European Review for Medical and Pharmacological Sciences 2024; 28: 4621-4633

Bloodstream infections caused by *Staphylococcus aureus* in patients admitted to King Abdulaziz University Hospital, Jeddah, Saudi Arabia

A. ALBUHAIRY[1,2], D. ATTALLAH[1], S. QASHQARI[3], M. AL-RABIA[4], R. KAKI[5,6,7], S. HARAKEH[8,9], K. ALKUWAITY[10,11], T. ABUJAMEL[10,11], T. ALTORKI[10,11], J. MOKHTAR[1,4,11], O. ALHARBI[12], M. ISMAIL[13], M. MUFRRIH[10,14], A. SAIT[10,15], H. MOMIN[16], I. ABU[17], B. SALEH[4], T. EKHMIMI[4], A. ALFADIL[4], K.A. IBRAHEM[4]

[1]Department of Clinical Microbiology Laboratory, King Abdulaziz University Hospital, Jeddah, Saudi Arabia
[2]Department of Medical Laboratories, East Jeddah General Hospital, Ministry of Health, Jeddah, Saudi Arabia
[3]Department of Medical Laboratories, Al Aziziyah Children Hospital, Ministry of Health, Jeddah, Saudi Arabia
[4]Department of Clinical Microbiology and Immunology, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia
[5]Department of Infection Control and Environmental Health, King Abdulaziz University Hospital, Jeddah, Saudi Arabia
[6]Department of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia
[7]Department of Infectious Disease, King Abdulaziz University Hospital, Jeddah, Saudi Arabia
[8]King Fahd Medical Research Center, King Abdulaziz University, Jeddah, Saudi Arabia
[9]Yousef Abdul Latif Jameel Scientific Chair of Prophetic Medicine Application, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia
[10]Department of Medical Laboratory Sciences, Faculty of Applied Medical Sciences, King Abdulaziz University, Jeddah, Saudi Arabia
[11]Vaccines and Immunotherapy Unit, King Fahd Medical Research Center, King Abdulaziz University, Jeddah, Saudi Arabia
[12]Department of Microbiology and Parasitology, Faculty of Medicine, Umm Al-Qura University, Makkah, Saudi Arabia
[13]Department of Medical Education, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia
[14]Special Infectious Agents Unit BSL-3, King Fahd Medical Research Center, King Abdulaziz University, Jeddah, Saudi Arabia
[15]Regenerative Medicine Unit, King Fahd Medical Research Center, King Abdulaziz University, Jeddah, Saudi Arabia
[16]Medical Service Center, King Abdulaziz University, Jeddah, Saudi Arabia
[17]Department of Community Medicine, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia

Abstract. – OBJECTIVE: Currently, there is a limited amount of published data on the incidence of bloodstream infections (BSI) caused by both methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-susceptible *Staphylococcus aureus* (MSSA) in most parts of the Arabian Peninsula. Thus, it is extremely important to have information concerning the distribution and prevalence of MRSA and MSSA to better handle and manage future epidemics. This study aimed to investigate the correlation between MRSA and/or MSSA with BSI at King Abdulaziz University Hospital (KAUH), Jeddah, Saudi Arabia.

***PATIENTS AND METHODS:* This investigation took place at King Abdulaziz University Hospital in Jeddah, Saudi Arabia, for four years. During this period, we meticulously collected and documented clinical data on blood cultures that tested positive for MRSA or MSSA.**

***RESULTS:* BSI caused by *S. aureus* bacteria was found in 461 individuals; 232 (50.3%) of these patients had MSSA, and 229 (49.7%) had MRSA. The data showed that patients with dia-**

Corresponding Author: Karem A. Ibrahem, MD; e-mail: kaibrahem@kau.edu.sa

betes, renal, and heart disease were most at risk of contracting *S. aureus* associated with BSI (at 46%, 37%, and 23%, respectively). Hospital-acquired (HA) MRSA was associated with higher rates of BSI compared to HA-MSSA. Device and procedure-related infections were mostly associated with HA-BSI, whereas superficial skin and soft-tissue infections were more commonly connected to community-acquired BSI (CA-BSI).

CONCLUSIONS: Such information will probably lead to a reduction in hospital-acquired infections and will improve hospital infection-preventative procedures.

Based on the data obtained, diabetic patients are most at risk of contracting *S. aureus* BSI. To prevent the spread of MRSA infection among healthcare centers, patients with MRSA must undergo MRSA screening tests, appropriate therapeutic follow-up, and contact precautions. Moreover, appropriate therapeutic management of diabetes may protect the patients from getting infected with *S. aureus*.

