comorbidities using scales such as the Charlson Comorbidity Index. An additional novelty of this study is the identification of risk factors associated with post-discharge mortality, given that an increasing number of patients with SAB are surviving beyond the length of their hospital stay.[33-35] Our finding that peripheral vascular and cerebrovascular disease, COPD, diabetes, and primary malignancy increased the risk of post-discharge mortality (but not in-hospital mortality) demonstrates that not all concurrent comorbidities are alike in effect. Furthermore, a significant majority of post-discharge mortalities occurred beyond 90 days after leaving the hospital, suggesting that patients sustain long-term adverse consequences from SAB long after they are treated for their acute episode.[33]

Our study also extends the findings of a Canadian population-based analysis in 2007 by Laupland and colleagues, who observed MRSA bacteremia in 11% of bacteremic *S. aureus* infections.[8] The proportion of methicillin resistance among SAB isolates is significantly higher in our study, but is comparable to several American studies.[2,13,36-38] Klevens *et al* reported that MRSA strains accounted for 64% of hospital-acquired *S. aureus* infections isolated from intensive care units,[5] while Styers *et al*[15] observed that between 47.9% and 59.2% of hospital-acquired *S. aureus* isolates demonstrated methicillin resistance. Despite the implementation of infection control strategies and empiric treatment coverage for MRSA, the incidence of MRSA among SAB patients continued to rise significantly in our study, mimicking the trend seen in

many North American and European centres.[6,8,26,39] Additionally, methicillin resistance was found to be a significant predictor of mortality in our study, corroborating observations by Cosgrove *et al*[14] and Blot *et al.*[29] Interestingly, a large retrospective cohort study at an American centre[27] showed that methicillin resistance was not associated with increased risk of death, suggesting that genetic variations between MRSA strains in different geographic regions[16] can affect disease severity and alter outcomes. Nevertheless, our observations affirm the need for increased awareness and rigorous treatment of MRSA infections,[8,13,31] as well as continued vigilance in screening and identifying patients colonized with MRSA.[6,40]

The male preponderance and older age of our study population supports previous observations that males and elderly individuals are at increased risk for developing SAB.[8] However, the patient-specific comorbidities associated with mortality in our study (peripheral and cerebrovascular disease, COPD, malignancy, and diabetes) are different from the risk factors associated with the acquisition of SAB (diabetes, heart disease, cancer, need for dialysis, and hepatitis C) as identified by Laupland *et al*,[8] suggesting that the interaction between patient-specific factors and pathogen virulence plays a critical role in determining eventual outcome, rather than patient comorbidities alone.

This study also highlights the impact of SAB and its complications on healthcare resource utilization. Our rate of complicated SAB (45%) is similar to a prospective study by Fowler *et al,*[9] in which 43% of 724 patients with SAB were found to have developed a complicated SAB infection during a twelve-week period. In our study, a significant proportion of patients required admission to the ICU, while a smaller number required prolonged mechanical ventilation or dialysis for renal failure. These complications, in addition to the infectious consequences of SAB such as IE and osteomyelitis, significantly increase the morbidity of

SAB,[1,11,12] prolong hospital stay,[41] and reduce survival.[9,11,12] The results of our study, therefore, may prompt a closer examination of treatment strategies for SAB, in order to optimize outcomes.

Although this study benefits from its large size, it is limited by its retrospective design and single-center setting. Additionally, we may have underestimated the incidence of SAB disease if patients in the region sought health care from other facilities. We were also unable to assess the duration and adequacy of antibiotic therapy for all study patients, limiting our ability to control for these confounders by multivariable analysis. While complications of SAB can be difficult to identify at the time of the initial positive result of blood culture and may be prone to selection bias, our review of the medical records throughout patients' hospital stay is likely to have helped to reduce the bias, and improve the identification of complications. Selection bias is also likely to have contributed to our finding that operative intervention was associated with reduced overall and post-discharge mortality, given that patients selected for surgery may be healthier than their non-surgical counterparts. Therefore, further stratification and analysis of the subgroup undergoing surgical intervention, and comparison with a matched non-surgical cohort, is necessary to better understand the effect of surgery on survival in SAB.

