Infection (2019) 47:961–971
https://doi.org/10.1007/s15010-019-01330-5

ORIGINAL PAPER

Epidemiology and Outcome Determinants of *Staphylococcus aureus* Bacteremia Revisited: A Population-Based Study

John C. Lam[1] · Daniel B. Gregson[2] · Stephen Robinson[3] · Ranjani Somayaji[4] · John M. Conly[5] · Michael D. Parkins[4]

Received: 3 February 2019 / Accepted: 27 May 2019 / Published online: 3 July 2019

Abstract

Purpose *Staphylococcus aureus bacteremia* (SAB) is associated with significant morbidity and mortality. We sought to re-define the burden, epidemiology and mortality-associated risk factors of SAB in a large Canadian health region.

Methods Residents (> 18 years) experiencing SAB from 2012 to 2014 were assessed. Incidence rates were calculated using civic census results. Factors associated with 30-day mortality were determined through multivariate logistic regression. Incidence and risk factors for SAB were compared to 2000–2006 data.

Results 780 residents experienced 840 episodes of SAB (MRSA; 20%). Incidence rates increased from 23.5 to 32.0 cases/100,000 from 2012 to 2014; [IRR 1.15 (95% CI 1.07–1.23); $p < 0.001$]. Compared to a decade ago, incidence of SAB has increased [IRR 1.28 (95% CI 1.21–1.36); $p < 0.001$] despite minimal change in nosocomial SAB. MRSA proportion did not change through the study ($p = 0.3$), but did increase relative to a decade ago (20.0% vs 11.0%, $p < 0.001$). Thirty-day mortality rates were 30.6% and 21.3% for MRSA and MSSA, respectively ($p = 0.01$), similar to rates from 2000 to 2006. Several clinical, demographic, and biochemical factors were independently associated with SAB mortality.

Conclusions SAB is common within our population resulting in significant mortality. Incidence rates of SAB are increasing in our health region; however, 30-day mortality rates remain stable.

Keywords Bacteremia · *Staphylococcus aureus* · MRSA · Mortality · Epidemiology

✉ Michael D. Parkins
mdparkin@ucalgary.ca

John C. Lam
john.c.lam@ucalgary.ca

Daniel B. Gregson
Dan.Gregson@cls.ab.ca

Stephen Robinson
stephen.ross.robinson@gmail.com

Ranjani Somayaji
rsomayaji@gmail.com

John M. Conly
john.conly@cls.ab.ca

[1] Department of Medicine, University of Calgary, 3330 Hospital Drive NW, Calgary, AB T2N 4N1, Canada

[2] Departments of Medicine and Pathology and Laboratory Medicine, Calgary Laboratory Services, Snyder Institute for Chronic Disease, University of Calgary, 3330 Hospital Drive NW, Calgary, AB T2N 4N1, Canada

[3] Department of Medicine, Dalhousie University, 5849 University Ave, Halifax, NS B3H 4R2, Canada

[4] Departments of Medicine and Microbiology, Immunology and Infectious Diseases, Snyder Institute for Chronic Disease, University of Calgary, 3330 Hospital Drive NW, Calgary, AB T2N 4N1, Canada

[5] Departments of Medicine, Microbiology, Immunology and Infectious Diseases, Pathology and Laboratory Medicine, Snyder Institute for Chronic Disease, University of Calgary, 3330 Hospital Drive NW, Calgary, AB T2N 4N1, Canada

Introduction

Staphylococcus aureus bacteremia (SAB) is a common cause of community-acquired and health-care-associated bloodstream infections with an annual population-based incidence rate ranging from 20 to 30 cases/100,000 population in higher income countries [1].

Patterns of SAB epidemiology differ depending on geography. In the United Kingdom, rates of methicillin-resistant *S. aureus* (MRSA) bacteremia have dropped significantly over the last decade—thought to be secondary to improved hospital-based infection prevention and control measures, including improved rates of hand hygiene [2]. However, North American studies have demonstrated an increase in MRSA bacteremia rates while observing relatively stable rates of methicillin-susceptible *S. aureus* (MSSA) bacteremia [3]. The role of community-acquired MRSA has been highlighted as a factor for driving this increase in North American SAB incidence rates [4, 5].

In the pre-antibiotic era, SAB mortality rates were as high as 75%. With effective antibacterial therapies, and source control strategies, mortality rates have fallen to ~ 25% over the last 2 decades. Factors associated with death have been pursued in multiple studies and include age and increasing number of comorbidities, with varying magnitude of impact reported depending on the study [6]. In particular, multiple contemporary studies have consistently demonstrated a higher mortality rate associated with MRSA compared to MSSA [7]. Herein, we sought to characterize the epidemiology of SAB in a large Canadian health region and compare mortality and risk factors in our region to those reported 10 years previously in a comparable study by Laupland et al. [8].

Methods

Patients

The Calgary Health Zone (CHZ) is an integrated health region responsible for providing all medical care to metropolitan Calgary and surrounding communities totaling a population of 1.4 million individuals. The four adult hospitals in Calgary average 134,000 discharges annually [9]. We sought to characterize SAB amongst adult Calgarians, using postal code data to exclude nonresidents from our analysis. Annual civic census results were used to determine population and rates of common comorbidities in Calgary in a given year [10]. Of note, population data by age group increments of 4 years are only available twice every 5 years as per Calgary census bylaws. Because 2014 was the only year in which such data were available, we calculated the proportion of those less than 14 years of age in 2014 (18%) and extrapolated them to 2012 and 2013 when estimating our incidence rates.

Data sources

The region-wide Microbiology Laboratory Information System, which serves the entire population base of Calgary and surrounding area, was used to identify all adult patients with positive blood cultures for *S. aureus* admitted to any one of the four adult acute cares hospitals, emergency rooms, or urgent care facilities. Blood cultures were drawn by a regional protocol using standard phlebotomy and cultures grown for 5 days aerobically and anaerobically using the BacTAlert system (bioMérieux St. Laurent, Quebec). Clinical and Laboratory Standard Institute guidelines were utilized to identify and determine the susceptibility profiles of *S. aureus* [11]. Patient demographics and comorbidities, length of hospitalization and disposition, biochemical and microbiology data at incident blood culture draw and clinical outcomes were captured in a detailed manual chart review. Residents were followed throughout their hospitalization. Relapses were defined as identification of the same organism within 90 days of a negative blood culture for *S. aureus* and excluded from annual incidence calculations. Bacteremias that developed ≥ 90 days following negative blood culture or with differing susceptibilities were classified as new infections or relapses. This study was approved by the Conjoint Health Research Ethics Board at the University of Calgary (REB 14_1456).