Key Words:

Staphylococcus aureus, Bacteremia, Methicillin-susceptible, Methicillin-resistant, Community-acquired, Hospital-acquired.

Introduction

Bloodstream infections (BSIs) are one of the most common fatal infections globally[1]. *S. aureus* can be considered one of the most commonly encountered organisms implicated with BSI-caused mortality[2]. *S. aureus* is a Gram-positive bacterium, mainly inhabiting the human nostrils, skin, axilla, and gastrointestinal tract, and it is often associated with high mortality rates in infected patients[3]. Among the organisms, *S. aureus* is the predominant cause of bloodstream infections, both acquired in hospitals and within the community globally[4]. *S. aureus* in the bloodstream may lead to sepsis, which is a systemic inflammatory reaction as a result of infection. An inherent characteristic of sepsis is a contradictory immunosuppressive response that occasionally occurs with inflammation. The simultaneous presence of the inflammation and immunosuppression harms nearby tissues and leaves the host susceptible to the primary organism and subsequent infections[5]. The inflammatory responsiveness may alter the balance between pro- and anti-coagulant processes, which may lead to the development of disseminated intravascular coagulation (DIC).

The antibiotic resistance of various S. aureus strains, particularly methicillin-resistant *Staphylococcus aureus* (MRSA) strains, has been worsening, leading to the rapid spread of these pathogens in both healthcare and community settings. CA-MRSA, in particular, has demonstrated the ability to spread quickly among healthy individuals[6]. The occurrence of bloodstream infections (BSI) caused by *S. aureus*, along with its associated consequences, has significantly increased in recent years because of the rising frequency of invasive medical operations, higher numbers of patients associated with weakened immune systems, and the increasing resistance of *S. aureus* strains to the existing antibiotics[7]. Besides, it is important to mention that there are other risk factors, such as surgical wounds, diabetes mellitus, and cancer[8].

It has been reported[9] that 74% of S. aureus bloodstream infections (SA-BSI) identified at King Abdulaziz University Hospital were hospital-acquired (HAI), while 25% were community-acquired (CAI). Additionally, methicillin-resistant *S. aureus* (CA-MRSA) accounted for 29% of the community-acquired cases.

However, the study[9] provided limited data regarding the risk factors, mortality rate, and antibiotic sensitivity profile.

This study attempts to investigate the prevalence and distribution of BSI caused by *Staphylococcus aureus* over four years, spanning from 2017 to 2021, focusing on the proportion of methicillin-sensitive *S. aureus* (MSSA) and MRSA infections. It also aims to identify demographic and clinical factors associated with an elevated risk of contracting *S. aureus* BSI, including comorbidities like diabetes, renal disease, and heart disease. Additionally, the study aims to compare the rates of hospital-acquired (HA) BSI among MRSA and MSSA infections and explore the association between specific infection types and acquisition settings. Additionally, it aims to assess the mortality rates associated with MSSA and MRSA infections by analyzing the sources of bloodstream infections and investigating the role of invasive devices or procedures in the transmission of these infections (Figure 1).

Patients and Methods

Sample Collection and Technique of Sample Collection

The bacterial species were deducted from clinical specimens of blood cultures that have tested positive for a period of four years (01-10-2017 to 01-10-2021). The study evaluated the clinical and

epidemiological characteristics of patients across various age groups who had BSI caused by *S. aureus* bacteria. The inclusion criteria included patients with positive culture results for *S. aureus* and signs and symptoms of infection. The study included all underlying illnesses and concurrent disorders for each patient, considering only the first bacteremia event for each individual. Patients were excluded if they had a second *S. aureus* BSI episode/90 days following the first episode. In this study, approval was received from the Research Ethics Committee of King Abdulaziz University Hospital (KAUH) under approval number HA-02-J-008. The protocol was thoroughly reviewed and found to be in full compliance with the relevant ethical standards. The committee granted a waiver for individual patient consent, allowing the study to proceed without direct patient interaction, while patient isolates used for infection diagnosis are, as standard practice in hospitals, managed in compliance with strict ethical guidelines.

Microbial Identification of the Bacterial Isolates

The Molecular and Clinical Microbiology Laboratory at KAUH processed all blood culture bottles, both aerobic and anaerobic, using the automated microbial identification system BACT/Alert VIRTUO (BioMérieux, Durham, NC, USA), which provides real-time results.

These bottles were kept in an incubator until a signal-positive alarm was activated or a maximum of five days had elapsed. Positive blood culture bottles were subjected to Gram staining, with results recorded in the system and communicated verbally to the office.