In conclusion, we present one of the largest retrospective cohort studies of SAB in Canada, and highlight the significant clinical impact of an important and pervasive disease. In addition to describing the incidence and burden of SAB in a Canadian population, we have also identified important risk factors associated with overall, in-hospital, and post-discharge mortality. The results of our study may help in the inpatient management of SAB, provide prognostic clarity for affected patients, and aid in the follow-up of at-risk patient populations after their hospital stay.

Disclosure

The authors do not have any actual or potential conflicts of interest to declare.

Author Contributions

Ram Anantha was responsible for the study design, data collection, statistical analysis and interpretation, drafting of the manuscript, and assisting with obtainment of funding. Januvi Jegatheswaran and Daniel Pepe collected the data. Fran Priestap performed the statistical analysis and contributed to the drafting of the initial manuscript. Johan Delport and Mansour Haeryfar contributed to the study design and interpretation of the data. John McCormick and Tina Mele obtained funding, and supervised all aspects of the study. All of the authors revised the manuscript for critical and important intellectual content, and approved the final version to be published.

Acknowledgements

Ram Anantha is supported by the Clinical-Investigator Program (Royal College of Physicians and Surgeons of Canada), an Ontario Graduate Scholarship (Ontario Ministry of Education), and a Canadian Institutes of Health Research (CIHR) Canada Graduate Scholarship. This study was supported by grants from CIHR to John McCormick (MOP 64176) and Mansour Haeryfar (MOP 130465). Mansour Haeryfar holds a Canada Research Chair in Viral Immunity & Pathogenesis. Tina Mele is also supported by the Department of Surgery (Western University) and the Lawson Health Research Institute (London, Ontario).

References

1. Lowy FD. Staphylococcus aureus infections. *N Engl J Med.* 1998;339:520-32.
2. Fowler VG, Jr., Miro JM, Hoen B, et al. Staphylococcus aureus endocarditis: a consequence of medical progress. *JAMA.* 2005;293:3012-21.
3. Miro JM, Anguera I, Cabell CH, et al. Staphylococcus aureus native valve infective endocarditis: report of 566 episodes from the International Collaboration on Endocarditis Merged Database. *Clin Infect Dis.* 2005;41:507-14.
4. Diekema DJ, Pfaller MA, Schmitz FJ, et al. Survey of infections due to Staphylococcus species: frequency of occurrence and antimicrobial susceptibility of isolates collected in the United States, Canada, Latin America, Europe, and the Western Pacific region for the SENTRY Antimicrobial Surveillance Program, 1997-1999. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2001;32 Suppl 2:S114-32.
5. Klevens RM, Edwards JR, Tenover FC, et al. Changes in the epidemiology of methicillin-resistant Staphylococcus aureus in intensive care units in US hospitals, 1992-2003. *Clin Infect Dis.* 2006;42:389-91.
6. Simor AE, Ofner-Agostini M, Bryce E, et al. The evolution of methicillin-resistant Staphylococcus aureus in Canadian hospitals: 5 years of national surveillance. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne.* 2001;165:21-6.
7. Tadros M, Williams V, Coleman BL, et al. Epidemiology and Outcome of Pneumonia Caused by Methicillin-Resistant Staphylococcus aureus (MRSA) in Canadian Hospitals. *PLoS One.* 2013;8:e75171.
8. Laupland KB, Ross T, Gregson DB. Staphylococcus aureus bloodstream infections: risk factors, outcomes, and the influence of methicillin resistance in Calgary, Canada, 2000-2006. *The Journal of infectious diseases.* 2008;198:336-43.
9. Fowler VG, Jr., Olsen MK, Corey GR, et al. Clinical identifiers of complicated Staphylococcus aureus bacteremia. *Arch Intern Med.* 2003;163:2066-72.
10. Park KH, Chong YP, Kim SH, et al. Clinical characteristics and therapeutic outcomes of hematogenous vertebral osteomyelitis caused by methicillin-resistant Staphylococcus aureus. *J Infect.* 2013.
11. Corey GR. Staphylococcus aureus bloodstream infections: definitions and treatment. *Clin Infect Dis.* 2009;48 Suppl 4:S254-9.
12. Mitchell DH, Howden BP. Diagnosis and management of Staphylococcus aureus bacteraemia. *Intern Med J.* 2005;35 Suppl 2:S17-24.
13. Kuehnert MJ, Hill HA, Kupronis BA, Tokars JI, Solomon SL, Jernigan DB. Methicillin-resistant-Staphylococcus aureus hospitalizations, United States. *Emerging infectious diseases.* 2005;11:868-72.
14. Cosgrove SE, Sakoulas G, Perencevich EN, Schwaber MJ, Karchmer AW, Carmeli Y. Comparison of mortality associated with methicillin-resistant and methicillin-susceptible Staphylococcus aureus bacteremia: a meta-analysis. *Clin Infect Dis.* 2003;36:53-9.
15. Styers D, Sheehan DJ, Hogan P, Sahm DF. Laboratory-based surveillance of current antimicrobial resistance patterns and trends among Staphylococcus aureus: 2005 status in the United States. *Ann Clin Microbiol Antimicrob.* 2006;5:2.