We compared our results with those of Laupland et al., who published the last SAB epidemiological study in the CHZ over a decade ago [8]. In this population-based study of children and adults, SAB was categorized based on methicillin susceptibility and acquisition (i.e., community acquired, nosocomial, etc.). Incidence rates of SAB were reported as an average from 2000 to 2006, but represented with figures by annum.

Definitions

Acquisition of SAB was categorized into community, health-care associated or nosocomial. Bacteremias within 72 h of admission without extensive health-care involvement were considered community-acquired [12]. Health-care-associated community-acquired infections were defined as bacteremias diagnosed within 72 h of admission in patients with recent and repeated health-care interactions [13]. Patients with bacteremia diagnosed 72 h or more following admission were categorized as nosocomial.

Sources of infection were ascertained from detailed chart review coupled with review of biochemical and

microbiological data. Cases in which no identifiable source was identified after extensive review by the clinical team were deemed to be primary bacteremias. Surgical site infections were defined as infections occurring at the operative site within 30 days of a procedure involving skin and deeper tissues manipulated during the operation [14]. Intravascular catheters included both peripheral and central venous (including hemodialysis) catheters, with catheter related bloodstream infections defined using IDSA guidelines [15]. Endovascular infections included venous catheter infections and bacteremias associated with vascular grafts, cardiac devices, including pacemakers and sternal wires. Infectious endocarditis was defined using Modified Duke's criteria [16]. Patients with *S. aureus* bacteriuria, regardless of urinary symptoms, were reviewed to determine if recent urinary tract manipulation had occurred given its association with SAB [17]. In cases of ambiguous or unclear documentation, a second independent chart reviewer was involved. During the years of our study, infectious disease consultation was not mandated for cases of SAB in the CHZ.

Statistical analysis

Incidence of SAB was calculated by dividing incident infections by annual reported census data of the Calgary total population [18]. Rates for MSSA and MRSA were calculated separately. Prior to analysis, individual variables were interrogated using histograms to identify underlying distribution. Means and standard deviations (SD) were utilized to describe variables with normal or near normal distributions and compared using the Student *t* test. Non-normally distributed variables were described by medians with inter-quartile ranges (IQR). Categorical variables were compared using the Fisher's exact test. Odds ratios (OR) were calculated by dividing the proportion with a given factor against those without and reported with 95% confidence intervals (CI) derived from the Woolf approximation. Factors known to be associated with SAB mortality were incorporated into a logistic regression model via backward stepwise variable elimination. The Hosmer–Lemeshow goodness of fit test was used to assess the calibration of the final model using the area under the receiver operator characteristic curve. Model results are reported as OR with 95% CI. A two-sided p value of < 0.05 was deemed significant for all comparisons. All statistical analyses were performed using STATA version 15.0 (College Stn., TX).

Results

Between January 1, 2012 to December 31, 2014, 780 adults experienced 840 episodes of SAB in the CHZ—of which 799 were incident infections for the corresponding year [median age 62 (IQR 49–76, 64.3% male)], while 41 were SAB episodes that represented recurrence within the calendar year.

Incidence

Seven hundred and twenty-seven patients experienced one bacteremic episode, 47 patients experienced two, and 6 patients three or more during this time period. For those with multiple SAB episodes, median time in between bacteremias was 160 days (IQR 84–360) of which 12 patients relapsed within 90 days. All but one individual was admitted to one of the local hospitals for investigation and management. Of all SAB, 168 (20.0%) were MRSA and 672 (80.0%) were MSSA. Incidence rates of SAB amongst adults were 23.5, 28.8, and 32.0 per 100,000 population/year for 2012, 2013, and 2014, respectively, and represented statistically significant increases with each year of study. Relative to the earlier study period of 2000–2006, we observed a significantly increased rate of SAB in our cohort (19.7 vs 28.2 per 100,000/year $p < 0.001$) (Fig. 1a). Rate ratios for nosocomial acquired MSSA bacteremia did not change from 2012 to 2014 [IRR 0.95 (95% CI 0.78–1.16); $p = 0.6$], while community-acquired and health-care-associated community-acquired cases increased [IRR 1.19 (95% CI 1.08–1.30); $p = 0.01$] and [IRR 1.23 (95% CI 1.07–1.42); $p = 0.01$], respectively (Fig. 1b). Whereas nosocomial and health-care-associated community-acquired MRSA bacteremia rates remained stable in our 3 years of study, community-acquired MRSA bacteremia between 2012 and 2014 trended towards an increase (IRR 1.21 (95% CI 0.99–1.48); $p = 0.10$). Figure 2 outlines increasing incidence rates of both MSSA and MRSA bacteremia in all age groups.

Mortality

All-cause 30-day mortality from SAB between 2012 and 2014 was 23.2% (195/840), with mortality rates for MRSA higher than the mortality rate for MSSA (30.6% vs 21.3%, $p = 0.01$). Nosocomial acquired bacteremia was associated with higher mortality compared to community and health-care-associated community acquired (28.9% vs 23.1% vs 20.5%, $p = 0.05$). Along with increasing age (OR 1.06/year, 95% CI 1.04–1.07, $p < 0.001$), clinical, biochemical, and microbiological factors associated with 30-day mortality are detailed in Fig. 3. When mortality from MSSA and MRSA were evaluated separately, age, cirrhosis, and ICU admission were epidemiological factors associated with higher 30-day mortality in both MSSA and MRSA SAB, whereas the presence of toxic changes on blood smear (defined as identification of course granules in granulocytes on peripheral blood smear examination) and unknown source of bacteremia

