Incidence and Outcomes of *Staphylococcus aureus* Bacteriuria: A Population-based Study

By © William Stokes

A Thesis submitted to the School of Graduate Studies in partial fulfillment of the requirements for the degree of Masters of Science, from the discipline of Clinical Epidemiology

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Abstract

Background

Our objective was to describe *S. aureus* bacteriuria (SABU) at a population-based level and determine patient characteristics associated with *S. aureus* bacteremia (SAB).

Methods

A retrospective study was performed using electronic databases. All urine cultures positive for *S. aureus* between 2010-2013 within the Calgary Health Zone were included. Patient characteristics were compared among patients with and without SAB and risk factors identified using multiple logistic regression modelling.

Results

A total of 2540 urine cultures positive for *S. aureus* from 2054 patients were analyzed. The incidence of SABU was greatest amongst geriatric males with multiple comorbidities. 175 (6.9%) of the cohort had SAB. Those with concurrent SAB were more likely to be hospitalized, male, have a recent urinary procedure, have pure *S. aureus* culture in urine and have laboratory findings suggesting systemic infection. In-hospital mortality in patients with SABU and SABU + SAB was 9.2% and 17.5%, respectively. Patients with SABU detected ≥48 hours before SAB had the highest risk of death.

Conclusions

Less than 7% of patients with SABU have or will develop SAB. Characteristics associated with SABU were identified that established higher risk for systemic infection. Investigating SABU patients with these characteristics for systemic infection is warranted since a delay in diagnosis is associated with increased mortality.

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List of Abbreviations

ALS	Amyotrophic lateral sclerosis
CFU	Colony forming units
CHZ	Calgary Health Zone
CI	Confidence interval
CLS	Calgary Laboratory Services
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CVA	Cardiovascular accident
DAD	Discharge Abstract Database
DIMR	Data Integration, Management and Reporting
ESRD	End stage renal disease
FGM	Female genital mutilation
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
Hpf	High-power field
ICD	International classification of diseases
mL	Milliliter
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-sensitive *Staphylococcus aureus*
OR	Odds ratio
PRISMA	Preferred reporting items for systematic reviews and meta-analysis
RBC	Red blood cell
ROBINS	Risk of bias in non-randomized studies
RoC	Receiver operating characteristic
S. aureus	*Staphylococcus aureus*
SAB	*S. aureus* bacteremia
SABU	*S. aureus* bacteriuria
STI	Sexually transmitted infection
USA	United States of America
UTI	Urinary tract infections
WBC	White blood cell

INTRODUCTION

Staphylococcus aureus

Staphylococcus aureus is a common pathogen of worldwide importance. It is a Gram-positive coccus that can colonize the skin and mucosa of animals and humans. It causes a wide range of infections, from benign skin infections such as folliculitis to deep-seated infections such as endocarditis and osteomyelitis. It is also a critical pathogen in nosocomial infections, being the most prevalent microorganism detected in sterile sites among hospitalized inpatients (18.7%).[1]

Invasive *S. aureus* infections are rising. For example, the average annual incidence of *S. aureus* invasive infections in Calgary between 2012 - 2014 was 26.3 cases per 100,000 people compared to 19.7 cases per 100,000 people in 2000-2006.[1,2] Infections due to methicillin-resistant *Staphylococcus aureus* (MRSA) are also increasing, with national MRSA infections from 2012 – 2015 increasing annually by approximately 5%.[3] Increasing *S. aureus* infections are a major concern for several reasons. First, invasive *S. aureus* infections can be lethal, with thirty-day mortality at approximately 25% among individuals with *S. aureus* bacteremia.[1,2,4,5] Second, the costs of treating *S. aureus* infections can be substantial. For instance, 6 month median costs per methicillin-sensitive *Staphylococcus aureus* (MSSA) and MRSA infection, including bacteremia, are approximately US $15,923 and US $34,657, respectively.[6]

So why is mortality so high among invasive *S. aureus* infections? The answer lies in *S. aureus'* many virulence factors that include the production of numerous adhesins, toxins and coagulases. *S. aureus* has over 20 adhesin genes and over 30 toxin genes.[7-10] Compare this to other Staphylococci, such as coagulase negative Staphylococcus, that produce less than ten adhesin genes and no toxin or coagulase genes. *S. aureus* is considered a "sticky" bacterium through the production of numerous adhesions. These adhesins allow *S. aureus* to colonize skin and foreign devices such as urinary catheters.[11,12] Up-regulation of adhesins is also thought to allow *S. aureus* to migrate from the skin into the bloodstream, attach to endothelial cells within the bloodstream and subsequently invade into host tissues.[11] Other *S. aureus* virulence factors include toxins such as proteases, hemolysins and leukotoxins which can lead to surrounding tissue destruction and destruction of white blood cells that help it evade the immune system.[13] Lastly, the production of coagulases (staphylocoagulase and von Willebrand factor) allow *S. aureus* to form fibrin clots which helps with abscess formation, immune system evasion, and formation of biofilms.[13] In *S. aureus* bacteriuria, abnormal tissue or foreign devices (i.e. urinary catheter) allow *S. aureus* to attach and form biofilms, creating an environment for *S. aureus* to thrive in the bladder. Eventually, the presence of *S. aureus* in the bladder may lead to urinary tract inflammation followed by translocation into the bloodstream.

S. aureus is a critical player in the era of multidrug resistant pathogens. By having many capabilities to share genetic material with itself and other *Staphylococcal* species, *S. aureus* has evolved into an antimicrobial resistant capable pathogen. When penicillin was

first introduced in the 1940s, *S. aureus* quickly became drug resistant, through the production of penicillinase, to the point that the majority of clinically isolated *S. aureus* are resistant to penicillin. As new drugs were developed to counteract *S. aureus* resistance, *S. aureus* continued to evolve to increase its resistance profile. Since the 1950s, a *S. aureus* resistant to many antibiotics, called methicillin-resistant *Staphylococcus aureus* (MRSA), has emerged. At present day, MRSA is now the dominant *S. aureus* strain circulating in some US centers (60%) and, in a Canadian city like Calgary, represents 22.6% of *S. aureus* isolated from blood cultures collected from the Calgary community facilities and emergency rooms.[14,15] MRSA is a critical pathogen because it not only causes invasive disease but the main drug developed to help combat it (i.e. vancomycin) is inferior and more toxic than drugs, such as cloxacillin, that are used to treat its less resistant counterpart, methicillin-sensitive *Staphyloccocus aureus* (MSSA).[16] Moreover, MRSA infections are associated with increased mortality compared to MSSA infections. For instance, thirty-day mortality rates for MSSA and MRSA bacteremia in Calgary was 21.2% and 31.0%, respectively.[2]

S. aureus infections usually occur from *S. aureus* residing on an individual's skin flora. *S. aureus* can be part of normal skin flora with approximately 20 - 27% of the normal population having the microorganism residing in the anterior nares at any given time.[17] Approximately 60% of the population carries *S. aureus* intermittently, 20% persistently, and 20% never.[18] Other less common sites of colonization include the mouth, intestine, vagina, intertriginous skin folds, the axillae, the groin and the perineum. Different activities can influence an individual's risk of acquiring *S. aureus* and MRSA. Nasal

carriage of *S. aureus*, for instance, increases with healthcare exposure, diabetes, dialysis, drug addiction and human immunodeficiency virus infection (HIV).[18] Sites of *S. aureus* colonization also differ based on certain risk factors. An evaluation of *S. aureus* carriage among patients presenting to a community based sexually transmitted infection (STI) clinic found a preferential carriage for the throat (41.5%) compared to the anterior nares (31.7%) [p = 0.01].[19] Increased risk of throat carriage was associated with >6 heterosexual sexual contacts in the last 6 months, practicing oral sex and trimming of pubic hair.[19] Although the majority of people with *S. aureus* colonization do not develop symptomatic disease, they are at increased risk of *S. aureus* infection, as evidenced by the fact that 82.2% of patients with *S. aureus* bacteremia exhibit prior/current colonization with the same strain.[20,21,22] In *S. aureus* bacteriuria (SABU), nasal colonization was detected in 75% of patients in one study.[23] Other sites of *S. aureus* colonization, particularly the perineum, have yet to be explored among SABU individuals.

S. aureus Bacteriuria (SABU)

Despite being a common, sometimes life-threatening and often multidrug resistant pathogen, *S. aureus* is not typically associated with urinary tract infections. The most recent literature suggests that *S. aureus* represents only 0.2 to 4% of positive urine samples and 1% of uncomplicated urinary tract infections (UTIs).[24-27] Urinary tract infections generally occur when uropathogens from the gut colonize the urethra, usually via contamination, and migrate upwards into the bladder through the use of motility structures such as flagella and pili.[27] Most uropathogens have unique characteristics that allow them to flourish in the bladder. These include adhesins and pili that can adhere to

the uroepithelium, obtain nutrients from host cells through specific protease and toxin production, and evade the immune system present within the urinary tract by invading into the cytoplasm of uroepithelial cells.[27] If left untreated, urinary pathogens can eventually ascend to the kidneys, cross the tubular epithelial barrier, and enter the bloodstream.[28] Unlike common uropathogens such as *E. coli* or *K. pneumoniae*, *S. aureus* lacks many of these characteristics to reach and thrive within the bladder. In simpler terms, *S. aureus* "sticks", but doesn't "swim."

The prevalence of *S. aureus* increases in complicated UTIs (3%), defined as those associated with urinary catheterization or urinary tract abnormalities.[27] As mentioned previously, the presence of a urinary catheter allows *S. aureus* to adhere and colonize the catheter inside the bladder which can subsequently lead to *S. aureus* infection. In fact, urinary catheterization appears to be the most common cause of SABU, impacting over 60% of SABU individuals in many studies.[23,25,29,30] Several studies have also implicated urinary catheters as a site of MRSA acquisition and colonization during MRSA outbreaks.[31,32] Other associations with SABU include urinary tract procedures such as cystoscopy,[23,25,26,29,30,33] urinary tract abnormalities and obstruction,[25,29] nursing home resident,[34] healthcare exposure,[25,29,33,34] male gender,[25] and older age.[26,33,35-37]

Interestingly, high rates of SABU have been reported among asymp tomatic pregnant women in certain African countries. In studies on asymptomatic pregnant females in Nigeria, Ethiopia, Ghana, Sudan, and Uganda, *S. aureus* was detected in 6.2 – 45.9% of positive isolates.[38-46] It is thought that female genital mutilation (FGM) might be the

reason behind higher SABU rates in these settings.[47] The abnormal perineal tissue caused by FGM may provide *S. aureus* with better affinity to colonize the genitourethral area, thereby leading to SABU in improperly collected samples. However, the prevalence of female genital mutilation among women aged 15 – 49 is <10% in countries such as Ghana and Uganda which makes this explanation less likely.[48] Regardless of the etiology, SABU in pregnant females should not be taken lightly since *S. aureus* is the most common cause of neonatal sepsis within these countries.[49-53] The association between SABU and neonatal sepsis due to *S. aureus* within these settings remain unclear and further studies are warranted.

S. aureus Bacteremia in Individuals with *S. aureus* Bacteriuria

While SABU often represents urinary colonization, contamination or an uncommon cystitis, a small portion may be a harbinger of deep-seated pyogenic infections and *S. aureus* bacteremia (SAB). Unfortunately, the literature on the development of SAB in individuals with SABU is scarce, with only 9 studies found during a literature review conducted by this author.[23-26,29,35,37,54,55] Among the studies, the definition of SABU varied, with the most common being *S. aureus* $>10^5$ CFU/mL.[23,25,29] Regardless, all the studies have suggested that SABU is a potential marker of *S. aureus* bacteremia, with 12.0 - 48.8% of SABU individuals having or developing SAB.[23-26,29,35,37,54,55] Most SAB cases occurred within 48 hours of SABU detection. However, a not insignificant number of bacteremic cases (27.0% - 38.0%) and non-bacteremic invasive *S. aureus* disease (41.1% - 66.7%) were detected after 48 hours of urine collection, highlighting the potential need for follow up investigations when SABU is detected.[23,24,37]

Risk factors associated with SAB in SABU vary among published cohorts, emphasizing the need for population-based studies such as ours. Potential risk factors associated with SAB in SABU are male gender,[55] urinary catheterization,[23] gross hematuria,[23] and inpatient status.[24] A review examining SABU's association with deeper-seated S. *aureus* infections, including SAB, identified anti-Staphylococcal antibiotics, the absence of UTI symptoms, inpatient status and MRSA as risk factors for invasive *S. aureus* disease.[24] Those less likely to have concurrent SAB during SABU included patients with urinary tract abnormalities or recent intervention,[55] and pyuria.[55] However, all studies examining SAB in SABU have had small sample sizes and weak external validity. Indeed, the largest study included only 41 individuals with SAB[24] while others had <20. Studies generally were conducted at single centers and most assessed selected populations such as males in veteran hospitals or inpatients.

Associated infections in SABU + SAB varies in the medical literature. Many studies report the underlying diagnosis as being isolated urinary tract infection, though many do not provide proper definitions. In one study, most SABU + SAB cases occurred one to three days after a urinary tract procedure (cystoscopy, transurethral prostatic resection or urinary catheterization).[25] In the largest study which examined for invasive disease over the course of 12 months from SABU detection, the most common associated site of infection in patients with SABU + SAB was bacteremia of unclear etiology (41.9%), followed by pneumonia (13.3%), endocarditis (9.3%) and osteomyelitis (7.0%).[24] In another smaller study, the most common associated infection for bacteremia was wound infection (27.3%), endocarditis (22.7%), UTI (22.7%), and pneumonia (9.1%).[37]

S. aureus Bacteriuria in Individuals with *S. aureus* Bacteremia

Many studies have examined SABU in individuals with SAB. Within those studies, SABU occurred in approximately 7 - 34% of individuals with SAB.[56] Comparatively, SABU was present in 8.1% of SAB cases in the Calgary Health Zone over 2012 - 2014 [unpublished data]. In a recent meta-analysis examining SABU in individuals with SAB, individuals with SABU + SAB had increased mortality (OR 1.97, 95% CI 1.28 – 2.88) and more persistent bacteremia than individuals with SAB alone.[56] These findings are thought to be due to SABU + SAB individuals having a more serious invasive infection, such as endocarditis with septic emboli and bone/joint infections.[56]

Study Aims

In this study, we aimed to describe the incidence and outcomes of SABU from a large, diverse Canadian population (over 1.4 million individuals) and to identify population-based risk factors associated with SAB and deeper-seated *S. aureus* infection amongst those with SABU. We hypothesize that *S. aureus* is an uncommon urinary tract isolate in general populations and represents a marker of invasive *S. aureus* infection in only specific populations with SABU. The identification of those specific individual characteristics and clinical presentations that associate with invasive disease can be used to help clinicians identify individuals at risk.