BioFire (Biomerieux Inc., Durham, NC, USA) was employed for early detection and treatment of sepsis utilizing molecular technology, specifically the BioFire Blood Culture Identification 2 (BCID2) panel, which is proficient in identifying pathogens and antimicrobial resistance genes in positive blood cultures. This device can detect both *S. aureus* and resistant genes (*mecA*/*mecC*, MREJ and *vanA*/*vanB*) within approximately one hour, using the positive blood culture results. Positive blood culture bottles were grown on 5% sheep blood agar, chocolate agar, or MacConkey agar (provided by Saudi Prepared Media Laboratories, Riyadh, Saudi Arabia). The MacConkey agar plates were maintained in a conventional incubator at 35-37°C for 18 hours, while the blood agar and chocolate agar plates were placed in an incubator at 35-37°C with 5-10% CO_2. Immediately collected material from the bottles with positive blood cultures was used to inoculate Mueller-Hinton plates (Saudi Prepared Media Laboratories, Riyadh, Saudi Arabia) and incubated at 37°C for 18 hours. After 24 hours of incubation, colonies of Gram-positive cocci were analyzed using the VITEK 2 system (BioMérieux, Marcy-L'Étoile, Lyon, France) in accordance with the manufacturer's guidelines.

Confirmatory and Screening Tests for MRSA

The GeneXpert system (Cepheid; Sunnyvale, CA, USA) is a rapid diagnostic tool that uses real-time polymerase chain reaction (PCR) and delivers results within two hours. The specificity and sensitivity of GeneXpert MRSA were tested with a nasal or skin swab and a GeneXpert MRSA ID kit at 99% and 100%, respectively. The nasal or skin swabs were prepared on mannitol salt agar supplemented with 4 µg/ml oxacillin (Saudi Prepared Media Laboratories) to isolate MRSA. The isolates were analyzed for antibiotic susceptibility using either the disk diffusion test or the VITEK-2 identification system. The GeneXpert test, which was employed as a validation test for MRSA, was also verified by a routine technique using a pure bacterial colony.

Antimicrobial-Susceptibility Testing (AST)

The VITEK 2 system was employed for antibiotic susceptibility testing (AST). The AST of Gram-positive bacteria (AST-GP) susceptibility cards (P580 panel) were operated in adherence to the manufacturer's guidelines. The AST-GP panel involves the following antibiotics which are Tobramycin, Oxacillin, Benzylpenicillin, Levofloxacin, Gentamicin, Moxifloxacin, Linezolid, Clindamycin, Erythromycin, Teicoplanin, Vancomycin, Fosfomycin, Tigecycline, Tetracycline, Nitrofurantoin, Fusidic acid, Mupirocin, Trimethoprim/Sulfamethoxazole and Rifampicin. The VITEK 2 system performed the cards autonomously and produced the results within a span frame of 10 to 18 hours. The results received from the VITEK 2 system were then compared with the Gram-positive bacteria designation database. Clinical and molecular microbiology laboratory antibiotic susceptibility documenting standards were set according to the CLSI M100 performance guidelines (https://clsi.org/standards/products/microbiology/documents/m100/) for AST. These criteria are utilized to assess resistance, susceptibility, and intermediate resistance. Ultimately, results were