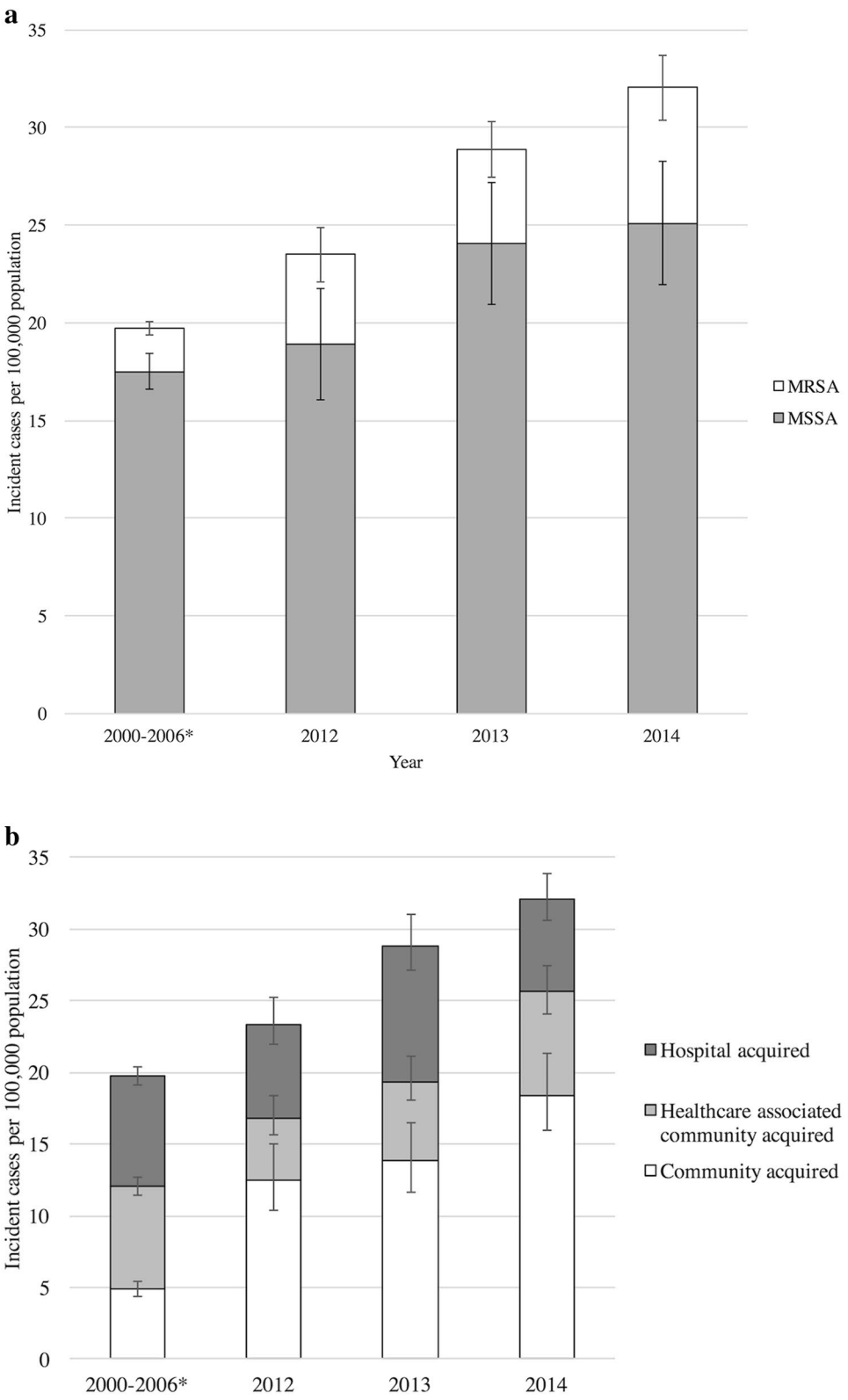

Fig. 1 **a, b** Annual incident cases per 100,000 population of *S. aureus* bacteremia in the Calgary Health Zone from 2012 to 2014. Error bars indicated 95% CIs MSSA: methicillin-susceptible *Staphylococcus aureus.* MRSA: methicillin-resistant *Staphylococcus aureus.* *Data derived from [8]

were found to be associated with 30-day mortality in MSSA but not MRSA bacteremia. There was an overall trend towards improved 30-day survival post-bacteremia with community-acquired SAB, but this was not found to be statistically significant. All-cause 90-day mortality during the same 3 years also demonstrated higher mortality rates with MRSA compared to MSSA (36.9% vs 28.4%, $p = 0.02$).

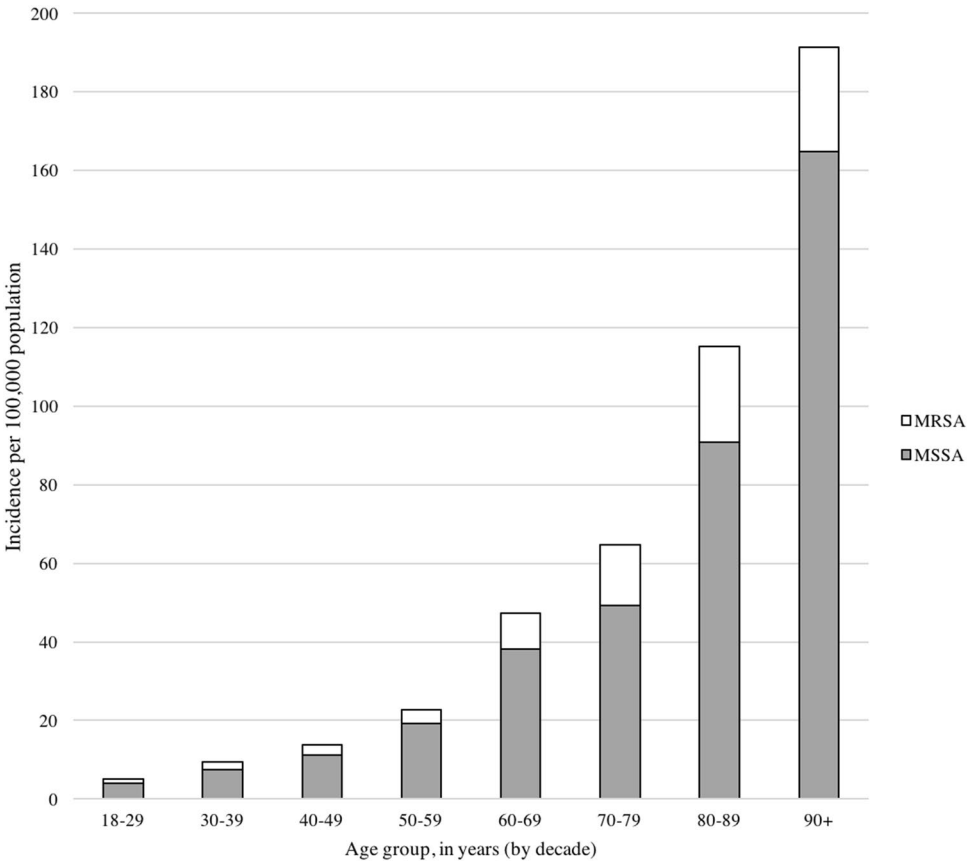

Fig. 2 Incident cases of MSSA and MRSA bacteremia per 100,000 population per year in the Calgary Health Zone from 2012 to 2014 by age group. MSSA: methicillin-susceptible *Staphylococcus aureus.* MRSA: methicillin-resistant *Staphylococcus aureus*