METHODS

Data Collection

All urine culture results reported as positive for *S. aureus* between January 1, 2010, to December 31, 2013, from Calgary Laboratory Services (CLS) were examined. CLS is a centralized laboratory for the Calgary Health Zone (CHZ) that covers all 43 health care centers, including 12 acute care sites, and serves over 1.4 million people.[58,59]

Cultures were reported as positive for *S. aureus* when the urine culture grew pure *S. aureus* at $10^6 – 10^7$ colony forming units (CFU)/L or $>10^7$ CFU/L with no more than 1 other organism present. *S. aureus* from non-routine urine cultures (defined below under subheading "definitions") were reported as positive if the *S. aureus* colony count was $>10^4$ CFU/L with no more than one other organism present. The presence of periurethral flora, defined as organisms resembling periurethral flora that were $<10^7$ CFU/L in the presence of a uropathogen $\geq 10^7$ CFU/L was excluded. Only individuals ≥18 years of age were included. Urine cultures within 3 months of each other and of the same *S. aureus* antibiogram were excluded as these were presumed to represent the original infection.

Data on individual's demographics, microbiologic and laboratory data, underlying comorbidities, urinary procedures and outcomes were extracted from ICD-9 codes using Data Integration, Management and Reporting (DIMR) and the Alberta Discharge Abstract Database (DAD).[60] Population data was obtained from the Alberta Health Services Interactive Health Data Application.[61]

Laboratory data collected within 48 hours of positive urine culture results were included in the analysis. This included urinalysis, complete blood counts (CBCs), serum creatinine and C-reactive protein (CRP), where available. If laboratory data was repeated within 48 hours, only values closest to the time of urine culture were included. Blood cultures and cultures from sterile fluid, tissue, cerebrospinal fluid (CSF), hardware, catheter tips, and deep abscesses that were positive for *S. aureus* growth were included if they occurred within 3 months of any SABU. Procedures related to the urinary tract, including cystoscopy and surgery of the urinary tract, were also reported if they occurred within four weeks before urine culture. Sources of seeding in patients with SABU + SAB and SABU + deeper-seated *S. aureus* infection were determined through electronic chart review. This study received ethical approval from the Conjoint Health Regional Ethics Board of the University of Calgary (REB 14-1488).

Definitions

Non-routine urine culture is defined as any urine culture collected from a suprapubic bladder aspirate, nephrostomy tube, urinary stent, ureterosigmoidostomy, ureter, cystoscopy, kidney, or a mitroffanoff fluid.

Death was defined as all cause mortality during hospitalization – and recorded for only those who were hospitalized.

Recurrent or persistent SABU was defined as SABU occurring $\geq$3 months apart, or $\leq$3 months with different antibiograms.

Outpatients included those who had urine samples taken in community laboratories, urgent and long-term care facilities and emergency rooms. Patients with SABU who had their urine culture collected in an outpatient setting but were subsequently admitted were labelled as an outpatient in our study. Inpatients were defined as patients who had their urine culture collected >48 hours after hospital admission

Cardiovascular disease was defined as any of the following: myocardial infarction, cardiac pacemaker, aortic stenosis, arterial thrombosis, abdominal aortic aneurysm, coronary artery disease, peripheral vascular disease, ischemic heart disease and atrial fibrillation.

Neurologic disorder was defined as any disorder affecting the neurological system, including but not limited to Parkinson's disease, multiple sclerosis, paraplegia, hydrocephalus, spinal cord injury, cardiovascular accident (CVA), epilepsy, dementia, and amyotrophic lateral sclerosis (ALS).

Respiratory disease was defined as any of the following: pneumonia, sleep apnea and chronic obstructive pulmonary disease (COPD).

Urological disorder was defined as any disorder affecting the genito-urethral system, including but not limited to urinary retention, prostatitis, an artificial opening of the urinary tract, hypoplasia of the penis, urethral stricture, ureter stricture, urinary foreign body and urinary incontinence.

Immunosuppression was defined as any transplant recipient, chronic steroid use, hematological malignancy and patients with HIV. Chronic steroid use was based on ICD-9 coding.

The presence of urine leukocytes was defined as a positive leukocyte esterase urine dipstick.

Statistical Analysis

Characteristics between SABU individuals with or without SAB and with or without deeper-seated *S. aureus* infection were compared. A subgroup analysis for outpatients, including emergency room visits, and for individuals with or without a urinary catheter was conducted. Risk factors associated with death during hospital admission were also analyzed. Associations between predictive variables and aforementioned outcomes were independently evaluated using chi-square test or Fisher's exact test for discrete variables and independent two-sample t-test or Mann-Whitney U-test for continuous variables. Variables that had a p-value <0.10 were included in a stepwise multiple logistic regression model. Independent variables with $p<0.05$ after stepwise regression were included in the final multivariate logistic regression model and associations were reported as odds ratios (OR) with 95% confidence intervals (CI). Laboratory data were excluded from the multivariate regression model due to incomplete data (not all individuals with SABU had laboratory investigations). Instead, laboratory outcomes were individually adjusted using the final multivariate logistic regression model. All statistical analysis was done using STATA 14.0 (Stata Corp., College Station, TX, USA).

Systematic Review and Meta-Analysis

A systematic review using a predetermined protocol and in accordance with PRISMA standardized reporting guidelines was conducted.[62] Investigator WS searched electronic databases from inception to Janurary 6, 2018, including Google Scholar, Pubmed, Web of Science, EMBASE and MEDLINE. No language restrictions were applied. Conference proceedings from the Annual Meetings of the Infectious Diseases Society of America were searched from 2003 - onwards for relevant abstracts. The references of relevant articles were also searched. The search strategy combined the names and alternate names of "Staphylococcus aureus", "urinary tract infection" (or "bacteriuria") and "bacteremia" using the Boolean operator AND to map (search by keyword) and explode (search by subject heading where appropriate). Alternative names of *Staphylococcus aureus*, urinary tract infection and bacteremia were combined using the Boolean operator OR (see Appendix A). Our search was broad in order to capture all relevant publications.

Articles were included in the systematic review if they were articles presenting independent research related to *S. aureus* bacteremia in individuals with *S. aureus* bacteriuria. Case reports were excluded. Studies that examined *S. aureus* bacteriuria in individuals with *S. aureus* bacteremia were excluded.

Systematic Review and Meta-Analysis: Data Extraction and Quality Assessment

Data extracted in the systematic review included study characteristics (publication year, geographic location, sample size), individual characteristics (age, gender, comorbidities, symptoms), laboratory characteristics (MRSA, pyuria, colony count, mixed culture),

urinary procedures and outcomes (SAB, invasive *S. aureus* infection, death). Study quality was assessed using the Newcastle-Ottawa scale for assessing the quality of cohort studies.[63] This scale includes assessments of the exposed cohort, non-exposed cohort, ascertainment of exposure, assessment of outcomes, comparability of cohorts, and adequacy and length of follow-up.

For the meta-analysis, we sought to determine whether urinary catheters in SABU individuals increases the risk for developing SAB. For our secondary outcome, we pooled other characteristics found to be associated with SAB among SABU individuals. These included urinary obstruction, presence of urinary tract infection symptoms, pyuria, gender, inpatient status and diabetes. Pooled odds ratios were visually demonstrated using forest plots and heterogeneity among studies was assessed using the I^2 and Cochran Q statistics. Odds ratios of development of SAB in individuals with SABU who have urinary catheters were also pooled using random effects models, with individuals without urinary catheters as the reference group. As a sensitivity analysis for all pooled estimates, fixed effect models were generated to assess the robustness of the findings. Finally, small study effects, potentially indicative of publication bias, was assessed visually through a funnel plot and tested for using Begg and Mazumdar's rank correlation test for asymmetry.[64] A significant statistical test ($p<0.05$) or observed funnel plot asymmetry suggests small study effects that may potentially be caused by publication bias. All analyses were conducted using STATA 14.0 (Stata Corp., College Station, TX, USA)

RESULTS

Epidemiology of SABU

Between 1/1/2010-12/31/2013, 875,587 urine cultures with significant growth were collected. Of those, 3739 (0.4%) were reported positive for *S. aureus*. A total of 1199 cultures were excluded from analysis based on our exclusion criteria, leaving 2540 cultures from 2054 patients for analysis. This corresponded to a rate of 174/100,000 in the general population of the CHZ. Of the 1199 excluded cultures, 137 were from 100 individuals aged <18 years old, none of whom developed SAB. The other 1062 cultures were excluded for being within 3 months of each other and of the same *S. aureus* antibiogram. SAB occurred in 6.9% (175) of patients with SABU.

SABU cases as a proportion of the general population declined 14% from 2010 - 2013 ($p=0.04$, linear regression), whereas the number of SABU + SAB cases have remained relatively constant ($p=0.74$) (Figure 1). The presence of a urinary catheter at the time of urine collection also declined each year ($p<0.001$) (Figure 2). SABU was equally represented between genders (51.3% male). However, when comparing to the population of the CHZ, SABU occurred at a higher rate among males and disproportionally among the older population, reaching a peak incidence of 552/10,000 among males aged ≥85 years (Figure 3). For reference, the population of the Calgary Health Zone, by age cohort, is provided in Figure 4. Compared to SABU, the rate of SABU + SAB also occurred among slightly younger age cohorts (Figure 5).

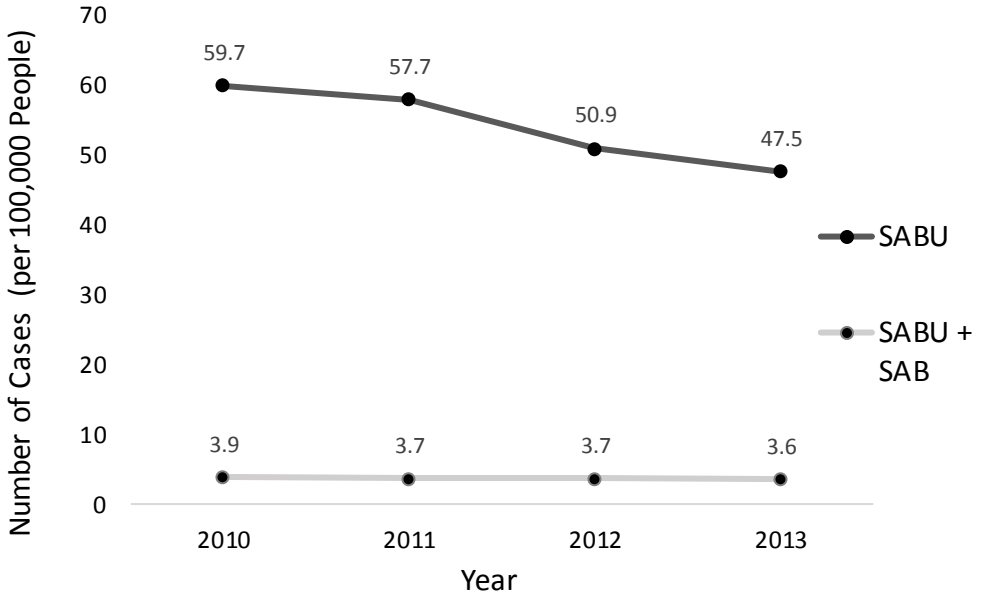


Figure 1 Rate of SABU and SABU + SAB cases within the Calgary Health Zone per year.

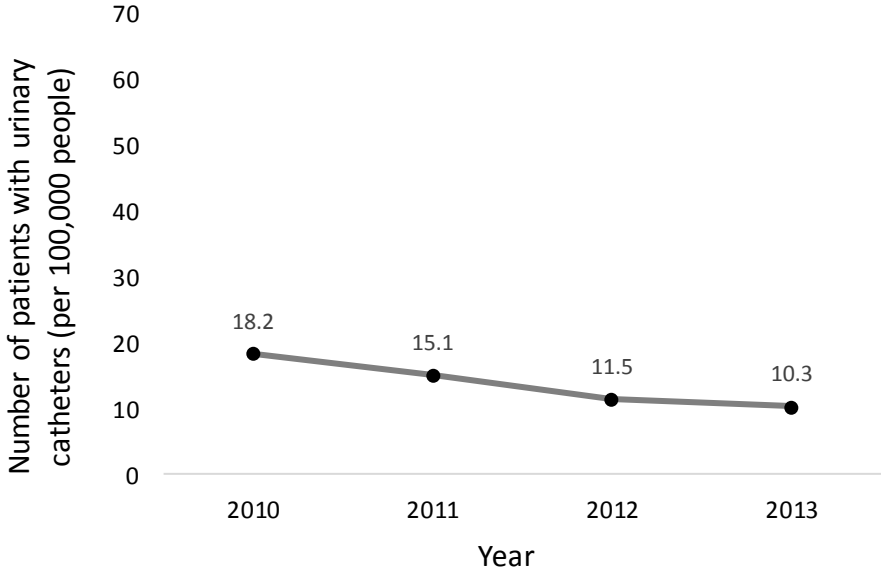


Figure 2 Percentage of individuals with a urinary catheter at time of urine collection within the Calgary Health Zone per year. Decrease in SABU for patients with and without urinary catheter declined by 10% and 39%, respectively ($p<0.001$).