16. Simor AE, Ofner-Agostini M, Bryce E, et al. Laboratory characterization of methicillin-resistant Staphylococcus aureus in Canadian hospitals: results of 5 years of National Surveillance, 1995-1999. *The Journal of infectious diseases.* 2002;186:652-60.
17. Statistics Canada. Census Profile - Population Centre. 2011; http://www12.statcan.gc.ca/census-recensement/2011/dp-pd/prof/details/page.cfm?Lang=E&Geo1=POPC&Code1=0480&Geo2=PR&Code2=35&Data=Count&SearchText=London&SearchType=Begins&SearchPR=01&B1=All&Custom=&TABID=1. Accessed January 29, 2014.
18. Conterno LO, Wey SB, Castelo A. Risk factors for mortality in Staphylococcus aureus bacteremia. *Infect Control Hosp Epidemiol.* 1998;19:32-7.
19. Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med.* 2003;31:1250-6.
20. Mylotte JM, Aeschlimann JR, Rotella DL. Staphylococcus aureus bacteremia: factors predicting hospital mortality. *Infect Control Hosp Epidemiol.* 1996;17:165-8.
21. Mylotte JM, Tayara A. Staphylococcus aureus bacteremia: predictors of 30-day mortality in a large cohort. *Clin Infect Dis.* 2000;31:1170-4.
22. Schonheyder HC, Gottschau A, Friland A, Rosdahl VT. Mortality rate and magnitude of Staphylococcus aureus bacteremia as assessed by a semiquantitative blood culture system. *Scand J Infect Dis.* 1995;27:19-21.
23. Jensen AG, Wachmann CH, Espersen F, Scheibel J, Skinhoj P, Frimodt-Moller N. Treatment and outcome of Staphylococcus aureus bacteremia: a prospective study of 278 cases. *Arch Intern Med.* 2002;162:25-32.
24. Hosmer DW, Lemeshow, S., and Sturdivant, Rodney X. *Applied Logistic Regression*. 2nd ed: Wiley; 2004.
25. Dellinger RP, Carlet JM, Masur H, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Critical care medicine.* 2004;32:858-73.
26. Benfield T, Espersen F, Frimodt-Moller N, et al. Increasing incidence but decreasing in-hospital mortality of adult Staphylococcus aureus bacteraemia between 1981 and 2000. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases.* 2007;13:257-63.
27. Pastagia M, Kleinman LC, Lacerda de la Cruz EG, Jenkins SG. Predicting risk for death from MRSA bacteremia. *Emerging infectious diseases.* 2012;18:1072-80.
28. Kang CI, Song JH, Chung DR, et al. Bloodstream infections in adult patients with cancer: clinical features and pathogenic significance of Staphylococcus aureus bacteremia. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer.* 2012;20:2371-8.
29. Blot SI, Vandewoude KH, Hoste EA, Colardyn FA. Outcome and attributable mortality in critically Ill patients with bacteremia involving methicillin-susceptible and methicillin-resistant Staphylococcus aureus. *Arch Intern Med.* 2002;162:2229-35.
30. Castillo JS, Leal AL, Cortes JA, et al. Mortality among critically ill patients with methicillin-resistant Staphylococcus aureus bacteremia: a multicenter cohort study in Colombia. *Revista panamericana de salud publica = Pan American journal of public health.* 2012;32:343-50.
31. Wang FD, Chen YY, Chen TL, Liu CY. Risk factors and mortality in patients with nosocomial Staphylococcus aureus bacteremia. *American journal of infection control.* 2008;36:118-22.