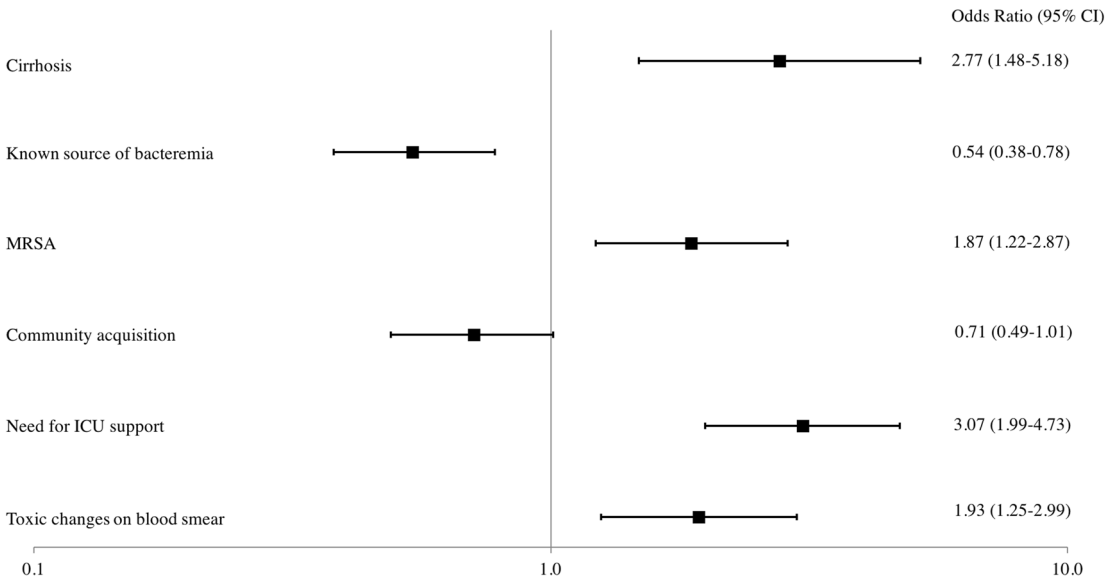

Fig. 3 Risks factors for death in SAB: Multivariate analysis of odds ratio for variables associated with 30-day mortality in SAB*. SAB: *Staphylococcus aureus* bacteremia. ICU: Intensive care unit. MRSA: methicillin-resistant *Staphylococcus aureus.* *: age as a continuous variable also associated with 30-day mortality (OR 1.06/year)

Table 1 Epidemiological characteristics at occurrence of *Staphylococcus aureus* bacteremia in patient cohort

Parameter	Entire cohort	CA	HCA-CA	Nosocomial	*P* value
Age, median (years)	62 (IQR 49–76)	61 (IQR 48–73)	65 (IQR 54–79)	64 (IQR 50–77)	0.019
Comorbidities, *n* (%)	*n* = 835	*n* = 435	*n* = 182	*n* = 218	
Altered immunity[a]	146 (17.5)	57 (13.1)	41 (22.5)	48 (22.0)	0.002
Diabetes mellitus	239 (28.6)	122 (28.0)	58 (31.9)	59 (11.4)	0.537
Rheumatological disease	192 (23.0)	108 (24.8)	39 (21.4)	45 (20.6)	0.426
Pulmonary disease	295 (35.3)	157 (36.1)	61 (33.5)	77 (35.3)	0.836
Cardiovascular disease	484 (58.0)	234 (53.8)	122 (67.0)	128 (58.7)	0.009
Pacemaker or ICD	47 (5.6)	19 (4.4)	14 (7.7)	14 (6.4)	0.196
Prosthetic valve	19 (2.3)	10 (2.3)	5 (2.7)	4 (1.8)	0.787
Liver disease[b]	132 (15.8)	93 (21.4)	14 (7.7)	25 (11.5)	0.000
Cancer	142 (17.0)	54 (12.4)	39 (21.4)	49 (22.5)	0.001
Prosthetic joint	86 (10.3)	52 (12.0)	21 (11.5)	13 (6.0)	0.040
Substance abuse[c]	156 (18.7)	101 (23.2)	15 (8.2)	40 (18.3)	0.000
Alcohol misuse[d]	95 (11.4)	57 (13.1)	7 (3.8)	31 (14.2)	0.000
Biochemical abnormalities	*n* = 834	*n* = 434	*n* = 182	*n* = 218	
WBC $< 4 \times 10^9$/L	78 (9.4)	29 (6.7)	16 (8.8)	33 (15.1)	0.002
WBC $> 11 \times 10^9$/L	490 (58.8)	283 (65.2)	101 (55.5)	106 (48.6)	0.000
Bandemia	122 (14.6)	80 (18.4)	16 (8.8)	26 (11.9)	0.005
Toxic changes[e]	155 (18.6)	97 (2.2)	27 (14.8)	31 (14.2)	0.020

CA community acquired, *HCA-CA* health-care-associated community acquired, *ICD* implantable cardioverter defibrillator, *WBC* white blood cells

[a]Altered immunity defined as patients meeting > 1 of the following criteria; human immunodeficiency virus, solid organ transplant recipient, hematopoietic transplant recipient, splenectomised, therapeutically immunosuppressed (usage of > 10 mg equivalent dose of prednisone daily, calcineurin inhibitor, cyclophosphamide, methotrexate, azathioprine, or tumor necrosis factor-alpha inhibitor)

[b]Liver disease includes cirrhosis, steatosis, and hepatitis

[c]Substance abuse is defined as hazardous use of psychoactive agents including alcohol, illicit non-prescription opioids (e.g., heroin) or amphetamines and hallucinogens (e.g., marijuana, lysergic acid diethylamide, etc.)

[d]Alcohol misuse is defined as consumption of greater than lower risk limits of alcohol (i.e., 14 units of alcohol consumption a week for males and 7 units of alcohol consumption a week for females)

[e]Toxic changes on blood smear is diagnosed with identification of course granules in granulocytes (including neutrophils) on peripheral blood smear examination

Clinical characteristics

Baseline characteristics of the cohort are shown in Tables 1 and 2 with risks of SAB associated with select underlying medical conditions, as summarized in Table 3. Median length of hospitalization was 17.7 days (IQR 9.5–38.1) and longer for patients experiencing MRSA bacteremia compared with MSSA bacteremia [25.0 days (IQR 10.4–48.1) vs 16.9 days (IQR 9.2–34.9), $p < 0.02$]. Length of stay was longest for patients with nosocomial acquired bacteremia [32.5 days (IQR 18.9–66.5)], compared with health-care-associated community acquired and community acquired [13.3 days (IQR 7.0–23.2)] and [14.9 days (IQR 8.2–31.3), $p < 0.001$], respectively.

Of patients who developed hospital-acquired bacteremia, median time to bacteremia from admission date was 9.6 days (IQR 4.9–23.1); longer with MRSA bacteremia compared to MSSA [18.1 days (IQR 7.8–36.1) vs 9.2 days (IQR 4.4–20.0), $p = 0.008$]. Patients with persistently positive *S. aureus* blood cultures for greater than 7 days not only were more likely to hospitalized for greater than 28 days from onset of bacteremias (72.5% vs 25.3%, $p < 0.001$), but also had increased risk of death 30-day post-bacteremia (28.8% vs 21.9%, $p < 0.05$).