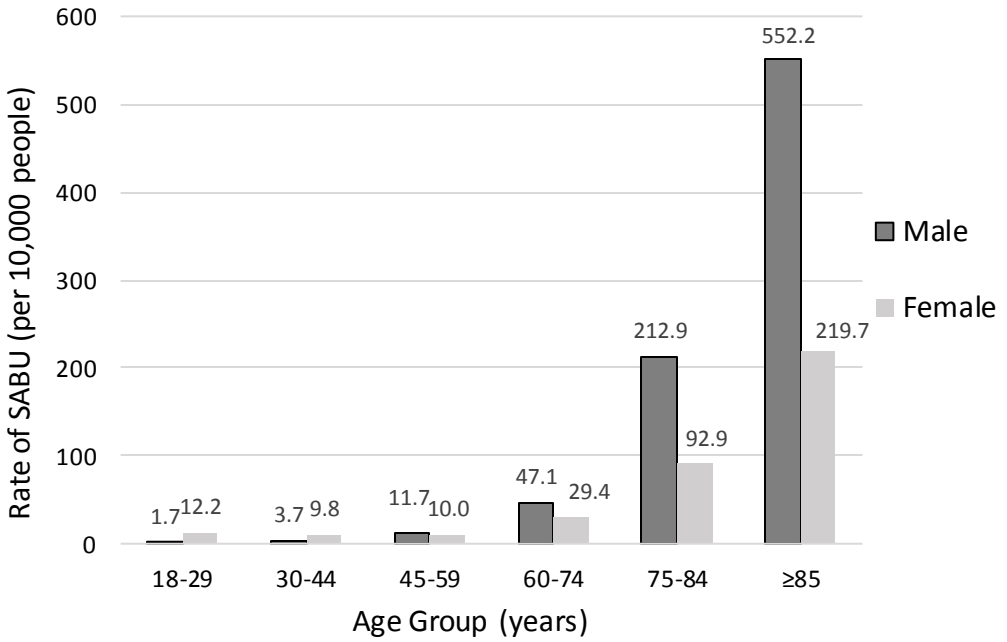


Figure 3 Rate of SABU within the Calgary Health Zone, by age cohort, averaged from 2010 – 2013.

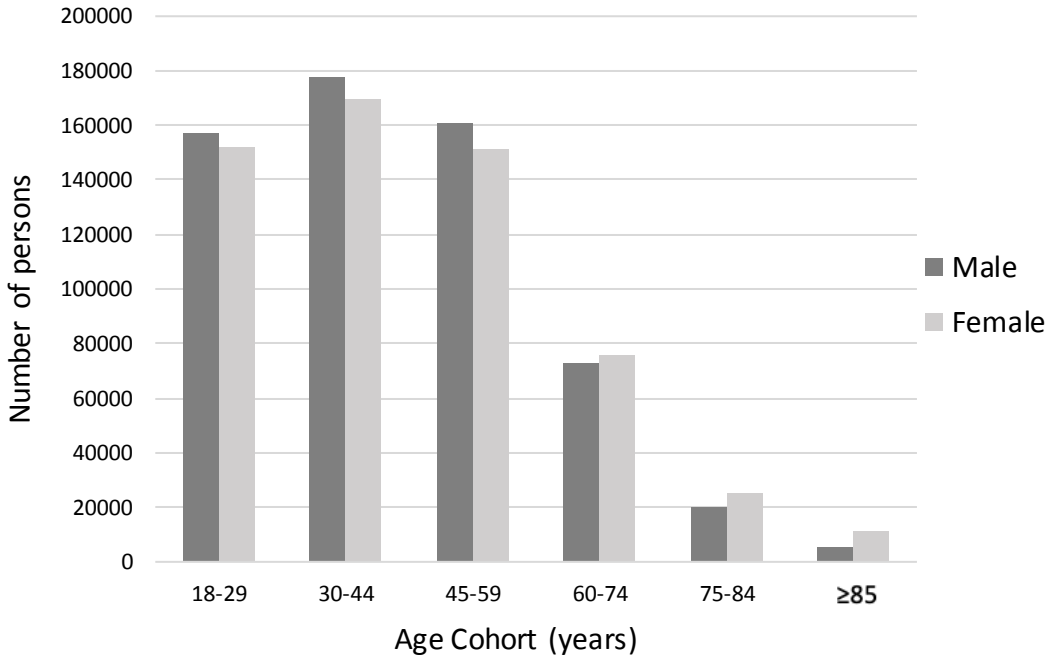


Figure 4 Population of Calgary Health Zone, by age cohort, averaged from 2010-2013.

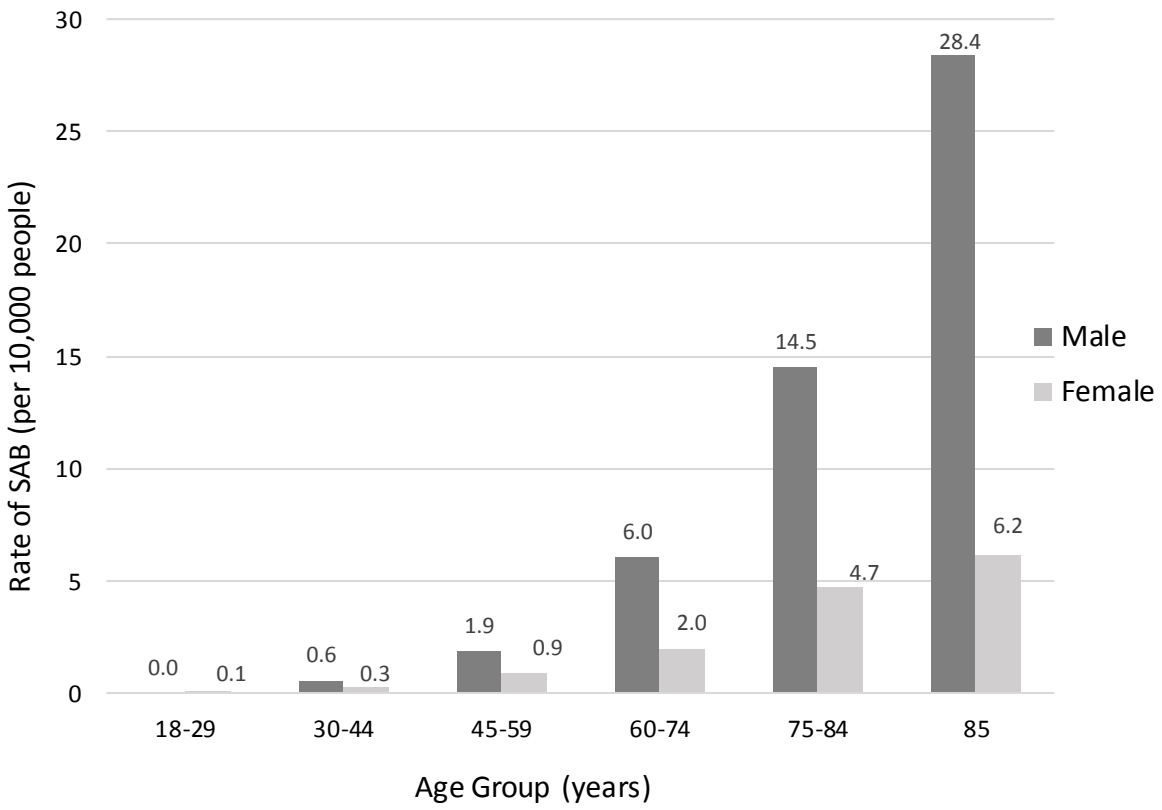


Figure 5 Rate of SAB in individuals with SABU within the Calgary Health Zone, by age cohort, averaged from 2010 – 2013.

Comorbidities were more prevalent among individuals with SABU or SABU + SAB than the Calgary Health Zone population (Table 1). In particular, diabetes in SABU individuals was more than double the prevalence among the CHZ general population and higher yet in individuals with SABU + SAB. Dementia in SABU individuals was more prevalent than the Calgary Health Zone population but lower than the SABU + SAB populations. Overall, more comorbidities were present in SABU individuals compared to SABU + SAB individuals or the general Calgary Health Zone population.

Most urine cultures had pure growth of *S. aureus*. *S. aureus* at $\geq 10^8$, 10^7 - 10^8, 10^6 - 10^7 colony forming units per liter (CFU/L) was detected in 53.0%, 33.2%, 13.4% of urine cultures, respectively. Colony count was not associated with increased risk of SAB. *S. aureus* was inappropriately reported as positive in 9 samples. This included 2 samples (0.08%) which were reported as positive for *S. aureus* when *S. aureus* was $<10^6$ CFU/L and 7 samples (0.3%) which were reported as positive for *S. aureus* when *S. aureus* was $10^6 – 10^7$ CFU/L in the presence of other organisms. By the protocol used in our laboratory, these samples should not have been reported as *S. aureus*. None of the 11 samples were from individuals who developed SAB. Reasons for reporting these samples include human error or by request from a medical microbiologist.

Urinary catheters accounted for 18.7% of our urine culture sources. An in/out catheter accounted for 2.3%. There were a total of 22 (0.87%) non-urine sources (17 nephrostomy tubes, 3 cystoscopies and 2 suprapubic catheters). In the 2540 urine culture specimens, 37.0% had the combination of pure *S. aureus* and a colony count $\geq 10^8$ CFU/L.

Table 1 Prevalence of comorbidities between Calgary Health Zone general population and individuals with SABU.

Comorbidity	Calgary Health Zone (%)[61]	SABU (%)	P-value	SABU + SAB (%)	P-value*
Diabetes	5.03	10.57	<0.001	18.86	<0.001
Multiple sclerosis	0.24	1.10	<0.001	1.14	<0.001
Cirrhosis	0.18	0.59	<0.001	2.29	<0.001
COPD	1.89	4.10	<0.001	4.00	<0.001
Dementia	1.80	6.72	<0.001	2.29	<0.001
ESRD	0.09	0.08	0.078	0.57	<0.001
Parkinson's	0.11	0.89	<0.001	0	<0.001
Epilepsy	1.32	0.30	<0.001	1.71	<0.001
Ischemic heart disease	2.99	1.73	<0.001	2.29	<0.001
Two or more comorbidities**	7.25	13.07	<0.001	12.00	<0.001
Three or more comorbidities**	2.05	4.14	<0.001	2.86	<0.001
Four or more comorbidities**	0.48	0.72	<0.001	0	<0.001

*P-value based on SABU + SAB compared to prevalence in Calgary Health Zone

**Comorbidities based on Parkinson's disease, end stage renal disease (ESRD), asthma, congestive heart failure, chronic obstructive lung disease (COPD), hypertension, ischemic heart disease, multiple sclerosis, diabetes, inflammatory bowel disease. Number of comorbidities examined was limited by the data available in the AHS interactive health data application.[61]

Periurethral flora, which was excluded in our study, was present in 7.5% of included SABU cultures. The most common concurrent organisms detected in mixed urine cultures was *Enterococcus faecalis* at 28%. MRSA was present in 23.1% of SABU specimens and is similar to the overall prevalence of MRSA among *S. aureus* blood culture isolates in community individuals within the Calgary Health Zone.[14]

S. aureus Bacteremia and its Association with SABU

Characteristics of individuals with SABU and SABU + SAB are displayed in Table 2. Compared to SABU, individuals with SABU + SAB were more likely to be younger, male, an inpatient, have a recent urinary procedure and have pure *S. aureus* culture. Individuals with SABU + SAB also had higher prevalence of liver cirrhosis, malignancy, diabetes, kidney disease and immunosuppression. SABU individuals were more likely to be from a nursing home and have dementia, MRSA, and recurrent or persistent SABU.

Laboratory characteristics of patients at time of SABU and SABU + SAB are outlined in Table 3. Overall, individuals with SABU + SAB had markers suggestive of systemic inflammation. Individuals with isolated SABU, in contrast, had higher rates of pyuria, the presence of urine leukocytes and positive urine nitrites. Microscopic hematuria was similar between groups.

Table 2 Demographics and characteristics of individuals with SABU and SABU + SAB.

Variable	SABU N=2365	SABU+SAB N=175	p-value	Alive N=888	Dead N=93	p-value
Median age (IQR)	74 (30)	65 (23)	0.052	75 (24)	80 (15)	<0.001
Age >65 (%)	62.6	51.4	0.003	66.8	86.0	<0.001
Male (%)	51.3	69.7	<0.001	60.9	59.1	0.738
Inpatient (%)	27.3	56.0	<0.001	69.7	88.2	<0.001
Nursing home resident (%)	16.7	6.9	0.001	5.4	3.2	0.368
Hospital admission (outpatients only)	19.2	38.3	<0.001	-	-	-
ICU admission (%)	0.2	2.9	<0.001	0.90	2.2	0.254
Recurrent or persistent SABU (%)	18.3	8.6	0.001	17.8	5.4	0.002
MRSA (%)	23.6	17.1	0.050	27.6	28.0	0.940
Pure *S. aureus* cultures* (%)	79.3	84.6	0.096	70.9	66.7	0.389
Colony count $10^6 – 10^7$ CFU/L (%)	13.3	14.9	0.565	10.6	12.8	0.515
Colony count $10^7 – 10^8$ CFU/L (%)	33.4	31.4	0.600	30.9	31.9	0.845
Colony count $>10^8$ CFU/L (%)	53.1	52.6	0.895	58.1	54.8	0.550
Pure *S. aureus* culture with colony count $>10^8$ CFU/L (%)	36.9	38.9	0.600	38.1	33.3	0.383
Presence of catheter (%)	18.5	21.1	0.391	17.0	15.0	0.632
Recent urinary procedure (%)	1.9	8.0	<0.001	5.41	7.53	0.399
Liver cirrhosis (%)	0.6	2.3	0.010	1.6	3.2	0.246
Cardiovascular disease (%)	6.1	7.4	0.464	11.0	24.7	<0.001
Malignancy (%)	5.0	8.6	0.043	10.5	23.7	<0.001
Urological malignancy (%)	2.4	2.9	0.683	5.1	10.8	0.023
Urological disorder (%)	11.5	10.3	0.637	17.1	22.3	0.204
Diabetes (%)	10.6	18.9	0.001	20.7	25.8	0.254
Chronic kidney disease (%)	2.6	6.3	0.005	6.0	12.9	0.011
Neurologic disorder (%)	17.2	12.6	0.117	32.8	36.6	0.460
Urinary foreign body (%)	1.6	3.4	0.085	2.0	3.2	0.447
Dementia (%)	6.7	2.3	0.021	13.1	11.8	0.736
Immunosuppressed (%)	1.3	3.4	0.019	2.5	7.5	0.006
Positive blood culture	-	-	-	15.5	28.0	0.002
SAB + SABU within 48 hours of each other (%)	-	81.1	-	13.2	21.3	0.031
SABU 48hrs before SAB** (%)	-	13.7	-	1.7	5.4	0.017
SAB 48hrs before SABU*** (%)	-	4.6	-	0.6	1.1	0.547

* Most common concurrent organism detected in mixed cultures was *E. faecalis* (28%)
** Median time from SABU to SAB: 409 hours (17.0 days)
*** Median time from SAB to SABU: 1389 hours (57.9 days)

Table 3 Laboratory characteristics of individuals with SABU and SABU + SAB.