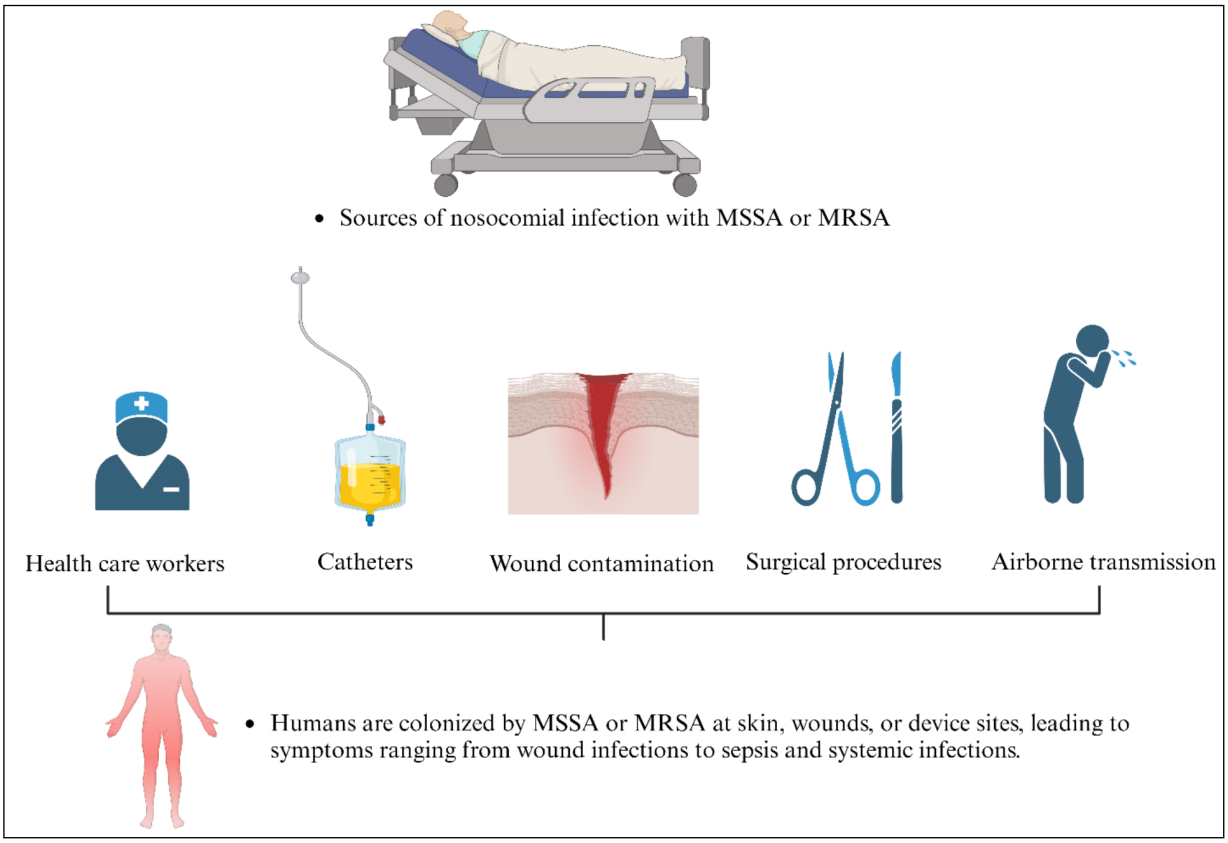

Figure 1. Sources of nosocomial infections with methicillin-susceptible *Staphylococcus aureus* (MSSA) and methicillin-resistant *Staphylococcus aureus* (MRSA) can include various routes such as healthcare workers, catheters, wounds, surgery, and airborne transmission. These factors contribute to the spread of MSSA or MRSA, leading to systemic infections and sepsis.

collected by the VITEK 2 system once the sample cycle (identification and AST) was completed, which typically took 10-18 hours.

The summary of the major steps involved in this study is presented in Figure 2.

Statistical Analysis

The statistical analysis was conducted using IBM SPSS version 22 software (IBM Corp., Armonk, NY, USA) to ensure robust data evaluation. Numerical data are presented as mean ± standard deviation, providing a measure of central tendency and variability. For categorical data, frequencies and percentages are reported to facilitate clear comparisons among groups. The relationships between study variables and pathogen types were analyzed using the Chi-square test, which is appropriate for determining associations in categorical data. A *p*-value threshold of 0.05 was established to determine statistically significant differences. Additionally, where applicable, post-hoc tests were performed to further explore significant findings. All analyses were two-tailed to account for possible relationships in both directions.

Results

461 patients with *S. aureus*-positive blood cultures were included; 232 (50.3%) of these patients were infected with MSSA, and 229 (49.7%) were MRSA-positive. The mean age of MSSA-positive patients was 46 ± 27, whereas that of MRSA patients was 43 ± 25. Sixty percent of the total patients were male.

Diabetes (46%), kidney disease (37%), and heart disease (23%) were identified as risk factors for SA-BSI. A higher number of infections (49%) were contracted from the emergency room. Hospital-acquired infections accounted for 52.6% of MSSA and 60% of MRSA infections. On the contrary, community-acquired infections were re-

sponsible for 47.4% of MSSA and 40% of MRSA infections. The nasal and skin colonization rate in the case of MRSA was 24%. CA-BSI was more likely to be implicated with superficial skin and soft-tissue infections, and HA-BSI was mainly linked with device- and procedure-related infections. The overall mortality rates were found to be 29.7%, whereby 33.2% of cases were associated with MSSA and 26.2% were with MRSA.