32. Joo EJ, Peck KR, Ha YE, et al. Impact of acute kidney injury on mortality and medical costs in patients with meticillin-resistant Staphylococcus aureus bacteraemia: a retrospective, multicentre observational study. *The Journal of hospital infection.* 2013;83:300-6.
33. Fatkenheuer G, Preuss M, Salzberger B, et al. Long-term outcome and quality of care of patients with Staphylococcus aureus bacteremia. *Eur J Clin Microbiol Infect Dis.* 2004;23:157-62.
34. Wolkewitz M, Frank U, Philips G, Schumacher M, Davey P, Group BS. Mortality associated with in-hospital bacteraemia caused by Staphylococcus aureus: a multistate analysis with follow-up beyond hospital discharge. *J Antimicrob Chemother.* 2011;66:381-6.
35. Wang HE, Szychowski JM, Griffin R, Safford MM, Shapiro NI, Howard G. Long-term mortality after community-acquired sepsis: a longitudinal population-based cohort study. *BMJ open.* 2014;4:e004283.
36. Strausbaugh LJ, Crossley KB, Nurse BA, Thrupp LD. Antimicrobial resistance in long-term-care facilities. *Infect Control Hosp Epidemiol.* 1996;17:129-40.
37. Klein E, Smith DL, Laxminarayan R. Hospitalizations and deaths caused by methicillin-resistant Staphylococcus aureus, United States, 1999-2005. *Emerging infectious diseases.* 2007;13:1840-6.
38. Federspiel JJ, Stearns SC, Peppercorn AF, Chu VH, Fowler VG, Jr. Increasing US rates of endocarditis with Staphylococcus aureus: 1999-2008. *Arch Intern Med.* 2012;172:363-5.
39. Frederiksen MS, Espersen F, Frimodt-Moller N, et al. Changing epidemiology of pediatric Staphylococcus aureus bacteremia in Denmark from 1971 through 2000. *Pediatr Infect Dis J.* 2007;26:398-405.
40. Loeb MB, Main C, Eady A, Walker-Dilks C. Antimicrobial drugs for treating methicillin-resistant Staphylococcus aureus colonization. *Cochrane Database Syst Rev.* 2003:CD003340.
41. Chang FY, MacDonald BB, Peacock JE, Jr., 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;82:322-32.

Figure Legends

Figure 1: Patients included and excluded from the study

Figure 2: Number of quarterly admissions for patients with *Staphylococcus aureus* bacteremia (SAB) between 2008 and 2012, and quarterly proportions of methicillin-resistant *S. aureus* (MRSA), in-hospital mortality, and intravenous drug users as a percentage of SAB patients. *$p<$ 0.05, **$p<$ 0.01, ***$p<$ 0.001 by Cochran-Armitage chi-square test for trend.