Laboratory analysis	Laboratory analysis	SABU	SABU + SAB	p-value	Alive	Dead	p-value
Urine findings	Pure *S. aureus* cultures (%)	79.3	84.6	0.096	70.9	66.7	0.389
	Urine RBC >10/hpf (%)	39.1 N=338	50.0 N=24	0.290	38.6 N=166	46.2 N=13	0.589
	Urine WBC >10/hpf (%)	88.3 N=332	58.3 N=24	<0.001	84.7 N=163	46.2 N=13	0.001
	Presence of urine leukocytes (%)	89.0 N=897	68.5 N=73	<0.001	85.4 N=425	83.3 N=42	0.717
	Presence of urine nitrites (%)	50.8 N=890	34.2 N=73	0.007	50.4 N=425	50.0 N=42	0.965
Serum findings	Hgb (g/L), median	118 N=687	115 N=89	<0.001	114 N=419	105 N=49	<0.001
	Hgb < 110g/L (%)	34.8 N=687	42.7 N=89	0.143	43.2 N=419	61.2 N=49	0.016
	Platelets x 10^9/L, median	239 N=685	190 N=89	<0.001	242 N=418	155.5 N=48	<0.001
	Platelets < 150 x 10^9/L (%)	13.3 N=685	40.4 N=89	<0.001	17.9 N=418	47.9 N=48	<0.001
	Platelets >400 x 10^9/L (%)	2.54 N=685	2.52 N=89	0.080	9.81 N=418	6.3 N=48	0.425
	Serum WBC x 10^9/L, median	9 N=702	11.2 N=91	<0.001	9.8 N=427	9.7 N=47	0.3796
	Serum WBC >11 x 10^9/L (%)	30.8 N=702	50.5 N=91	<0.001	37.4 N=428	37.5 N=48	0.987
	Presence of immature neutrophils (%)	9.9 N=704	46.2 N=93	<0.001	18.0 N=428	27.7 N=47	0.108
	CRP [mg/L], median	45.7 N=26	261.3 N=13	0.012	99.1 N=28	23.5 N=3	0.9201
	CRP >8mg/L (%)	92.3 N=26	92.3 N=13	1.00	89.3 N=28	100 N=3	0.551
	CRP >200mg/L (%)	15.4 N=26	76.9 N=13	<0.001	35.7 N=28	33.3 N=3	0.935
	Creatinine, median	86 N=728	94 N=98	0.099	88 N=439	94.5 N=50	0.788
	Creatinine > 120µmol/L	31.3 N=728	36.4 N=99	0.312	34.0 N=439	34.7 N=50	0.925

CRP: c-reactive protein.
WBC: white blood cells.
Hgb: hemoglobin.
RBC: red blood cell.
Hpf: high-power field.

Multivariate logistic regression showed that inpatient status, male gender, recent urological procedure, pure *S. aureus* growth, the presence of immature neutrophils, thrombocytopenia, leukocytosis and higher CRP levels were significantly associated with the presence of SAB in SABU (Table 4). In contrast, dementia, recurrent or persistent SABU, age >65 years, urine white blood cell (WBC) >10 cells/hpf and the presence of urine nitrites, was significantly associated with isolated SABU.

Associated infections in patients with SABU + SAB are presented in Figure 6. The most commonly identified associated infection was from osteomyelitis of the spine or pelvis at 23% (with many having concomitant epidural abscess), followed by infective endocarditis at 11%. Most individuals with infective endocarditis had signs of disseminated infection and 26% had seeding of the spine and/or pelvis. No associated infection was identified in 44 individuals (25%), although most of these individuals (25/44, 56.8%) were labeled as having "urinary tract infection" as their diagnosis from physician notes. Because details on urinary symptoms were not accessible by these authors, SABU + SAB individuals with a diagnosis of "urinary tract infection" were categorized as having "no associated infection identified."

Invasive *S. aureus* Infections without Bacteremia and their Association with SABU

Invasive *S. aureus* infections without documented SAB occurred in 21 individuals with SABU (0.8%). Microbiological samples taken from tissue, deep abscesses, abdominal fluid, and synovial fluid made up the majority of sources at 28.6%, 23.8%, 19.0%, and 14.3%, respectively.

Table 4 Multivariate logistic regression analysis of factors associated with SAB in SABU individuals (N=175/2540).

Predictor	Odds ratio*	Adjusted p-value	OR 95% CI
Risk factors			
Presence of immature neutrophils	7.3	<0.001	4.3 – 12.1
Serum platelets <120	5.4	<0.001	3.0 – 9.8
Serum WBC >15	4.4	<0.001	2.6 – 7.4
Inpatient	3.6	<0.001	2.6 – 5.0
Urinary procedure	2.2	0.020	1.1 – 4.3
Males	2.1	<0.001	1.5 – 3.0
Pure *S. aureus* growth	1.6	0.029	1.1 – 2.5
Protective factors			
Dementia	0.23	0.005	0.08 – 0.63
Urine WBC>10 cells/hpf	0.20	0.002	0.07 – 0.54
Presence of urine leukocytes	0.34	<0.001	0.19 – 0.60
Recurrent or persistent SABU	0.44	0.004	0.26 – 0.77
Presence of urine nitrites	0.51	0.012	0.31 – 0.87
Age>65	0.54	<0.001	0.39 – 0.75

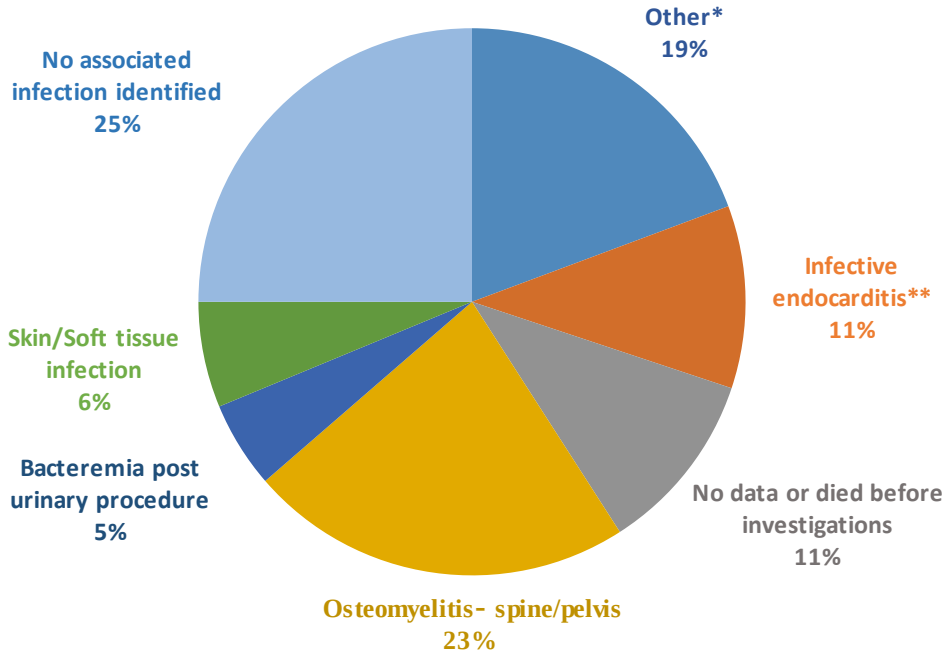
WBC: white blood cells.

Hpf: high-power field.

*Adjusted for inpatient status, gender, urinary procedure, dementia, recurrent or persistent SABU, age>65 and pure *S. aureus* culture.

- Calibration (Pseudo R2)=0.10, discrimination (area under receiver operating characteristic (RoC) curve)= 0.74**.

**Calibration of the final model was assessed using the Hosmer-Lemeshow goodness of fit test and discrimination was assessed using the area under the receiver operator curve.



*Other: Septic arthritis, pneumonia, central line infection, intra-abdominal infection, infected skull bone flap, extremity osteomyelitis, septic abortion, infected pericarditis.

**5 (26%) of individuals with infective endocarditis had confirmed osteomyelitis of spine/pelvis.

Figure 6 Associated infections of SAB in individuals with SABU (N=175).

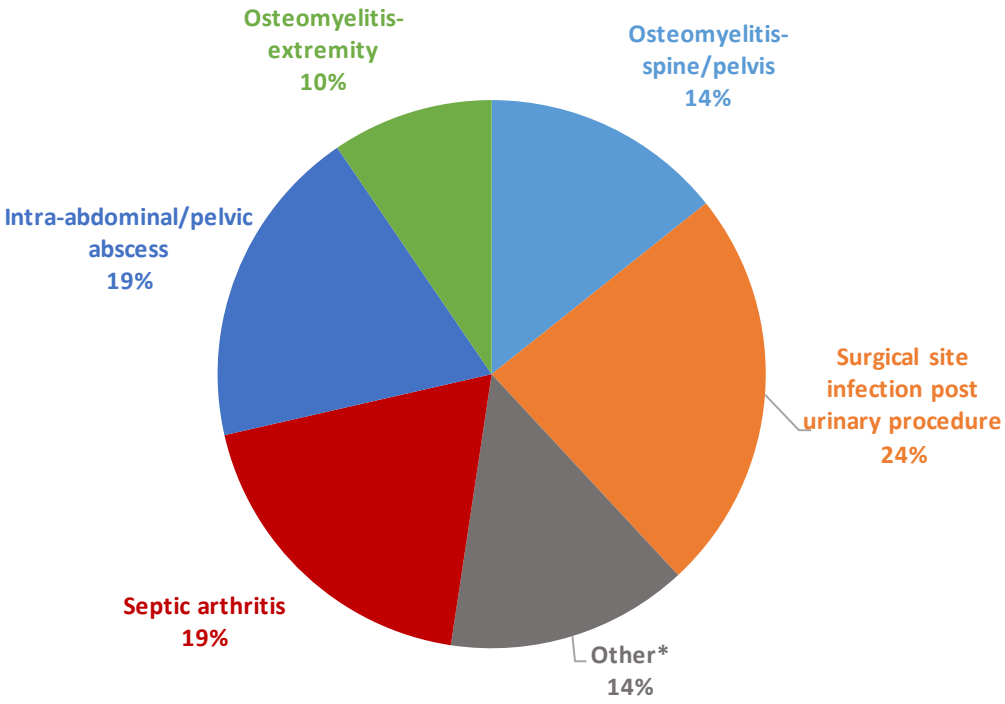
Twenty-four percent of SABU individuals with non-SAB invasive *S. aureus* infections had a skin and soft tissue infection post urinary tract procedure, 19% had septic arthritis, 19% had an intra-abdominal or pelvic abscess and 14% had osteomyelitis of the spine/pelvis (Figure 7).

In Hospital Death

In hospital death occurred in 93 of 981 hospitalized patients (9.5%). Risk factors for death in the multivariate logistic regression model included concurrent SAB + SABU, age >65 years, cancer, inpatient status, cardiovascular disease, respiratory disease and platelets $<150x10^9$/L (Table 5). Inpatient status reflects patients who were admitted to hospital before collection. Importantly, individuals who had SABU identified ≥48 hours before SAB were also more likely to die. Recurrent or persistent SABU and urine WBC >10 cells/hpf was significantly associated with lower risk of death.

Understanding SABU in the Context of the Community

SAB occurred in 77/1797 (4.3%) of outpatients (including emergency room patients) with SABU. All were subsequently hospitalized or died before hospitalization. Risk factors for SAB in outpatients with SABU were similar to that of isolated SABU with several differences noted (Table 6). Only individuals with a very elevated WBC count (WBC >15 x 10^9/L) had higher risk of SAB. Diabetes and the presence of a urinary catheter were associated with SAB in outpatients with SABU.



*Other: Fournier's gangrene, thigh abscess, positive central line blood culture with negative peripheral blood cultures.

Figure 7 Associated infections of deep seated *S. aureus* infection without SAB (N=21).

Table 5 Multivariate logistic regression analysis of risk factors for death in SABU individuals (N=93/981).

Predictors	Odds ratio*	Adjusted p-value	OR 95% CI
Risk factors			
SABU >48 hours before SAB	8.87	<0.001	2.96 – 26.6
Platelets < 150 x 10^9/L	4.16	<0.001	2.05 – 8.47
Age >65	3.44	<0.001	1.80 – 6.58
SAB + SABU concurrently	3.14	<0.001	1.73 – 5.69
Inpatient status	2.75	0.004	1.38 – 5.47
Cancer	2.54	0.001	1.45 – 4.44
Cardiovascular disease	1.94	0.020	1.11 – 3.40
Respiratory disease	1.91	0.021	1.10 – 3.29
Protective factors			
Urine WBC >10 cells/hpf	0.12	0.006	0.03 – 0.56
Recurrent or persistent SABU	0.30	0.015	0.11 – 0.79

*Adjusted for SABU >48 hours before SAB, age >65 years, SAB + SABU concurrently, inpatient status, cancer, cardiovascular disease, respiratory disease, and recurrent or persistent SABU.
- Calibration (Pseudo R2)=0.13, discrimination (area under RoC curve)= 0.77**.
**Calibration of the final model was assessed using the Hosmer-Lemeshow goodness of fit test and discrimination was assessed using the area under the receiver operator curve.

Table 6 Multivariate logistic regression analysis of risk factors for *S. aureus* bacteremia in outpatients with SABU (N=77/1797).

Predictor	Odds ratio*	Adjusted p-value	OR 95% CI
Risk factors			
Presence of immature neutrophils	8.84	<0.001	4.24 – 18.46
Serum platelets <150 x 10^9/L	5.83	<0.001	2.76 – 12.32
Serum WBC >15 x 10^9/L	3.13	0.004	1.44 – 6.78
Diabetes	3.77	<0.001	1.99 – 7.15
Presence of a urinary catheter	3.38	<0.001	1.89 – 6.03
Pure *S. aureus* culture	2.39	0.026	1.11 – 5.15
Males	1.80	0.020	1.10 – 2.96
Protective factors			
Urine WBC >10 cells/hpf	0.11	0.010	0.020 – 0.59
Presence of urinary leukocytes	0.24	<0.001	0.11 – 0.53
Recurrent or persistent SABU	0.26	0.002	0.11 – 0.61
Nursing home resident	0.31	0.002	0.15 – 0.65

Hpf = high-power field

* Adjusted for diabetes, the presence of a urinary catheter, pure *S. aureus* culture, gender, recurrent or persistent SABU and nursing home resident

- Calibration (Pseudo R2)=0.08, discrimination (area under RoC curve)= 0.73**

**Calibration of the final model was assessed using the Hosmer-Lemeshow goodness of fit test and discrimination was assessed using the area under the receiver operator curve.