Source of bacteremia

Forty-three percent (355/840) of bloodstream infections did not have a source identified. Amongst the bacteremias in which a source was identified, the commonest etiology was skin/soft tissue, followed by pulmonary and endovascular (Fig. 4). All sources deemed urinary had a history of recent

catheterization or urological surgery. No particular source of SAB changed significantly during the 3-year study period nor was source of bacteremia associated with methicillin susceptibility. Thirty-day mortality rates were highest in patients with a pulmonary source of infection or primary SAB (Fig. 5).

Secondary bacteremia from skin/soft-tissue infection and bone/joint infection were associated with community acquisition (29.1% vs 12.5%, $p < 0.001$ and 12.5% vs 4.3%, $p < 0.001$), respectively (Table 3).

Discussion

Calgary is an ideal place to study trends in incident onset SAB owing to the use of a region-wide centralized laboratory service that provides services to all emergency rooms, hospitals and urgent care facilities covering a region of 39,300 km^2 over 20 years [19]. The previous studies comparing the epidemiology and outcomes of SAB in Calgary in 1999–2000 and 2000–2006 had demonstrated an overall decrease in annual incidence of SAB owing to a decrease in MSSA bacteremia in spite of an increase in MRSA bacteremia [8, 20]. During a similar time period, Allard et al., in Eastern Canada determined the increase in SAB was due to increasing MRSA incidence in the context of stable rate of MSSA bacteremia. Our contemporary study contrasts both Laupland et al. [8], and Allard et al. [3], findings as we observe an overall increase in SAB incidence in Calgary from 2012 to 2014 [IRR 1.15 (95% CI 1.07–1.23); $p < 0.001$], attributable to increasing burdens of both MSSA and MRSA bacteremias. Notably, this increase is driven by changes in the burden of community-acquired disease. While community-acquired SAB increased significantly when compared to a decade ago [IRR 1.98 (95% CI 1.85–2.11); $p < 0.0001$], rates of

Table 2 Demographics of *S. aureus* bacteremia cohort as a function of methicillin resistance

Parameter	MSSA ($n = 669$)	MRSA ($n = 116$)	*P* value
Age, median (years)	62 (IQR 49–76)	64 (IQR 49–77)	
Comorbidities, *n* (%)			
Altered immunity[a]	128 (19.1)	18 (15.5)	0.012
Diabetes mellitus	185 (27.7)	54 (46.6)	0.126
Rheumatological disease	164 (24.5)	28 (24.1)	0.039
Pulmonary disease	220 (32.9)	75 (64.7)	0.004
Cardiovascular disease	381 (57.0)	103 (88.8)	0.254
Pacemaker or ICD	39 (10.3)	8 (6.9)	0.710
Prosthetic valve	17 (2.5)	2 (1.7)	0.395
Liver disease[b]	99 (14.8)	33 (28.4)	0.122
Cancer	125 (18.9)	17 (14.7)	0.008
Prosthetic joint	67 (10.0)	19 (16.4)	0.570
Substance abuse[c]	115 (17.2)	41 (35.3)	0.034
Alcohol misuse[d]	72 (10.8)	23 (19.8)	0.275
Biochemical abnormalities	$n = 670$	$n = 164$	
WBC $< 4 \times 10^9$/L	67 (10.0)	11 (6.7)	0.232
WBC $> 11 \times 10^9$/L	394 (58.9)	96 (58.5)	1.000
Bandemia	97 (14.5)	25 (15.2)	0.806
Toxic changes[e]	122 (18.2)	33 (20.1)	0.576

ICD implantable cardioverter defibrillator, *WBC* white blood cells

[a]Altered immunity defined as patients meeting > 1 of the following criteria; human immunodeficiency virus, solid organ transplant recipient, hematopoietic transplant recipient, splenectomised, therapeutically immunosuppressed (usage of > 10 mg equivalent dose of prednisone daily, calcineurin inhibitor, cyclophosphamide, methotrexate, azathioprine, or tumor necrosis factor-alpha inhibitor)

[b]Liver disease includes cirrhosis, steatosis, and hepatitis

[c]Substance abuse is defined as hazardous use of psychoactive agents including alcohol, illicit non-prescription opioids (e.g., heroin) or amphetamines and hallucinogens (e.g., marijuana, lysergic acid diethylamide, etc.)

[d]Alcohol misuse is defined as consumption of greater than lower risk limits of alcohol (i.e., 14 units of alcohol consumption a week for males and 7 units of alcohol consumption a week for females)

[e]Toxic changes on blood smear is diagnosed with identification of course granules in granulocytes (including neutrophils) on peripheral blood smear examination

Table 3 Relative risk for development of SAB with selective comorbidities in Calgary Residents from 2012–2014

Comorbidity	RR (95% CI), $p < 0.01$		
	Any SAB	MSSA	MRSA
ESRD—hemodialysis	234.84 (186.82–295.22)	176.48 (136.23–228.61)	50.23 (31.56–79.97)
Diabetes	7.18 (6.18–8.33)	5.11 (4.34–6.01)	1.22 (0.93–1.61)
Ischemic heart disease	10.32 (8.78–12.14)	7.33 (6.12–8.78)	2.04 (1.51–2.75)
COPD	11.07 (9.23–13.28)	6.95 (5.60–8.62)	3.23 (2.40–4.35)
Rheumatoid arthritis	2.47 (1.70–3.57)	2.03 (1.35–3.04)	3.90 (2.89–5.27)
Cirrhosis	42.2 (32.7–54.5)	33.63 (25.35–44.60)	7.54 (4.27–13.32)

Population data from Calgary Civic Results

SAB Staphylococcus aureus bacteremia, *MSSA* methicillin-susceptible *Staphylococcus aureus*, *MRSA* methicillin-resistant *Staphylococcus aureus*, *ESRD* end-stage renal disease, *COPD* chronic obstructive pulmonary disease