Table 1: Characterization of 1114 patients with *Staphylococcus aureus* bacteremia

Characteristic	Value
Age, y (range)	64 (18-102)
Male gender, n (%)	706 (63)
Comorbidities, n (%):	
HIV positive / AIDS	32 (2.9)
Injection drug use	214 (19)
Diabetes mellitus	306 (27)
Cardiac disease (CAD, CHF)	278 (25)
Peripheral vascular disease	97 (8.7)
Cerebrovascular Disease	171 (15)
Dementia	65 (5.8)
COPD	104 (9.3)
Liver disease:	228 (20)
Hepatitis B/C co-infection	73 (6.5)
Cirrhosis	36 (3.2)
Pre-existing renal disease	227 (20)
Solid malignancy	200 (18)
Leukemia and lymphoma	38 (3.4)
Metastatic malignancy	94 (8.4)
Infection characteristics, n (%):	
MRSA	477 (43)
Sepsis	775 (70)
Dominant focus of infection, n (%):	
Central or peripheral intravascular catheter	77 (6.9)
Pneumonia	126 (11)
Skin and soft tissue infection	219 (20)
Other[1]	10 (0.90)

[1] Includes foci that occur in less than 1% of cases each, such as central nervous system infection (3), lung abscess (3), urinary tract infection (4).

Table 2: Outcomes of 1114 patients with *Staphylococcus aureus* bacteremia

Outcome	Value
Complicated *S. aureus* bacteremia, n (%):	
Recurrent infections:	205 (18)
One recurrence	177 (16)
Two recurrences	14 (1.2)
Three or more recurrences	14 (1.2)
Infective endocarditis	122 (11)
Septic arthritis	24 (2.2)
Deep tissue abscess	56 (5.0)
Osteomyelitis:	
Vertebral	25 (2.2)
Non-vertebral (ie. hand or foot)	6 (0.54)
Epidural abscess	22 (2.0)
Septic thrombophlebitis	2 (0.18)
Psoas abscess	12 (1.1)
Meningitis	4 (0.36)
Embolic stroke	8 (0.72)
Other complications[1]	13 (1.2)
Complications during hospital stay, n (%):	
Operative intervention	364 (33)
Renal failure requiring dialysis	106 (9.5)
Hepatic failure	25 (2.2)
Prolonged ventilation (> 21 days)	63 (5.6)
Clostridium difficile infection	22 (2.0)
Ischemic colitis	17 (1.5)
Myocardial infarction	10 (0.90)
Admission to intensive care unit (ICU), n (%)	263 (24)
Length of stay in hospital, days (IQR[2])	14 (7-28)
Mortality, n (%):	463 (42)
In-hospital mortality	251 (23)
Mortality post-discharge:	212 (19)
30-day	30 (2.7)
90-day	60 (5.4)

[1] Includes patients with mycotic aneurysm (7), empyema (4), and pericarditis (2)

[2] Interquartile range (25-75 percentile)

Table 3: Univariable and multivariable analysis of risk factors contributing to overall mortality