Being a nursing home resident was associated with less risk of SAB. Unlike the data presented in Table 4 of the entire cohort, a recent urinary procedure was not associated with SAB in outpatient settings and dementia and age >65 was no longer statistically significant. This is likely due to a decrease in statistical power as a result of lower SAB rates in our study's outpatients.

Understanding SABU in Individuals with or without a Urinary Catheter

There were 475 (18.7%) SABU individuals who had a urinary catheter at the time of urine collection. SAB occurred in 37 (7.8%) of catheterized individuals. Risk factors for SAB in this population revealed similar results as the overall SABU population (Table 7). Immunosuppression became a significant risk factor among catheterized individuals, though its confidence interval is very wide. In terms of protective factors, dementia was lost but nursing home resident became statistically significant. In individuals without a urinary catheter, SAB occurred in 138/2065 (6.7%) of individuals and the results of multivariate analysis are also similar to those of the overall population (Table 8). Interestingly MRSA became a statistically significant protective factor for SAB among non-catheterized SABU individuals.

Systematic Review

A systematic review and meta-analysis was conducted to determine whether urinary catheters in SABU individuals increases the risk for developing SAB.

Table 7 Multivariate logistic regression analysis of risk factors for SAB in SABU individuals who do have a urinary catheter (N=37/475).

Predictor	Odds ratio*	Adjusted p-value	OR 95% CI
Risk factors			
Urinary procedure	12.28	<0.001	3.39 – 44.4
Immunosuppressed	10.86	0.013	1.6 – 72.0
Presence of immature neutrophils	5.44	0.002	1.8 – 16.2
Serum platelets <120	5.12	0.008	1.54 – 17.1
Protective factors			
Presence of urine leukocytes	0.17	0.012	0.04 – 0.68
Nursing home resident	0.33	0.009	0.15 – 0.76
Age>65	0.35	0.006	0.16 – 0.74
Presence of urine nitrites	0.42	0.007	0.23 – 0.79

*Adjusted for age >65 years, urinary procedure, nursing home resident and immunosuppression.
- Calibration (Pseudo R2)=0.12, discrimination (area under RoC curve)= 0.74**.
**Calibration of the final model was assessed using the Hosmer-Lemeshow goodness of fit test and discrimination was assessed using the area under the receiver operator curve.

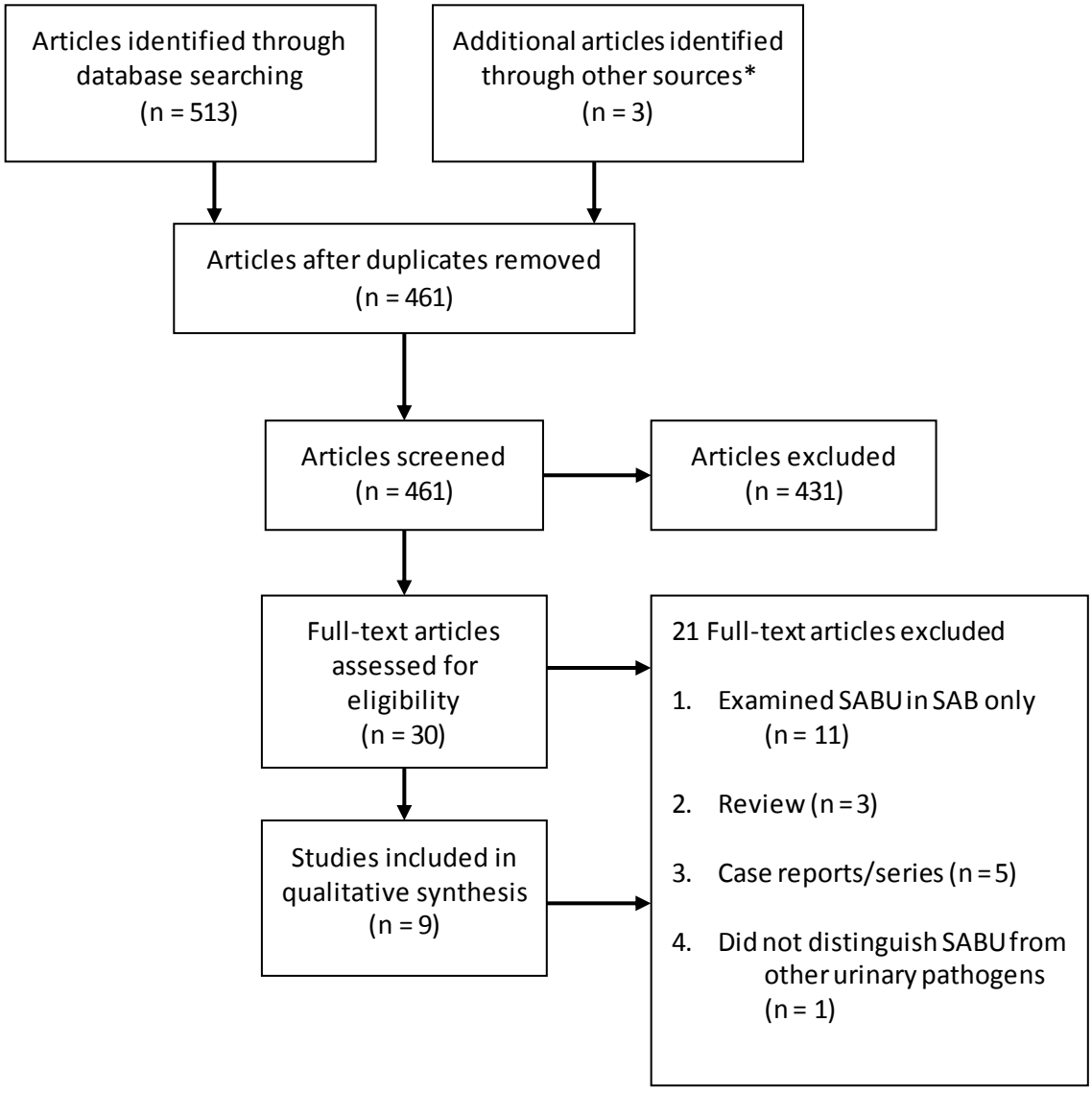
Table 8 Multivariate logistic regression analysis of risk factors for SAB in SABU individuals who do not have a urinary catheter (N=138/2065).

Predictor	Odds ratio*	Adjusted p-value	OR 95% CI
Risk factors			
Presence of immature neutrophils	8.51	<0.001	4.70 – 15.40
Serum WBC >15 x 10^9/L	5.46	<0.001	3.02 – 9.87
Serum platelets <150 x 10^9/L	5.29	<0.001	2.67 – 10.48
Inpatient	4.18	<0.001	2.87 – 6.10
Males	2.55	<0.001	1.72 – 3.79
Protective factors			
Presence of urine leukocytes	0.35	0.001	0.19 – 0.66
Urine WBC >10 cells/hpf	0.35	0.039	0.13 – 0.95
Recurrent or persistent SABU	0.37	0.006	0.18 – 0.75
Presence of urine nitrite	0.42	0.007	0.23 – 0.79
Age >65	0.49	<0.001	0.34 – 0.71
MRSA	0.59	0.038	0.35 – 0.97

WBC: white blood cells.
Hpf: high-power field.
*Adjusted for inpatient status, gender, recurrent or persistent SABU, age>65 and MRSA bacteriuria.
- Calibration (Pseudo R2)=0.11, discrimination (area under RoC curve)= 0.75**.
**Calibration of the final model was assessed using the Hosmer-Lemeshow goodness of fit test and discrimination was assessed using the area under the receiver operator curve.

The search strategy yielded 461 abstracts, of which 431 were excluded for not meeting inclusion/exclusion criteria (Figure 8). Subsequently, 30 papers were included for full text review, of which 9 papers met inclusion criteria for the systematic review.[23-26,29,35,37,54,55]

Characteristics of SABU individuals from the 9 included studies are provided in Table 9. All studies were retrospective cohort studies and 8 out of 9 were conducted in a single center. Studies varied widely in terms of geographic location, individual characteristics and outcomes. Many studies occurred in veteran hospitals within the United States of America (USA).[23,24,29] As a result, the vast majority of SABU individuals were male. SABU individuals were an average age of 66 years among studies. The presence of urinary catheters was high across studies and varied widely (23.9% – 82.0%). MRSA prevalence also varied widely across studies which is most likely due to differences in the time and location of study, with higher MRSA prevalence occurring among more recent American studies. The three studies that reported mixed vs pure growth of *S. aureus* in urine culture found that most cultures were of mixed growth (52.0% - 73.8%). Outcome definitions (SAB and death) varied between studies. For instance, some studies measured in hospital mortality[37,54] while others measured mortality from two weeks to one year after SABU.[23,24,26,29,37] Some studies excluded SAB due to known invasive *S. aureus* infection while others examined SAB within 72 hours or up to one year (Table 9).



*Other sources include conference proceedings from the Annual Meetings of the Infectious Diseases Society of America and references of relevant articles.

Figure 8 Search strategy results using preferred reporting items for systematic reviews and meta-analysis (PRISMA) flow diagram.[64]

Table 9 Characteristics of studies included in systematic review.

	Reller [56]	Reyes [38]	Arpi [26]	Bermejo [36]	Demuth [30]	Mohajer [25]	Muder [24]	Saidel-Odes [27]	Sheth [55]
Publication year	2004	2010	1984	2012	1979	2013	2006	2009	1997
Geographic location	USA	USA	Denmark	Argentina	USA	USA	USA	Israel	USA
Sample size	138	149	132‡	43	109	326	102	120	45
SAB (%)	39.1	28.2*	8.3†	48.8	14.7	8.6ᶜ·	13^	12.0	11.1°°
Invasive S. aureus disease without SAB	-	-	-	-	2.4	4.6	7.8	-	0.8
MRSA (%)	-	70	3.0	48.8		48.2	86	11.7	-
Average age	-	65	73	68.7	63.3	66.2	72.8	56	-
Urinary Catheter (%)	-	54	62.9	58.1	23.9	42.9	82.0	41.0	-
Male (%)	-	-	81	58.1	98	94.5	100	57	-
Pure S. aureus culture (%)	-	48	35	-	-	39.0	-	-	26.2
Colony count >10^8 CFU/L (%)	-	42	-	-	-	-	-	-	-
Recent urinary procedure (%)	-	-	9.2	-	-	-	7	-	-
Nosocomial SABU (%)	-	-	81	65.1	55	57.7	-	30	-
Recurrent or persistent SABU (%)	-	20	-	-	-	17.5§	58Δ	-	-
Symptomatic UTI (%)	33	33	46/116 (40%)	-	28/69 (40%)	31.9	15.7	20	-
Pyuria	-	-	78/99 (79%)	-	71	77.2	-	67.5	-
Nursing home resident (%)	-	-	-	-		-	70	6.6	-
Diabetes (%)	-	-	-	25.6	18.0	39.6	42	30	-
Death (%)	-	11**	-	23.2°	15.6Ω	23.6§§	12.7ΔΔ	12.5ΔΔ	13.3§§

* 14.8% had SAB concurrently and 13.4% developed SAB within 1 year.

**Death during hospitalization.

‡ Excluded mixed cultures.

† excluded SAB due to known invasive *S. aureus* infection.

ΔSABU after >2 months of initial SABU.

^An additional 8/102 (7.8%) had SAB up to 12 months after initial SABU.

ΔΔDeath within 30 days.

°Definition of death unknown.

°°An additional 4.4% developed invasive S. aureus disease 4 months after SABU.

§§Death within one year.

§ definition unknown.

· An additional 4.0% developed SAB within 12 months of initial SABU.

ΩDeath within two weeks of SABU.

Assessment of bias using the Newcastle-Ottawa quality assessment scale for cohort studies yielded similar results across studies (Table 10). Selection of participants was at low risk for all studies except for Arpi et al which excluded individuals who developed SAB due to known invasive *S. aureus* infections.[25] We analyzed various exposures but all were felt to be low risk for bias. Measurement of outcomes and reported results and similarity of controls were also all at low risk for bias. Missing data and appropriate statistical analysis provided the highest risk of bias in included studies. As seen in Table 10, data related to length of follow up of individuals were not consistent across studies. Several studies did not clarify duration of follow up[25,29,55] and two studies had inadequate duration of follow up for outcome measurement (72 hours or less from SABU).[26,35] The other studies examined SAB within 4 months to 1 year of SABU which was felt to be adequate. In terms of confounders, only one study clearly stated their use of statistical analyses for controlling potential confounders.[24] All other studies were at high risk for bias due to failure to control for confounders. This caused most studies to be labeled as high risk for bias in the overall result, since controlling for confounders is one of the most critical factors in achieving good internal validity within retrospective studies.

Unfortunately, all identified studies had poor external validity due to low sample sizes and studying SABU in very select populations. For example, the combined sample size of all studies was 1164, which represents only 46% of our study's sample size. Furthermore, most studies were conducted in single center hospitals, with many occurring in veteran hospitals that have high populations of elderly men. Only one study included a second center but it had a very small sample size (18 SABU cases).

Table 10 Risk of bias assessment for included studies, based on the Newcastle-Ottawa quality assessment scale for cohort studies

Study	Selection	Comparability	Outcome	Overall
Reller[36]	★★★★		★	★★★★★
Reyes[38]	★★★★		★★	★★★★★★
Arpi[26]	★★★		★	★★★★
Bermejo[36]	★★★★		★	★★★★★
Demuth[30]	★★★★		★	★★★★★
Mohajer[25]	★★★★	★★	★★★	★★★★★★★★★
Muder[24]	★★★★		★★★	★★★★★★★
Saidel-Odes[27]	★★★★		★	★★★★★
Sheth[55]	★★★★		★★★	★★★★★★★

Meta-Analysis

Characteristics used in the meta-analysis are included in Table 11. Only studies that provided separate characteristics between SABU and SABU + SAB individuals were included.[23-26,35] Our study was also included in the meta-analysis. Overall, there is a wide variation between characteristics among studies and many studies had missing data. Characteristics were combined using forest plots (see Figure 9 – 16). There was significant heterogeneity among studies and therefore a random effects model was used.