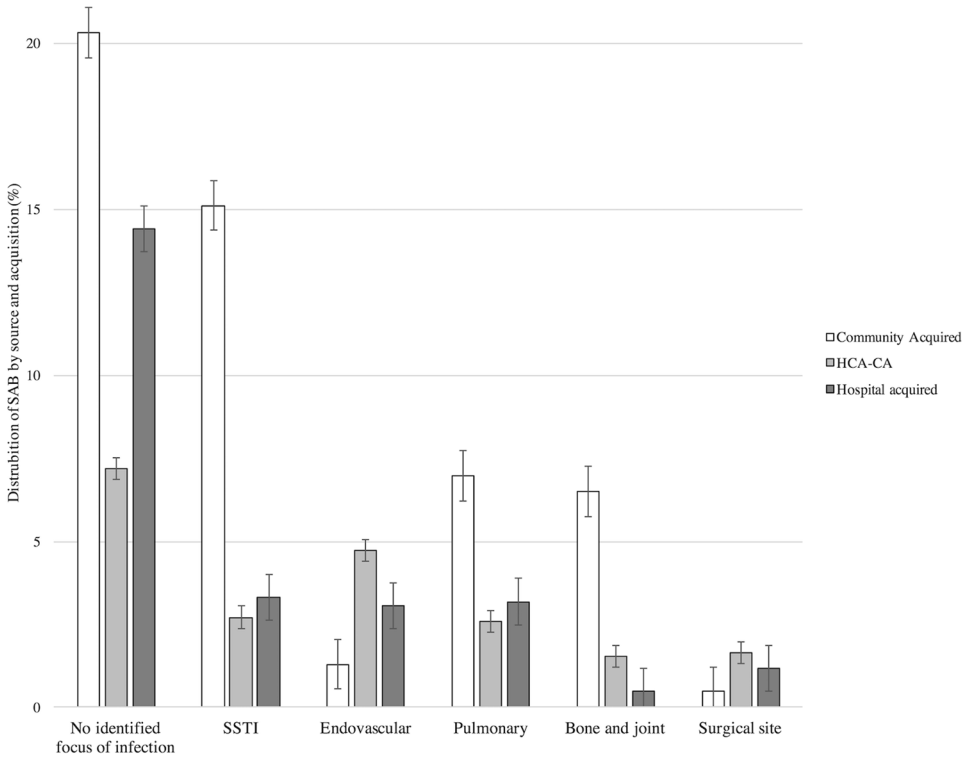

Fig. 4 Percentage of SAB by source and origin of acquisition from 2012 to 2014 in the Calgary Health Zone. SAB: *Staphylococcus aureus* bacteremia. Error bars indicated 95% CIs. SSTI: skin and soft-tissue infection. HCA-CA: healthcare-associated community-acquired

nosocomial SAB during our 3-year study period were not statistically different from 2000 to 2006 [IRR 0.99 (95% CI 0.88–1.11); $p = 0.8$], likely owing to successes achieved by the infection prevention and surveillance programs [21, 22]. Our study also echoes that of Taylor et al., which determined that MRSA bacteremia is increasingly a community, rather than a nosocomially acquired disease [23].

The distribution and association of select comorbidities are outlined in Table 3 and contrasts that of Laupland et al. [8]. Due to changes in CHZ's population-based data collection system, select comorbidities are unable to be collected at a population level; thus, we are unable to compare and contrast associations to all underlying conditions in Laupland's study [8]. However, the risk factors and magnitude of the most notable common comorbidities remain remarkably similar. Compared to a decade ago, hemodialysis remains the strongest risk factor associated with SAB, while heart disease and chronic obstructive pulmonary disease are now more strongly associated with SAB than previous. While Laupland et al.'s study demonstrated stronger association between acquisition of MRSA bacteremia and select comorbidities [8], our study found that risk of MSSA invasive disease was remarkably higher than MRSA with respect to the same chronic diseases. Although it is unclear what particular comorbidities are responsible for the increase in community-acquired MRSA bacteremia, our

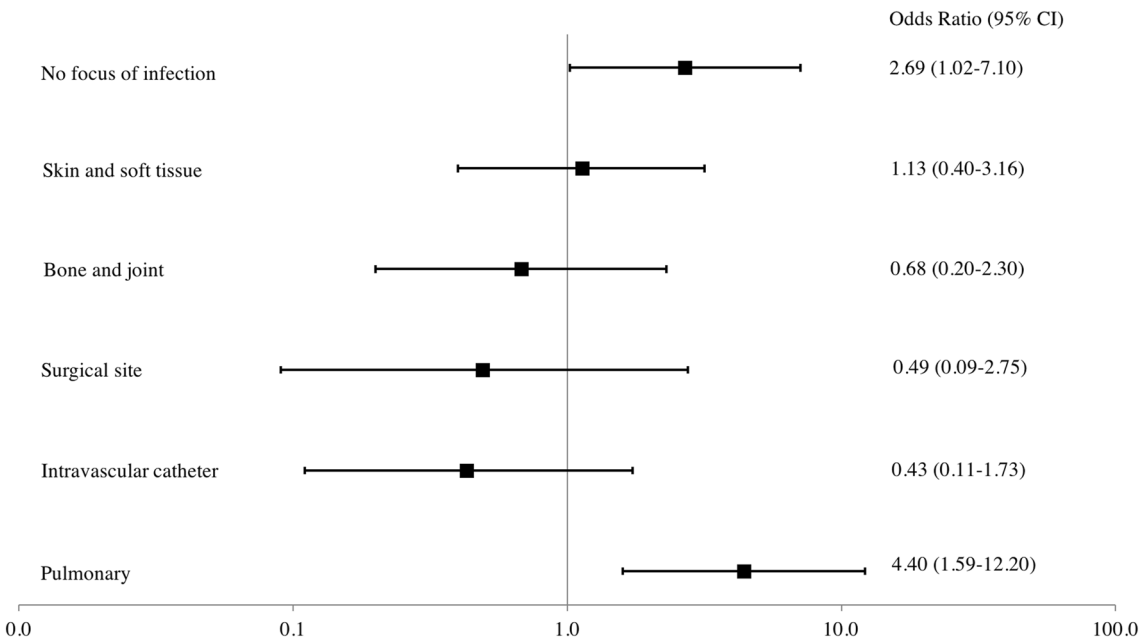

Fig. 5 Source of SAB and mortality: Multivariate analysis of odds ratio for sources of SAB variables associated with 30-day mortality in SAB. SAB: *Staphylococcus aureus* bacteremia

data demonstrate that MRSA bacteremia is now a prominent infection in previously healthy young individuals as opposed to a disease primarily of elderly individuals, as observed in Laupland et al.'s study [8].

We compared our epidemiological findings to the previous studies performed in Europe, Eastern Canada, and Australia [1]. A global collaboration in 2012 identified incidence rates of SAB in Canada, Scandinavia, and Australia and found heterogeneity in trends of increasing incidence rates of SAB. Increasing rates of community-acquired MSSA in Finland and western Sweden were responsible for overall increase in SAB, whereas increased community-acquired MRSA infections were attributed to growing cases of SAB in Victoria, Canada. Occurrence rates of SAB fluctuated, but did not change significantly over the 8 years in Sherbrooke, Canada, and Canberra, Australia. In northern Denmark including Copenhagen, the reduction in hospital- acquired bacteremias led to a decrease in total incident SAB. More contemporary studies demonstrate increasing incidence of community-acquired SAB in rural Thailand and Finland [24, 25]. Our study shows primarily an increase in community-acquired SAB, predominantly owing to MSSA bacteremia.