Parameter	Univariable Analysis		Multivariable Analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (decades)	**1.40 (1.30 - 1.50)**	**<0.0001**	**1.40 (1.30 - 1.51)**	**<0.0001**
Male gender	0.95 (0.74 - 1.21)	0.665	-	-
Injection drug use	0.36 (0.26 - 0.51)	<0.0001	-	NS[1]
Methicillin resistance	**1.35 (1.06 - 1.71)**	**0.015**	**1.33 (1.01 - 1.75)**	**0.041**
Sepsis	**1.68 (1.29 - 2.19)**	**0.0001**	**1.72 (1.27 - 2.33)**	**0.0005**
Pneumonia	2.04 (1.40 - 2.96)	0.0002	-	NS
Skin/soft tissue infection	0.79 (0.58 - 1.07)	0.126	-	-
Admission to ICU	**2.80 (2.09 - 3.74)**	**<0.0001**	**3.26 (2.28 - 4.67)**	**<0.0001**
Coronary artery disease	1.76 (1.29 - 2.42)	0.0004	-	NS
Congestive heart failure	1.84 (1.20 - 2.83)	0.005	-	NS
Peripheral vascular disease	1.42 (0.94 - 2.16)	0.099	-	NS
Acute kidney injury (dialysis-dependent)	1.59 (1.06 - 2.37)	0.024	-	NS
Hepatic failure	**4.60 (1.82 - 11.61)**	**0.001**	**4.62 (1.69 - 12.66)**	**0.003**
Prolonged ventilation >21 d	**3.49 (2.01 - 6.07)**	**<0.0001**	**2.15 (1.12 - 4.11)**	**0.021**
Operative intervention	**0.64 (0.48 - 0.84)**	**0.001**	**0.50 (0.36 - 0.69)**	**<0.0001**
Cerebrovascular disease	1.90 (1.37 - 2.64)	0.0001	-	NS
Dementia	2.72 (1.61 - 4.60)	0.0002	-	NS
COPD	**2.68 (1.77 - 4.08)**	**<0.0001**	**1.96 (1.24 – 3.11)**	**0.004**
Connective tissue disease	1.04 (0.52 - 2.09)	0.919	-	-
Peptic ulcer disease	1.17 (0.63 - 2.17)	0.623	-	-
Liver disease	0.60 (0.44 - 0.82)	0.001	-	NS
Hepatitis C infection	0.39 (0.21 - 0.69)	0.002	-	NS
Hepatitis B infection	1.41 (0.28 - 7.01)	0.676	-	-
Diabetes	1.35 (1.03 - 1.76)	0.027	-	NS
Pre-existing renal disease	1.30 (0.97 - 1.74)	0.079	-	NS
Solid malignancy	**2.56 (1.87 - 3.51)**	**<0.0001**	**1.67 (1.08 - 2.56)**	**0.020**
Leukemia	**2.72 (1.20 - 6.16)**	**0.016**	**3.47 (1.40 - 8.64)**	**0.008**
Lymphoma	1.98 (0.63 - 6.29)	0.245	-	-
Cirrhosis	1.00 (0.51 - 1.97)	0.990	-	-
Metastatic cancer	**3.70 (2.34 - 5.86)**	**<0.0001**	**2.54 (1.39 – 4.66)**	**0.003**
AIDS	0.46 (0.21 - 1.03)	0.060	-	NS

[1] NS: Not significant

Table 4: Multivariable analysis of in-hospital and post-discharge mortality among 1114 patients with *Staphylococcus aureus* bacteremia.

Parameter[1]	In-hospital Mortality		Post-discharge Mortality	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (decades)	1.54 (1.40 - 1.70)	<0.0001	-	NS[2]
Sepsis	1.62 (1.12 - 2.34)	0.011	-	-
Skin/soft tissue infection	0.61 (0.39 - 0.97)	0.036	-	-
Admission to ICU	4.78 (3.29 – 6.95)	<0.0001	-	NS
Coronary artery disease	-	NS	-	-
Congestive heart failure	-	-	-	NS
Peripheral vascular disease	-	-	1.94 (1.19 – 3.17)	0.008
Acute kidney injury (dialysis-dependent)	-	-	-	NS
Hepatic failure	6.28 (2.44 – 16.16)	<0.0001	-	-
Prolonged ventilation >21 d	2.16 (1.17 – 3.99)	0.0141	-	-
Operative intervention	-	-	0.61 (0.41 - 0.90)	0.012
Cerebrovascular disease	-	NS	1.50 (1.01 - 2.23)	0.042
Dementia	-	NS	-	NS
COPD	-	-	2.51 (1.61 - 3.91)	<0.0001
Liver disease	-	NS	-	NS
Hepatitis C infection	-	NS	-	-
Diabetes	-	-	1.50 (1.06 - 2.11)	0.021
Pre-existing renal disease	-	-		NS
Solid malignancy	-	NS	1.67 (1.15 - 2.44)	0.007
Leukemia	-	-	2.93 (1.26 - 6.82)	0.013
Metastatic cancer	3.15 (1.92 - 5.16)	<0.0001	-	NS

[1] In both models, variables that were significant in the univariable analyses and clinically-significant variables were independently analyzed by logistic regression and shown in the table.