In our pooled results, the presence of MRSA bacteriuria, urinary catheters, urinary obstruction, symptomatic UTI, and pyuria trended towards lower risk of SAB for individuals with SABU. Male gender, inpatient status, and diabetes trended towards higher risk of SAB for those experiencing SABU. However, only the presence of diabetes was statistically significant in the pooled results (OR 1.63, CI 1.14 – 2.33). Our primary question for meta-analysis - whether the presence of a urinary catheter is associated with increased risk of SAB in individuals with SABU - demonstrated a pooled OR of 0.75 (0.36 – 1.58) with significant heterogeneity among studies (I^2 74.3%). Using a fixed effects model did not change the result for MRSA, urinary catheter, urinary obstruction or diabetes. However, it did cause the pooled OR results among male gender, inpatient status, symptomatic UTI, and pyuria to become statistically significant. This is due to reduced weighting of studies with small sample sizes, leading to larger studies (especially ours) to have a larger effect on the pooled OR.

Table 11 Study characteristics used in meta-analysis.

	Arpi[26]		Bermejo[36]		Mohajer[25]		Muder[24]		Saidel-Odes[27]		Stokes	
	SABU n=121	SAB n=11	SABU n=22	SAB n=21	SABU n=270	SAB* n=56	SABU n=89	SAB n=13	SABU n=91	SAB n=12	SABU n=2365	SAB n=175
MRSA (%)	-	-	59.1	38.1	45.2	62.5	87.6	76.9	-	-	23.6	17.1
Urinary Catheter (%)	62.8	63.4	81.2	19.0	43.7	39.3	49.4	76.9	30.7	16.7	18.5	21.1
Male (%)	-	-	59.1	57.1	93.3	100	-	-	-	-	51.3	69.7
Obstruction (%)	54.5	72.3	-	-	-	-	-	-	26/90 (28.9)	1/11 (9.1)	-	-
Nosocomial SABU (%)	-	-	72.3	57.1	51.1	89.3	-	-	30.7	33.3	27.3	56.0
UTI symptoms (%)	43/116 (37.1)	3/9 (33.3)	-	-	35.9	12.5	29.2	53.8	17/85 (20.0 %)	1/10 (10%)	-	-
Pyuria (%)	70/99 (70.1)	8 (72.3)	-	-	-	-	-	-	47/69 (68.1)	6/9 (66.7)	293/332 (88.3)	14/24 (58.3)
Diabetes (%)	-	-	-	-	39.6	42.9	40.4	53.8	-	-	10.6	18.9

*Includes individuals with non-bacteremic, invasive *S. aureus* disease (n=15).

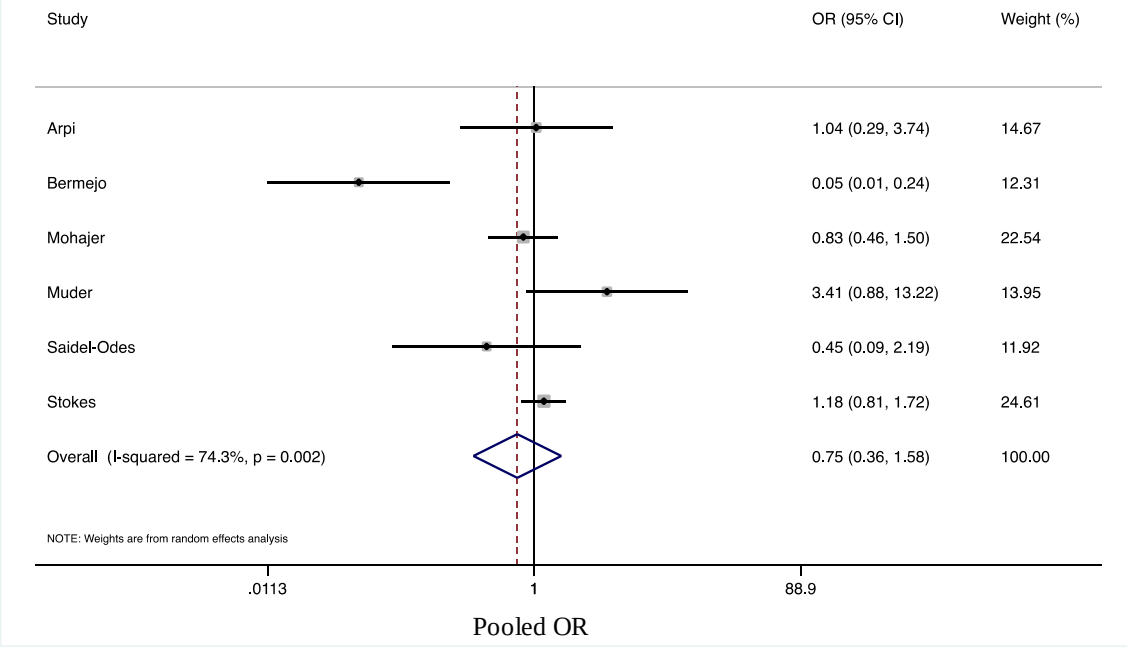


Figure 9 Forest plot of odds ratios of development of SAB in individuals with urinary catheters.

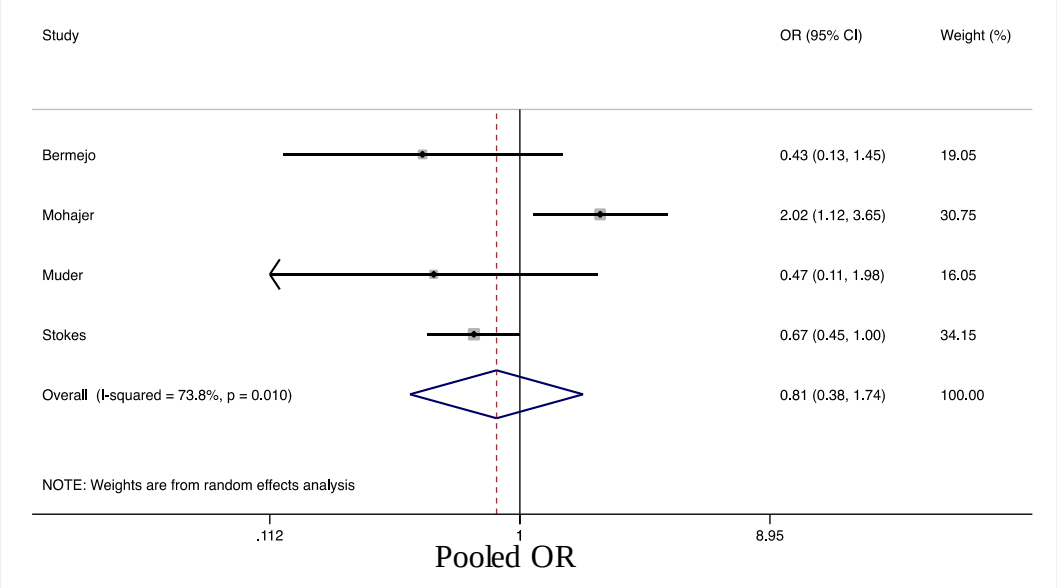


Figure 10 Forest plot of odds ratios of development of SAB in individuals with MRSA bacteriuria.

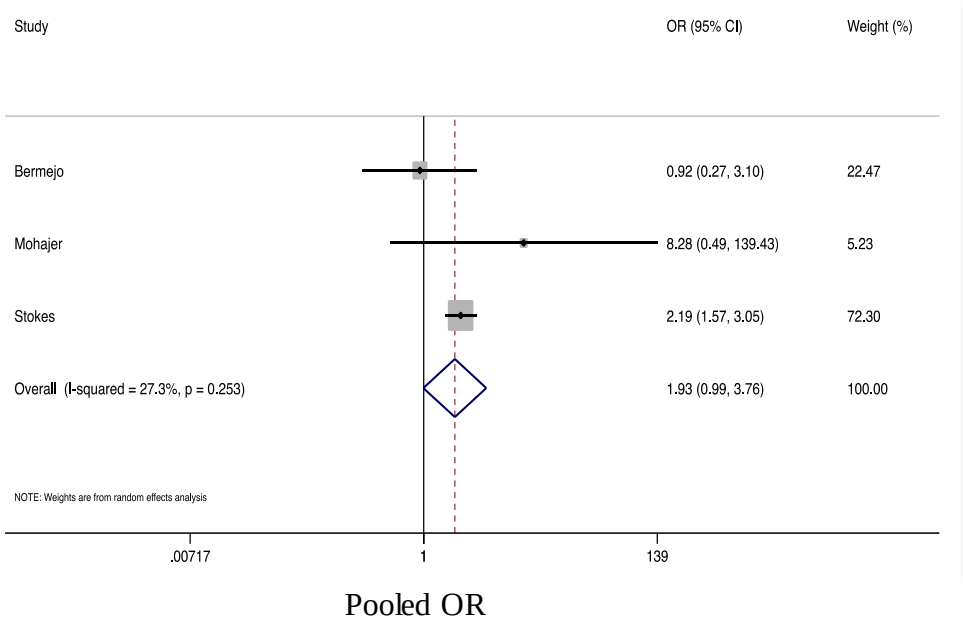


Figure 11 Forest plot of odds ratios of development of SAB in male individuals.

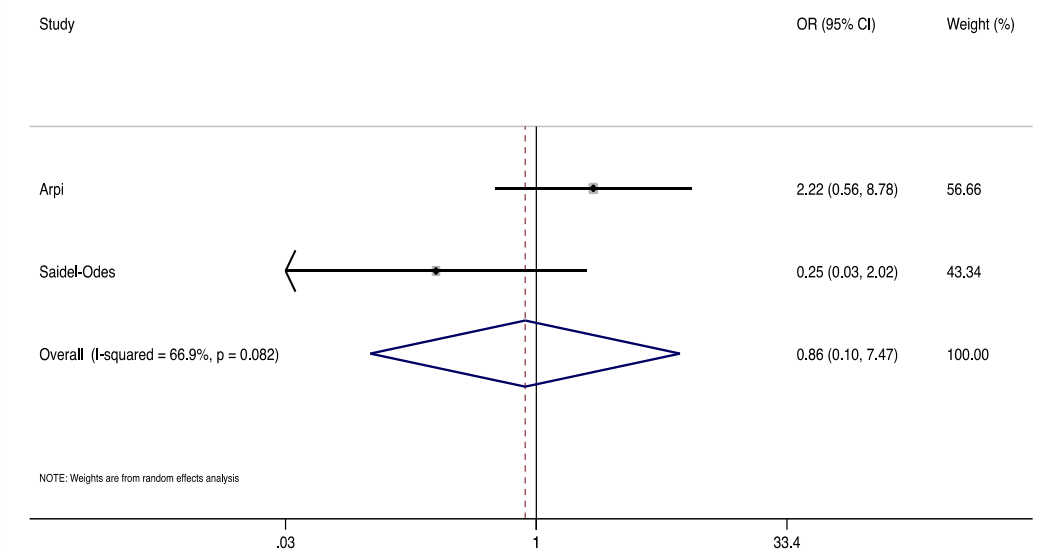


Figure 12 Forest plot of odds ratios of development of SAB in SABU individuals with urinary obstruction.

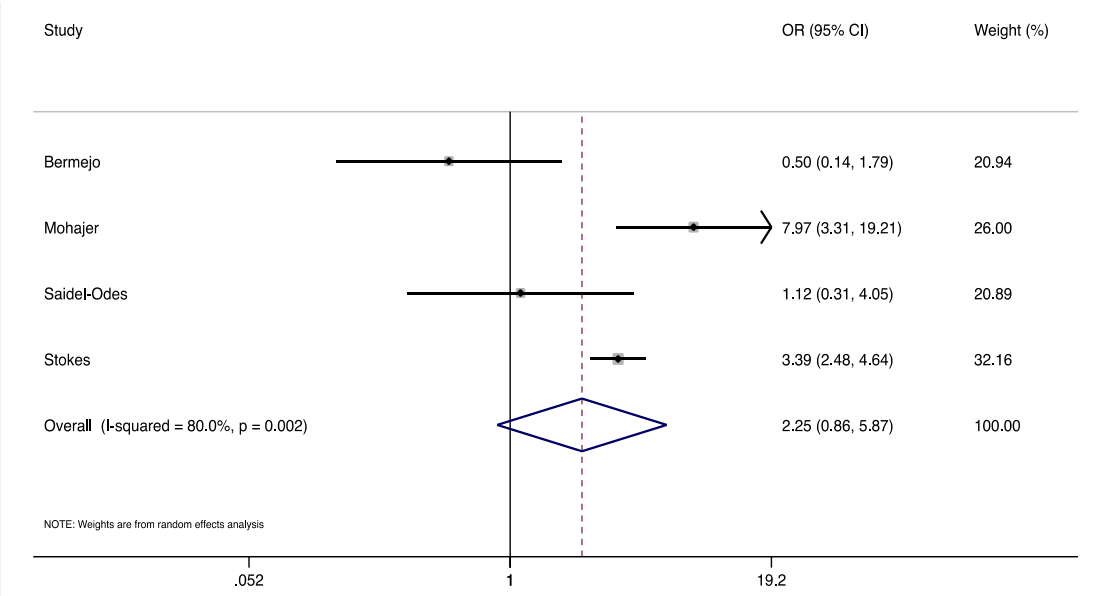


Figure 13 Forest plot of odds ratios of development of SAB in SABU individuals who are hospitalized.

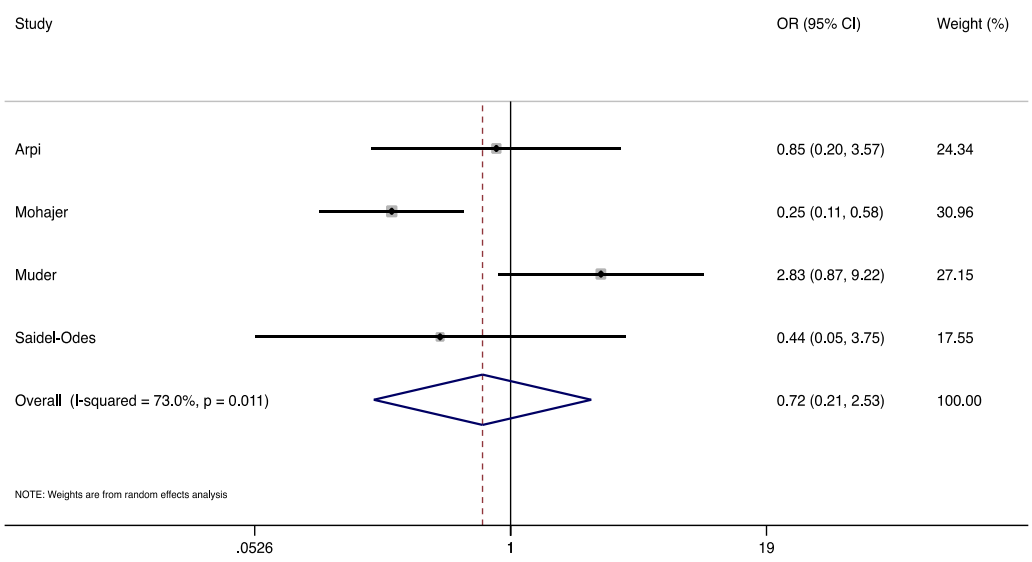


Figure 14 Forest plot of odds ratios of development of SAB in SABU individuals who have symptoms of urinary tract infection.