With respect to sources of SAB, primary bacteremia remained the commonest identified. Our observations were similar to that of Lauplaud et al., who also identified primary bacteremia as the cause of disease in approximately 40% of all cases of SAB [8]. Compared to their study, our data demonstrate an increase in proportion of skin and soft-tissue disease, but significantly lower numbers of bone and joint disease as foci of bacteremia. This is in keeping with recent studies identifying prosthetic joint infections as an important issue and undertaking steps to identify and treat these earlier, thus perhaps preventing complications such as bacteremia [26].

Median time from admission to development of nosocomial SAB did not differ when compared to a decade ago. Length of hospitalization in the context of methicillin susceptibility and location of bacteremia acquisition were also similar to Laupland et al. [8]. This is congruent with the previous studies demonstrating nosocomial acquired bloodstream infections correlating with longer hospitalizations compared to non-nosocomial acquisition [27].

Despite improvements in many health outcomes, SAB-associated mortality rates have remained frustratingly steadfast over the last 2 decades. Multiple studies, including ours, demonstrate a mortality rate approximating 25%. The higher mortality associated with MRSA compared to MSSA bacteremias in our study is comparable to those in the previous reports. Factors associated with increased fatality with MRSA over MSSA are poorly understood. It is hypothesized that under appreciation of MRSA by clinicians and pharmacokinetic properties of vancomycin delaying therapeutic, anti-Staphylococcal levels contribute to the excess mortality based on methicillin resistance [28]. Other studies identified that although MRSA bacteremia was not associated with increased mortality after adjustment of prognostic factors, it was associated with poorer long-term morbidity compared to MSSA bacteremia [29].

Of great concern is the fact that we observed no improvement in mortality rates in our health region when comparing our 30-day SAB mortality rates to that of Laupland's case-fatality rate a decade earlier [8, 30]. Several studies have recently established that infectious disease consultation in the management of SAB is associated with significant reduction in mortality rates with hazard ratios less than one [31]. Certainly, a policy to ensure automated and mandatory IDC in the management of all SAB as has been suggested by others may be a means by which SAB-associated 30-day mortality rates can be reduced in population-based studies [32]. Similar to this study, others have demonstrated 90-day mortality from SAB upwards of 40% [6, 33].

S. aureus bloodstream infections from either a pulmonary source or primary bacteremia were strongly associated with disproportionate 30-day mortality. Associations with a pulmonary source of bacteremia and mortality have been almost universally documented in other studies [34, 35]. This is not specific to *S. aureus* but is observed in most cases of bacteremia [36]. Though not reaching statistical significance herein, SAB from intravascular catheters and bone/joint source trended towards better 30-day survival post-bacteremia—a finding that has been noted previously as well [37, 38].

The impact of the mode of acquisition of bacteremia and mortality is controversial with some studies, including ours demonstrating association between hospital acquisition and mortality and others illustrating that setting of bacteremia had little effect on mortality rates [39, 40]. Compared to nosocomially acquired bacteremias, community-acquired SAB was associated with lower mortality in our study. The reasons for this are unclear and require further study.

Multiple limitations are worthy of note in our study. We are limited in collecting data for pediatric patients with SAB due to a different infrastructure in obtaining research ethics approval. Second, Calgary census bylaws do not collect aged-categorized population data annually. Therefore, to calculate incidence rates in this study, it is assumed that the proportion of individuals in Calgary less than 18 years is the same in the 3 years of study based on the percentage of individuals less than 14 years of age in the 2014 census (218,555, or 18% of total 2014 Calgary population). Such an estimate would likely underestimate the true incidence of SAB amongst adults in Calgary. Identification of the bacteremia source was based upon electronic detailed chart reviews of discharge summaries and the investigations completed by the attending physicians. As such, the accuracy of the diagnosis is subject to change based on the types and intensity of diagnostic tests employed by the attending service and their subsequent documentation. However, our ability to draw from microbiologic records of other positive *S. aureus* positive cultures (wound, sterile site anaerobic cultures, central venous catheter, etc.) and second independent chart reviewer was involved when documentation within a particular chart was unclear. Finally, given our study encompassed 3 years, trends are difficult to ascertain. However, community-acquired infections now make up the majority of both MSSA and MRSA bacteremias compared to less than a third in the early 2000s [8].

Conclusions

S. aureus bacteremia remains a serious diagnosis. We found increasing SAB incidence rates compared with that which was documented previously secondary to increasing incidence of both MSSA and MRSA acquired in community settings. When compared with a decade ago, distribution and significance of comorbidities as risks for developing SAB have changed. Source of bacteremia and setting of bacteremia remains associated with mortality. Unfortunately, clinical outcomes associated with SAB remain poor. Given the increase in community-acquired SAB, further investigation into interaction between host, pathogen and environmental factors should be undertaken to identify the causes of this increase and potential interventions to prevent these infections.

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors

Compliance with ethical standards

Conflict of interest All authors declare that they do not have any conflict of interest relevant to this manuscript.

Presented in part Association of Medical Microbiology and Infectious Disease Conference 2018, Vancouver, BC. Abstract SP 44.

References

1. Laupland KB, Lyytikäinen O, Søgaard M, et al. The changing epidemiology of *Staphylococcus aureus* bloodstream infection: a multinational population-based surveillance study. Clin Microbiol Infect. 2013;19:465–71.
2. Public Health England: *Staphylococcus aureus* (MRSA and MSSA) bacteraemia mandatory reports 2016/17. United Kingdom.
3. Allard C, Carignan A, Bergevin M, et al. Secular changes in incidence and mortality associated with *Staphylococcus aureus* bacteraemia in Quebec, Canada, 1991–2005. Clin Microbiol Infect. 2008;14:421–8.
4. David MZ, Daum RS. Community-associated methicillin-resistant *Staphylococcus aureus*: epidemiology and clinical consequences of an emerging epidemic. Clin Microbiol Rev. 2010;23:616–87.
5. Liu C, Graber CJ, Karr M, et al. A population-based study of the incidence and molecular epidemiology of methicillin-resistant