[2] NS: Not significant

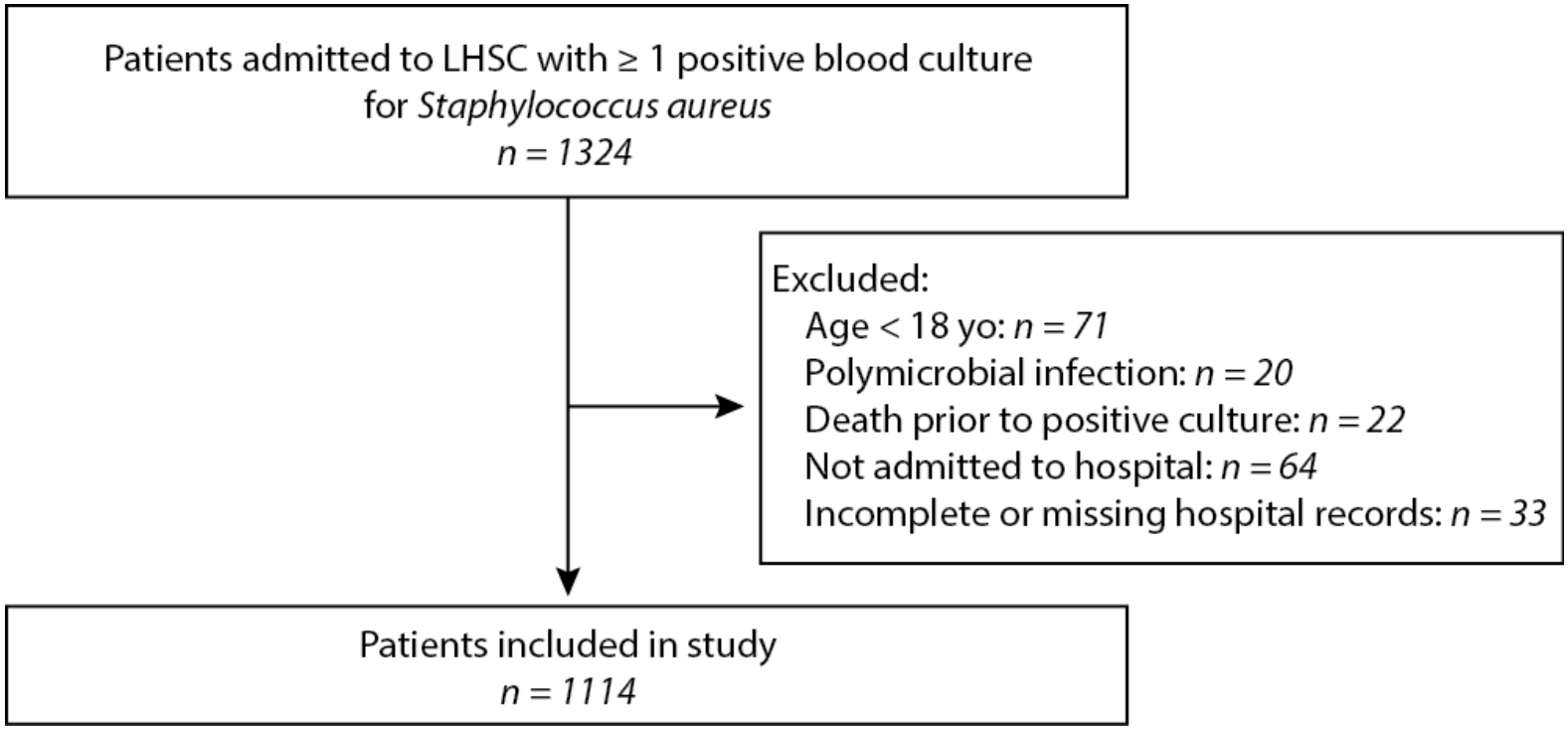
Patients admitted to LHSC with ≥ 1 positive blood culture
for *Staphylococcus aureus*
n = 1324
Excluded:
Age < 18 yo: *n = 71*
Polymicrobial infection: *n = 20*
Death prior to positive culture: *n = 22*
Not admitted to hospital: *n = 64*
Incomplete or missing hospital records: *n = 33*
Patients included in study
n = 1114