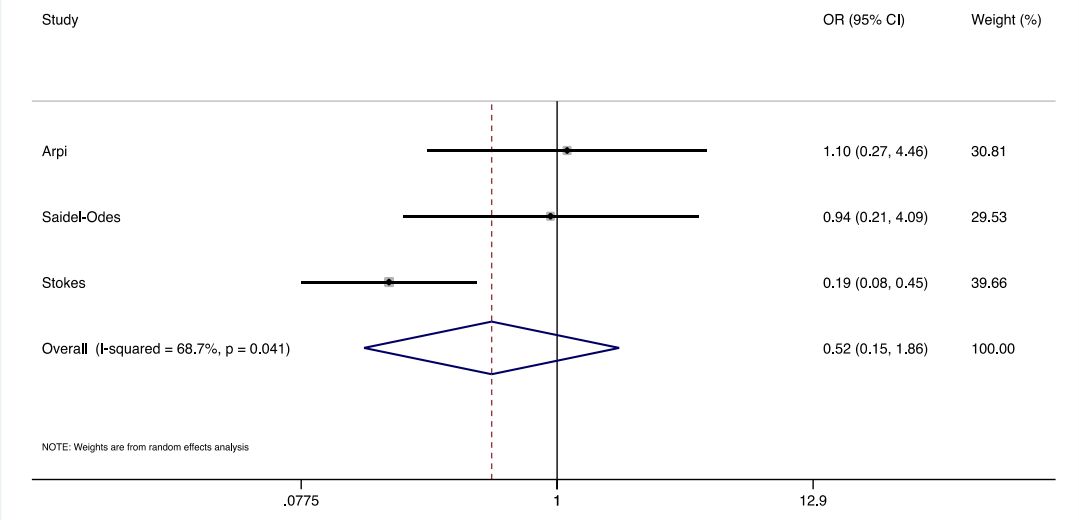


Figure 15 Forest plot of odds ratios of development of SAB in SABU individuals who have pyuria.

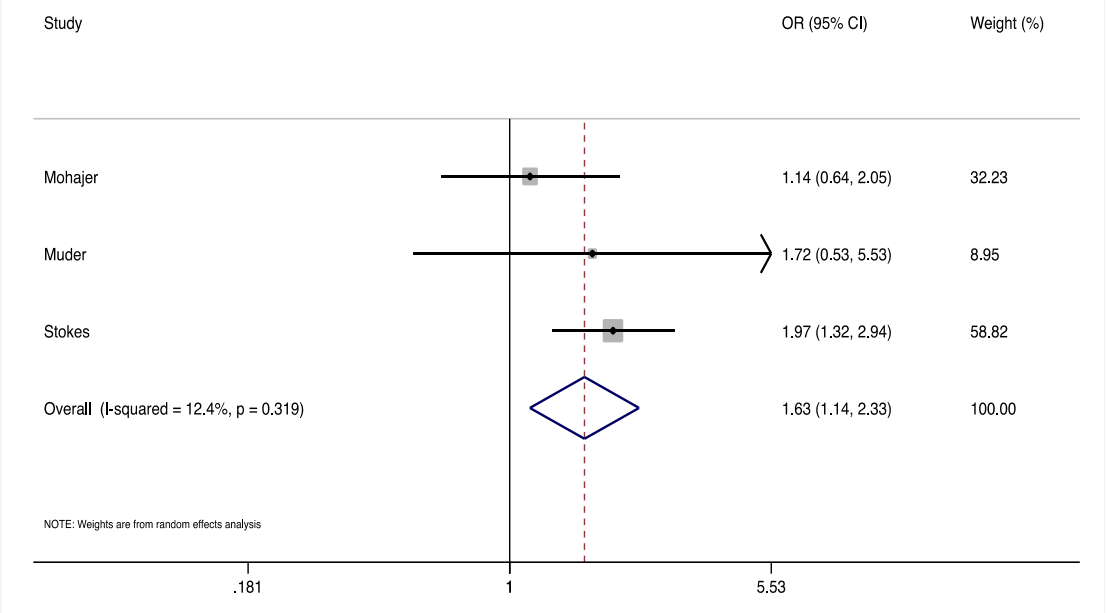


Figure 16 Forest plot of odds ratios of development of SAB in SABU individuals who have diabetes.

Assessment for publication bias was conducted based on the association of urinary catheters and SABU + SAB. Begg and Mazumdar's rank correlation test for asymmetry was 0.707 suggesting that there is no publication bias. Visually, the associated funnel plot does not appear symmetrical which suggests that publication bias may be present (Figure 17). The funnel plot also demonstrates an outlier, which corresponds to Muder et al.[23]

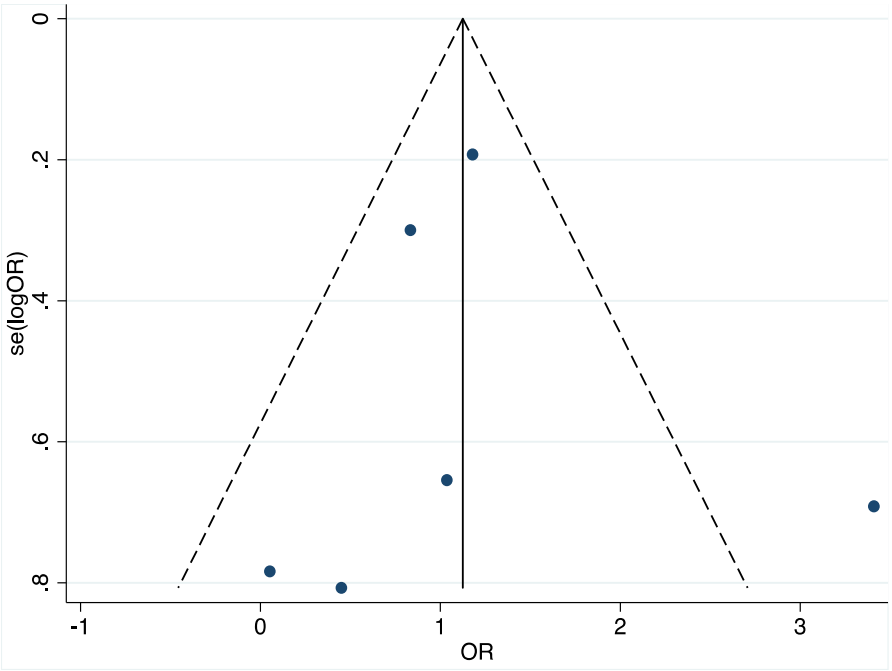


Figure 17 Assessment of publication bias using funnel plot with pseudo 95% confidence limits among studies examining the association of urinary catheterization and SAB in individuals with SABU

DISCUSSION

Epidemiology of SABU

We have discovered that SABU is a rare occurrence, representing a mere 0.4% of all positive urine cultures in our region over 4 years. Furthermore, SABU cases have been decreasing annually in the CHZ while SABU + SAB rates remain constant. In discussion with the medical microbiologists and senior microbiology technicians in Calgary's centralized laboratory, no significant changes to the collection, transportation, processing or reporting of urinary specimens that might have impacted these results occurred during the study period. Part of the decrease in SABU prevalence may be related to the decreasing prevalence of urinary catheters observed in our study. Decreased catheter use may be the result of local, national and international education and awareness campaigns related to the inappropriate use and potential harm of urinary catheters that have been ongoing for at least the last two decades.[66] These campaigns exist because urinary catheters are often unnecessary, alternatives such as condom catheters exist and major complications including urinary tract infection and death can result.[67,68] It is also economically beneficial to reduce inappropriate catheter use since complications from urinary catheters can cost healthcare systems millions of dollars. In the USA, for example, these complications are projected to cost over $450 million per year.[69]

Compared with the CHZ population, SABU occurred disproportionally in the geriatric male population (median age 74) with a high number of comorbidities, particularly diabetes (10.6%) and dementia (6.7%). This correlates with current published literature

that showed SABU occurred more commonly among older age groups (average age 66 – 73 years),[23-26,30,33,37] in men,[25] and individuals with multiple comorbidities.[23-26,33,34,37] Specific comorbidities such as urological disease and diabetes were also frequently observed within our study, though these comorbidities were not associated with increased risk for SAB with the exception of diabetes in outpatients with SABU. In most studies, diabetes was generally higher among SABU individuals (18.0% – 42.0%) compared to our study individuals (21.8%). Poor external validity associated with conducting studies at single center hospitals in selected individual populations (i.e. veterans) could account for the higher diabetes prevalence detected in the literature. However, our study may have lower comorbidity rates due to incomplete data - described in detail under study limitations.

In our study, most *S. aureus* urine cultures were of pure growth. This is in contrast to four other studies which found most *S. aureus* urine cultures had mixed growth (52.0% - 73.8%).[24,25,37,54] No other studies were found that commented on microorganisms seen in mixed SABU cultures. In our study, *Enterococcus* spp. was the most common microorganism detected in mixed SABU cultures. Since *S. aureus* and *Enterococcus* can be part of normal perirectal flora, this finding would suggest that many mixed SABU cultures were due to contamination during sample collection. While the presence of pure *S. aureus* urine culture is associated with SAB in our study, the association is not strong (OR 1.6). This leads us to conclude that *S. aureus* present in the urine should not – in-and-of-itself – be a cause for concern by care providers regardless of purity.

Association of Death Among SABU individuals

Risk factors associated with death among SABU individuals in our study, based on multivariate logistic regression, represented common risk factors in any population, such as inpatient status; increasing age; cancer; cardiovascular diseases such as congestive heart failure; and respiratory diseases such as chronic obstructive pulmonary disease. However, we also discovered that SABU detected 48 hours or more before SAB was independently associated with higher risk of death and had a much higher probability of death than individuals who had concurrent SAB + SABU. This highlights the importance of quickly identifying SAB when SABU is detected and may suggest a role for the microbiology laboratory to communicate the urgency of these findings to clinicians. On the other hand, pyuria and recurrent or persistent SABU was associated with less risk of death and is possibly related to the inverse association of these variables with SAB and other deeper-seated *S. aureus* infections.

Association of SAB in SABU

While SABU in the context of SAB is uncommon, it represents an entirely different disease entity and every effort is required to distinguish it. From our population data, we discovered that individuals with SABU + SAB have more comorbidities than the general population, but less comorbidities than SABU individuals. This can be explained by certain populations who are at high risk for SAB but unlikely to have isolated SABU otherwise. For example, intravenous drug users will almost certainly have SAB when SABU is detected and are often young in age with few comorbidities.

Epidemiologic risk factors associated with SAB in individuals with SABU, in our study, were male gender, inpatient status, pure *S. aureus* culture, urinary procedure and systemic signs of infection (leukocytosis, thrombocytopenia and presence of immature neutrophils). Some studies were able to associate inpatient status and male gender with deeper-seated *S. aureus* infection or SAB.[24,55] Other studies were not able to demonstrate a similar relationship; though many were conducted predominately among inpatients and/or males. Diabetes, liver cirrhosis, malignancy, diabetes, and immunosuppression were all risk factors for SAB on univariate analysis but not when imputed into the multivariate regression model.

Our findings on urinary procedures and its association with SABU + SAB contradict current literature that has previously suggested no association or a reduced association of urinary procedures and risk of SABU + SAB.[35,55] However, we feel our results correlate better with the pathophysiology behind urinary tract procedure complications. For instance, any manipulation of human tissue can increase the risk of bacteremia, and urinary procedures such as cystoscopy or percutaneous nephrostomy tube placement are no exception.[70-74] During nephrostomy tube placement, endogenous skin flora such as *S. aureus* may become exposed to the disrupted tissue. Subsequently, *S. aureus* may propagate its infection within the underlying skin, the deeper tissue (i.e. ureter) and eventually the bloodstream leading to SABU + SAB. During cystoscopy, the cystoscope may become contaminated with *S. aureus* during initial insertion from *S. aureus* colonization of the urethra and surrounding area. *S. aureus* contaminating the cystoscopy device can then invade and infect underlying tissue that is disrupted during the procedure,

leading to SABU + SAB. While it is possible that these procedures could inoculate the bladder with *S. aureus* without causing bacteremia, we would think that the inflamed and damaged uroepithelial tissue post procedure would make these SABU individuals more susceptible to bacteremia compared to other SABU individuals.

Factors that were uncommon in SABU individuals with concurrent SAB included dementia, recurrent or persistent SABU, age ≥65 years and the presence of pyuria and urine nitrites. The presence of pyuria correlates with another study that demonstrated decreased risk of SAB in individuals with pyuria.[55] If *S. aureus* bacteriuria in the context of SAB is a result of hematogenous seeding, perhaps the urinary tract would have less opportunity to mount a local inflammatory response and therefore less likely to have pyuria.[75] Compared to *Staphylococcus saprophyticus* and other urinary pathogens, *S. aureus* has lower affinity for uroepithelial cells and therefore SABU secondary to hematogenous seeding may quickly be eliminated from the bladder before significant local reaction.[76] The corollary would be that SABU isolated to the urinary tract would persist for longer periods of time thereby generating inflammation, and nitrite (*S. aureus* has a nitrite reductase but it takes 4 to 6 hours to occur within the bladder).[75,76] Moreover, age ≥65 years and recurrent or persistent SABU negatively associate with SAB in SABU. This is supported by nursing home residents being a protective factor on univariate analysis as it correlates with established literature demonstrating SABU among elderly nursing home residents with asymptomatic bacteriuria (many of whom have dementia).[77,78] Asymptomatic bacteriuria among nursing home residents often is not associated with a UTI or systemic infection and this may apply to SABU as well, so long

as a deeper seated infection has been ruled out.[79] Importantly, this information can be used by clinicians to deprioritize individuals at perceived lower risk for immediate investigations.