Staphylococcus aureus disease in San Francisco, 2004-2005. Clin Infect Dis. 2008;46:1637–46.
6. van Hal SJ, Jensen SO, Vaska VL, Espedido BA, Paterson DL, Gosbell IB. Predictors of mortality in *Staphylococcus aureus* Bacteremia. Clin Microbiol Rev. 2012;25:362–86.
7. Whitby M, McLaws ML, Berry G. Risk of death from methicillin-resistant *Staphylococcus aureus* bacteraemia: a meta-analysis. Med J Aust. 2001;175:264–7.
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. J Infect Dis. 2008;198:336–43.
9. Alberta Health Services Annual Report 2015-2016: Alberta Health Services.
10. The City of Calgary—Past census results. Available at: http://www.calgary.ca/CA/city-clerks/Pages/Election-and-Information-Services/Civic-Census/CensusResults.aspx. Accessed October 11 2018.
11. Performance Standards for Antimicrobial Susceptibility Testing. Supplement M100. Wayne: Clincal and Laboratory Standards Institute; 2017.
12. Friedman ND, Kaye KS, Stout JE, et al. Health care–associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. Ann Intern Med. 2002;137:791–7.
13. Lenz R, Leal JR, Church DL, Gregson DB, Ross T, Laupland KB. The distinct category of healthcare associated bloodstream infections. BMC Infect Dis. 2012;12:85.
14. Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Emori TG. CDC definitions of nosocomial surgical site infections, 1992: a modification of CDC definitions of surgical wound infections. Infect Control Hosp Epidemiol. 1992;13:606–8.
15. Mermel LA, Allon M, Bouza E, 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;49:1–45.
16. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis. 2000;30:633–8.
17. Stokes W, Parkins MD, Parfitt ECT, Ruiz JC, Mugford G, Gregson DB. Incidence and outcomes of *Staphylococcus aureus* bacteriuria: a population-based study. Clin Infect Dis. 2018;3:1.
18. The City of Calgary—Past census results. Available at: http://www.calgary.ca/CA/city-clerks/Pages/Election-and-Information-Services/Civic-Census/CensusResults.aspx. Accessed October 11, 2018 2018.
19. Services AH. Available at: https://www.albertahealthservices.ca/about/calgaryzone.aspx. Accessed December 20 2018.
20. Laupland KB, Church DL, Mucenski M, Sutherland LR, Davies HD. Population-based study of the epidemiology of and the risk factors for invasive *Staphylococcus aureus* infections. J Infect Dis. 2003;187:1452–9.
21. Rhodes D, Cheng AC, McLellan S, et al. Reducing *Staphylococcus aureus* bloodstream infections associated with peripheral intravenous cannulae: successful implementation of a care bundle at a large Australian health service. J Hosp Infect. 2016;94:86–91.
22. Freixas N, Bella F, Limón E, Pujol M, Almirante B, Gudiol F. Impact of a multimodal intervention to reduce bloodstream infections related to vascular catheters in non-ICU wards: a multicentre study. Clin Microbiol Infect. 2013;19:838–44.
23. Taylor G, Bush K, Leal J, Henderson E, Chui L, Louie M. Epidemiology of meticillin-resistant *Staphylococcus aureus* bloodstream infections in Alberta, Canada. J Hosp Infect. 2015;89:132–5.
24. Jokinen E, Laine J, Huttunen R, et al. Trends in incidence and resistance patterns of *Staphylococcus aureus* bacteremia. Infect Dis (Lond). 2018;50:52–8.
25. Jaganath D, Jorakate P, Makprasert S, et al. Bacteremia incidence and methicillin resistance in rural Thailand, 2006–2014. Am J Trop Med Hyg. 2018;99:155–63.
26. Renaud A, Lavigne M, Vendittoli PA. Periprosthetic joint infections at a teaching hospital in 1990–2007. Can J Surg. 2012;55:394–400.
27. Pittet D, Tarara D, Wenzel RP. Nosocomial bloodstream infection in critically ill patients. Excess length of stay, extra costs, and attributable mortality. JAMA. 1994;271:1598–601.
28. 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.
29. Yaw LK, Robinson JO, Ho KM. A comparison of long-term outcomes after meticillin-resistant and meticillin-sensitive *Staphylococcus aureus* bacteraemia: an observational cohort study. Lancet Infect Dis. 2014;14:967–75.
30. Lam J, Robinson S, Gregson D, et al. *Staphylococcus aureus* bacteremia (SAB) management in a large metropolitan integrated health region: quality of care determinants (QoCD). In: ID Week. (San Diego, California). Open Forum Infectious Diseases pp S557–S8.
31. Bai AD, Showler A, Burry L, et al. Impact of infectious disease consultation on quality of care, mortality, and length of stay in *Staphylococcus aureus* bacteremia: results from a large multicenter cohort study. Clin Infect Dis. 2015;60:1451–61.
32. Lam JC, Gregson DB, Robinson S, et al. Infectious diseases consultation improves key performance metrics in the management of *Staphylococcus aureus* bacteremia: a multicentre cohort study. J Assoc Med Microbiol Infect Dis Canada. 2019;4:24–32.
33. Hanses F, Spaeth C, Ehrenstein BP, Linde HJ, Schölmerich J, Salzberger B. Risk factors associated with long-term prognosis of patients with *Staphylococcus aureus* bacteremia. Infection. 2010;38:465–70.
34. Benfield T, Espersen F, Frimodt-Møller N, et al. Increasing incidence but decreasing in-hospital mortality of adult *Staphylococcus aureus* bacteraemia between 1981 and 2000. Clin Microbiol Infect. 2007;13:257–63.
35. Kaye MG, Fox MJ, Bartlett JG, Braman SS, Glassroth J. The clinical spectrum of *Staphylococcus aureus* pulmonary infection. Chest. 1990;97:788–92.
36. Magret M, Lisboa T, Martin-Loeches I, et al. Bacteremia is an independent risk factor for mortality in nosocomial pneumonia: a prospective and observational multicenter study. Crit Care. 2011;15:R62.
37. Chen SY, Wang JT, Chen TH, et al. Impact of traditional hospital strain of methicillin-resistant *Staphylococcus aureus* (MRSA) and community strain of MRSA on mortality in patients with community-onset S aureus bacteremia. Medicine (Baltimore). 2010;89:285–94.
38. Kang CI, Song JH, Chung DR, et al. Clinical impact of methicillin resistance on outcome of patients with *Staphylococcus aureus* infection: a stratified analysis according to underlying diseases and sites of infection in a large prospective cohort. J Infect. 2010;61:299–306.
39. Holmes NE, Turnidge JD, Munckhof WJ, et al. Antibiotic choice may not explain poorer outcomes in patients with *Staphylococcus aureus* bacteremia and high vancomycin minimum inhibitory concentrations. J Infect Dis. 2011;204:340–7.
40. Turnidge JD, Kotsanas D, Munckhof W, et al. *Staphylococcus aureus* bacteraemia: a major cause of mortality in Australia and New Zealand. Med J Aust. 2009;191:368–73.