Figure 1

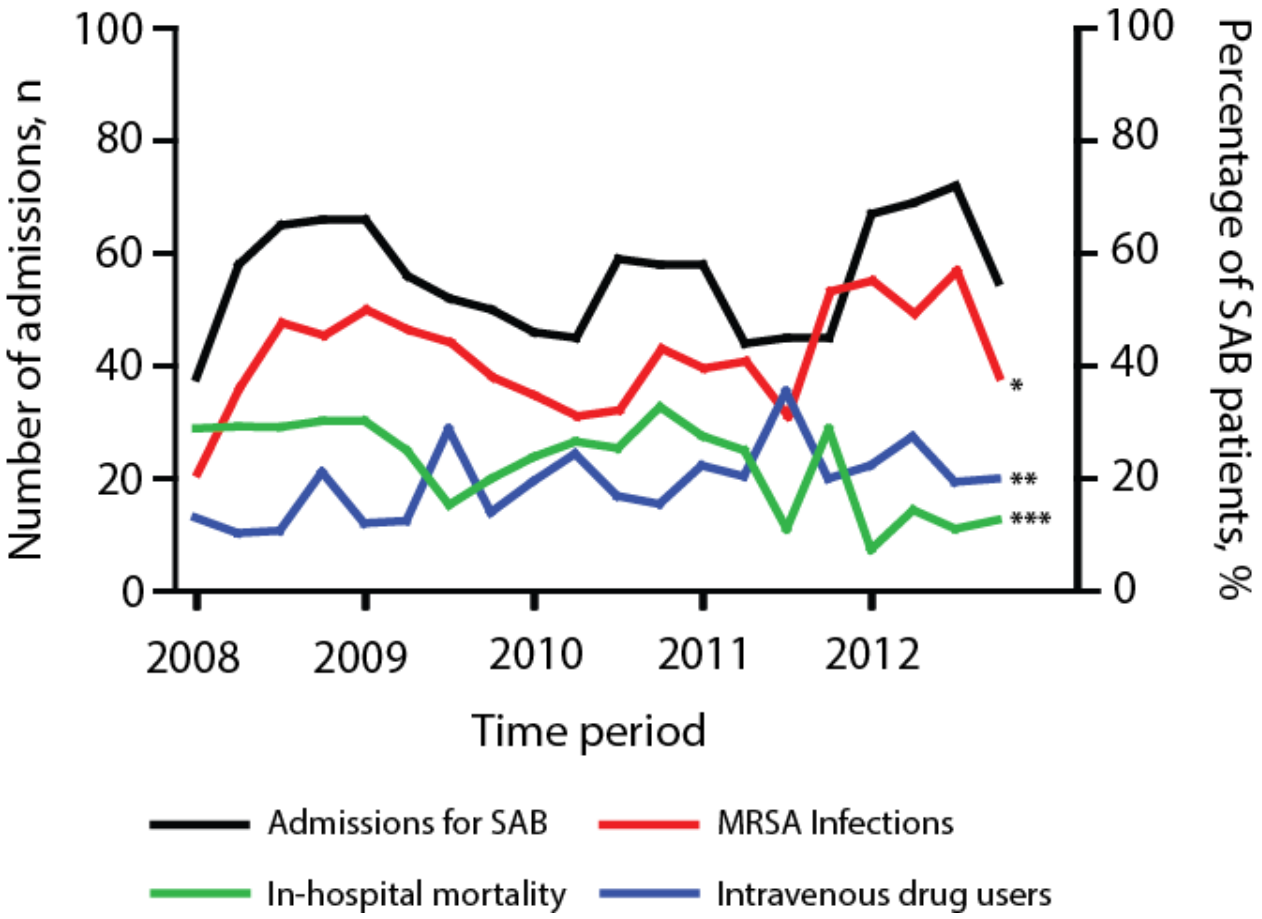
Number of admissions, n
Percentage of SAB patients, %
100
80
60
40
20
0
2008
2009
2010
2011
2012
Time period
*
**
***
Admissions for SAB
MRSA Infections
In-hospital mortality
Intravenous drug users

Figure 2