Association of SAB in Outpatients with SABU

We specifically examined the association of SAB in outpatients with SABU as they represent a clinical challenge compared to inpatients. Investigation and monitoring for SAB can be easily achieved amongst hospitalized individuals, outpatients must be contacted and referred immediately to the laboratory for repeat testing– or perhaps even the emergency room for investigations. In our study, risk factors for SAB in outpatients included males, serum biochemical markers of inflammation, the presence of a catheter, pure *S. aureus* culture and diabetes. Why the presence of a urinary catheter becomes a risk factor for SAB in SABU as an outpatient only is unclear. Perhaps it is because our study was not able to distinguish individuals who had a long-term, indwelling urinary catheter versus individuals who had a temporary catheter or in/out catheterization. In this regard, the presence of a urinary catheter in outpatient SABU individuals may better represent people who have chronic indwelling urinary catheters which are at higher risk of *S. aureus* acquisition and, perhaps, subsequent complications such as ascending urinary tract infection.[33] Furthermore, the presence of pure *S. aureus* among catheterized SABU individuals may represent infection as opposed to colonization or poor sampling which would be associated with other microorganisms such as *Enterococcus* spp.

Association of SAB in SABU Individuals with or without the Presence of a Urinary Catheter

A sensitivity analysis was done on individuals with or without a urinary catheter since SABU is often associated with urinary catheter use. In our study, we found that the majority (81.3%) of SABU individuals did not have a catheter at the time of urine culture collection. This counters findings from many hospital-based studies that reported catheter use among the majority of their SABU individuals.[23,25,26,35,37] Furthermore, the development of SAB in our SABU cohort with or without a urinary catheter was roughly equal between the groups at 7.8% and 6.7%, respectively. Risk factors associated with SAB occurrence in SABU individuals without a urinary catheter was approximately the same as the overall results, with the exception that urinary procedure and pure *S. aureus* growth was not associated with increased risk of SAB. The lack of pure *S. aureus* growth as a risk factor for SAB in individuals with SABU implies that the presence alone of *S. aureus* in the urine should be considered a marker for systemic infection in individuals without a urinary catheter, regardless of other bacteria present. Furthermore, the presence of dementia was not associated with decreased risk of SAB but the presence of MRSA was. This is in contrast with Mohajer et al who demonstrated increased risk of SAB in individuals with MRSA bacteriuria.[24] Given that Mohajer et al's study was in a single hospital setting, the presence of MRSA may be due to confounders related to MRSA nosocomial acquisition and *S. aureus* bacteremia, such as critically ill individuals with central venous lines in the intensive care unit.[24]

In catheterized individuals with SABU, there are several interesting changes to the risk factors associated with SAB. For instance, a recent urinary procedure becomes the most significant risk factor for developing SAB among catheterized individuals. This is interesting, since recent urinary procedures for non-catheterized individuals is not a risk factor for SAB, indicating that many SAB + SABU cases post urinary procedure occurred among catheterized individuals (despite urinary procedures among catheterized and non-catheterized individuals being similar at 2.3% vs 2.5%, respectively). Since SABU is more common among catheterized individuals, it is likely that the increased risk of SABU + SAB in these individuals is simply due to an increased likelihood that *S. aureus* is present in the urinary tract prior to a urinary procedure in these individuals (and subsequently more likely for invasive *S. aureus* infection to occur).

Invasive *S. aureus* Infection without SAB

Individuals with SABU and invasive infections without documented SAB represented a small proportion in our study (0.8%) – although our cohort represents the largest published to date. This is in contrast to the 4.6% of SABU and invasive *S. aureus* infections without SAB in the only study that assessed for it.[24] This may be secondary to our study having strict microbiological criteria for deeper-seated *S. aureus* infection compared to Mohajer et al who used a combination of clinical, microbiological and radiographic data.[24] In their study, the most common associated infection in individuals who had an invasive *S. aureus* infection without bacteremia over 12 months from SABU was pneumonia in 56.3% followed by osteomyelitis in 25.0%.[24] In our study, surgical site infections post urological surgery was the most common (24%) followed by intra-

abdominal/pelvic abscess (19%). These infections could cause SABU but not SAB due to their anatomical proximity to the kidneys that could lead to *S. aureus* seeding of the urinary tract without seeding into the blood. However, it is possible that many of these infections had transient *S. aureus* bacteremia that allowed for seeding of the urinary tract instead.

Associated Infections of Invasive *S. aureus* Infection Complicating SABU, Regardless of SAB

In both SAB and deeper-seated *S. aureus* infection, we (similar to others) detected a large proportion of SABU individuals with pyogenic spine/pelvic infection with the vast majority having lumbar discitis and epidural abscess.[80] A recent meta-analysis also demonstrated an association of bone/joint infections as well as septic emboli among SAB individuals who were found to have SABU.[56] Osteomyelitis due to Gram-negative urinary tract infections is well established, particularly in older individuals who have higher rates of bacteriuria,[81] and is thought to be due to the connection of venous networks between the pelvic/spine area and bladder.[82] These results highlight that mere blood cultures may be inadequate in some cases to exclude deeper-seated disease when SABU is first identified, particularly in excluding vertebral osteomyelitis which was found to be common among SABU individuals with negative blood cultures but invasive *S. aureus* disease. This highlights that a thorough history and physical examination for potential occult focuses of infection – and especially vertebral osteomyelitis - should be sought whenever an individual is found to have SABU.

From the results of our study we believe *S. aureus* bacteriuria with *S. aureus* bacteremia is a result of one of three major processes. One is seeding of *S. aureus* from spinal osteomyelitis secondary to Batson's plexus. Second, *S. aureus* urinary tract infection ascending into the urinary tract and then the blood, resulting in both SAB and SABU (although we caution readers that this likely represents a minority of cases). The third is disseminated *S. aureus* bacteremia seeding into the urinary tract, as evidenced in animal studies injected with *S. aureus*,[83] that resulted in renal microabsccess; although one study failed to find autopsy evidence of a renal abscess among SABU patients[29] and only 2/6 (33.3%) of SABU patients were found to have a renal abscess in another study.[84] In our study, we could find no radiologic evidence of renal abscesses in our individuals with SABU + SAB who had abdominal imaging.

Systematic Review and Meta-Analysis

From our systematic review, we concluded that there was a paucity of literature on the association of SAB among SABU individuals. Only nine studies were identified when searching multiple databases, including conference abstracts. When examining the included studies, large variation and heterogeneity was detected. Internal validity in most studies, with the exception of Mohajer et al, was at high risk of bias due to the lack of controlling for confounders which is a significant limitation in retrospective cohort studies. Moreover, external validity was poor among studies, with most having very small sample sizes and most being conducted in single centers (often in veteran hospitals). Overall, we feel these studies were at high risk of bias and were not generalizable to Canadian hospitals or outpatient settings.

The results of our meta-analysis indicated that the presence of a urinary catheter among SABU individuals is not associated with the development of SAB. However, we did determine that diabetes was associated with the development of SAB when pooling odds ratios among studies. Increased risk of SAB in diabetic individuals is not surprising, since diabetic individuals (especially poorly controlled diabetics) are at increased risk of many infections, including UTI.[85] However, caution is made that the results from our meta-analysis of retrospective cohort studies could not control for confounding which is a significant limitation.

Strengths and Limitations

Our study is the largest investigating the association between *S. aureus* bacteriuria and *S. aureus* bacteremia and/or deeper-seated *S. aureus* infection. We were able to study SABU from a large, general Canadian population of over 1.4 million, providing strong external validity to our conclusions. Furthermore, we were able to determine the association of SABU + SAB in outpatient settings, in which the decision to investigate underlying SAB can be challenging.

Although a rigorous population-based design was utilized, there are study limitations warranting discussion. This study does not establish a causal relationship between SABU + SAB and mortality. The observed mortality rates may have been influenced by other illnesses and co-morbidities. Our multiple logistic regression models were of low calibration, making the strength of our associations weaker. Only cases of SABU associated with positive urine cultures were included in the study. Individuals with SABU

who did not have urine samples submitted for culture were not identifiable; as a result, the reported incidence of SABU is likely a conservative estimate. This limitation exists in all studies dependent on culture-proven infection. Although microbiologic data was collected prospectively, clinical data was retrospectively documented, and individuals were not assessed through the auspices of the study to determine the original infection source. We are unable to assess independent risk factors for SABU using logistic regression. We estimated the rates of underlying illnesses in the general population based on current disease prevalence registry data, but do not have individualized, linked data on all 1.4 million residents. This limitation is nearly universal to all population-based study designs.[86,87] There are also inherent limitations in using international classification of diseases (ICD)-9 codes for defining co-morbid illness.

When collecting data, we were dependent upon electronic databases that may have missing data such as the full extent of an individual's comorbidities. Data on individual comorbidities were only accessible if the individual had accessed one of Calgary's acute care centers or specialty clinics. Some *S. aureus* bacteremia and *S. aureus* deeper seated infections may have been missed if they occurred before or after our 3 months cut off from SABU without a repeat positive urine culture for *S. aur*eus. In addition, bias may have been created by studying bloodwork that was collected in only a portion of individuals. However, most would agree that our laboratory findings are biologically plausible and consistent with general knowledge about *S. aureus* bacteremia, and are supported by previous literature that demonstrated decreased SAB risk in the context of SABU with pyuria.[55]

Urinary catheterization, immunosuppression and death may have been underreported in our study. We could only confirm the presence of a urinary catheter if the urine culture specimen was taken from a catheter. Therefore, we were not able to determine if an individual with a mid-stream urine sample had a recent history of urinary catheterization. People on immunosuppression medication (e.g. chemotherapy, immunologics, etc) could not be captured with the database except for the ICD-9 code "chronic steroid use" which would not capture individuals who are on steroids for short or moderate durations. Furthermore, since death was defined as death occurring within the hospital, individuals who died outside the hospital would not have been detected.

Another limitation of our study is the inability to determine whether SABU represented asymptomatic bacteriuria versus symptomatic cystitis. In studies with strict definitions for symptomatic UTI, approximately 30% of individuals with SABU were symptomatic.[23,24] In the largest study, individuals with SAB were less likely to have urinary symptoms.[24] Indeed, in a study examining *E. coli* bacteriuria in a tertiary hospital, 61.7% were symptomatic.[88] This finding may be related to our association of pyuria with isolated SABU, although we are unable to draw any conclusions given the retrospective nature of our study. Further research on isolated SABU is required to help determine the true nature of its symptomatology, especially in outpatient settings where a paucity of SABU research exists.

Future Directions

Our next aim is to validate a risk score that clinicians can use at the bedside to help determine an individual's risk of SAB when SABU is identified. To create the risk score, regression coefficients from our multivariate regression model will be used. We can then validate the risk score by applying it to a new subset of SABU individuals within the Calgary Health Zone, such as those from different years (e.g. 2014 – 2017). Our objective is to ultimately help clinicians determine their patient's risk of developing SAB when SABU is detected. Similar to other risk scores, such as Wells' criteria for pulmonary embolism, a score can be calculated at the point of care (e.g. via a user friendly smartphone app) and, based on the score, the probability of SAB will be calculated (e.g. a score of five correlates with a 75% probability of SAB developing within three months). This score can help prompt clinicians to consider further testing, such as blood cultures, in high risk individuals.

There are other smaller projects related to the symptomatology and treatment of SABU that we are interested in carrying forward. To date, the relationship between SABU, UTI symptoms, and treatment are still not fully addressed. We can help answer these questions by pursuing chart reviews on a subset of individuals included in our current study. Charts will be reviewed to determine if the individual was symptomatic around the time of urine culture collection, had blood cultures drawn to assess for SAB, and to determine if the individual was given antimicrobial treatment for SABU. Using these data and data already obtained from our study, we can add to the literature by determining how many individuals with SABU have urinary tract symptoms and what factors might increase their

likelihood of having symptoms (e.g. presence of nitrites, presence of a urinary catheter, pure *S. aureus* culture, high *S. aureus* colony count, etc). We can also determine which individuals were treated and, if not, how many developed complications (e.g. SAB) when not treated. Most importantly, we can see whether we can apply the rule of "asymptomatic bacteriuria" to SABU, meaning that if *S. aureus* is discovered in an individual without urinary symptoms that the individual does not require treatment (though, of course, invasive *S. aureus* should be ruled out before foregoing treatment).[89]

Furthermore, as a quality improvement component, we can use blood culture data to help us determine how many individuals with SABU have had blood cultures taken. While most individuals with SABU do not have SAB, we do not currently have an easy way to exclude this. As such, until further tools are available to clinicians, we believe all individuals with SABU should have a blood culture done to rule out SAB. Our hypothesis, however, is that few SABU individuals from the Calgary Health Zone are getting blood cultures drawn when SABU is detected. If this is the case, we can use our data to help justify quality improvement initiatives that aim to improve blood culture collection among these individuals, such as providing a comment on positive *S. aureus* urine culture results that state, "blood cultures are suggested to help rule out systemic *S. aureus* infections."

Conclusion

SABU generally represents one of two very different disease processes; a marker of a potentially life threatening invasive infection or much more commonly isolated cystitis / asymptomatic bacteriuria. In the largest study to date examining SABU, we have discovered specific risk factors that can help clinicians distinguish between these scenarios. Based on an individual's risk factors and the clinician's judgment, investigation for SAB or deeper-seated *S. aureus* infections such as vertebral osteomyelitis should be sought if clinically suspected, especially since a delay in SAB detection is associated with increased mortality. Going forward, we recommend that clinical microbiology laboratories report in individuals with SABU that "*S. aureus* bacteriuria may be associated with severe systemic disease such as bacteremia - particularly in hospitalized patients and/or those with systemic symptoms. Clinical correlation is advised."

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APPENDICES

Appendix A: Search strategy (PubMed)

Database: PubMed

Search strategy:

1. *Staphylococcus aureus* [MeSH Terms]
2. *Staphylococcus aureus*
3. *S. aureus*
4. #1 OR #2 OR #3
5. urinary tract infection [MeSH Terms]
6. Urinary tract infection
7. UTI
8. Bacteriuria [MeSH Terms]
9. Bacteriuria
10. #5 OR #6 OR #7 OR #8 OR #9
11. Bacteremia [MeSH Terms]
12. Bloodstream infection
13. BSI
14. #11 OR #12 OR #13
15. #4 AND #10 AND #14