Demographics and Wards of Patients with SA-BSI

Table I reveals that out of the total number of patients who have MSSA, 140 (60.3%) were males and 92 (39.7%) were females. In the case of MRSA, out of 229 reported cases, 136 males (59.9%) and 93 females (40.1%) tested positive ($p = 0.834$). No statistically significant differences were found among the two groups of patients across different wards ($p > 0.05$). Finally, the average age for MSSA patients was 46 ± 27, while that of the MRSA group was 43 ± 25, indicating no major difference between the two groups. The p-value for age is 0.699 ($p > 0.05$).

Figure 3 shows the distribution of patients according to sex.

Sources of Bloodstream Infection

Table II shows that hospital-acquired infections (HAI) happened at a higher rate for both groups in comparison with community-acquired infections (CAI). Additionally, primary bloodstream infections occurred at a higher rate for both groups as compared to secondary bloodstream infections. Finally, the main sources of secondary bloodstream infections were associated with wound cultures, respiratory cultures, and urine cultures 40%, 26%, and 23%, respectively.

MRSA Screening

The MRSA screening results revealed that 24% of the tests for MRSA came back positive, while 76% came back negative with $p = 0.000$ ($p < 0.05$), highlighting a substantial disparity.

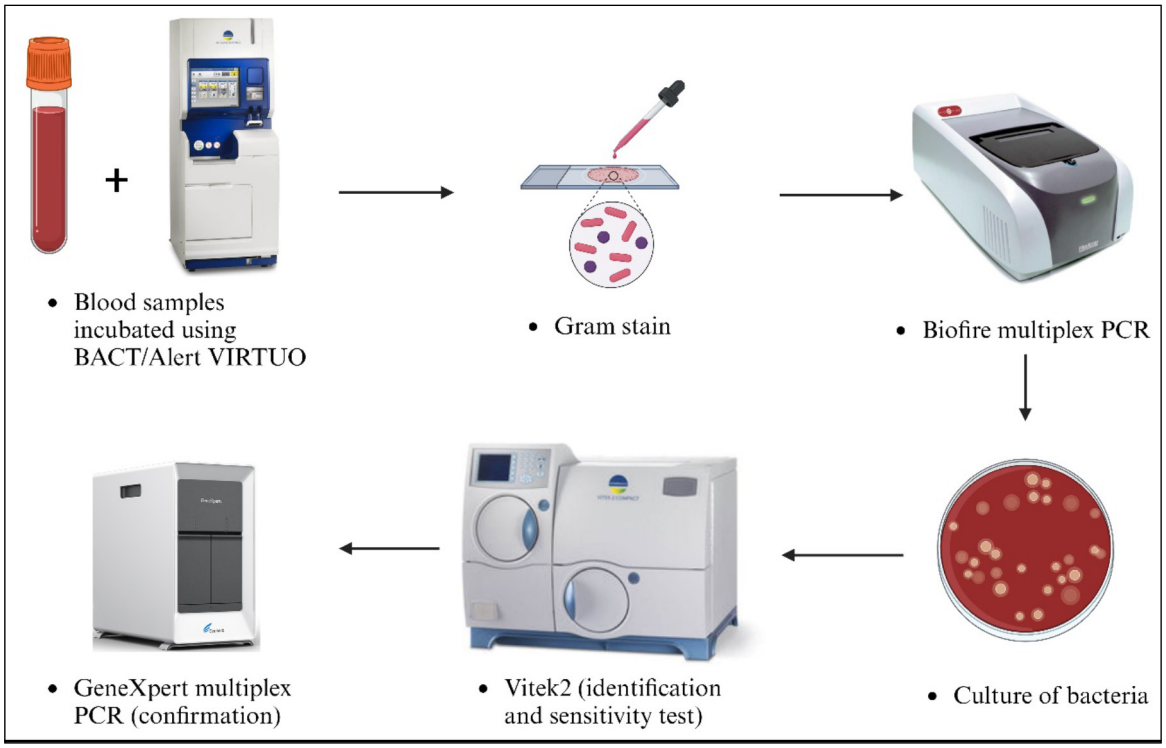

Figure 2. Blood samples collected from patients were incubated for 5 days using the BACT/Alert VIRTUO system. Subsequently, gram staining was performed on positive samples. These samples were then sent to the Biofire multiplex polymerase chain reaction (PCR) to detect methicillin-susceptible *Staphylococcus aureus* (MSSA) and methicillin-resistant *Staphylococcus aureus* (MRSA). Bacterial cultures were grown on 5% sheep blood agar, chocolate agar, or MacConkey agar. Further identification and sensitivity testing were conducted using Vitek2. Confirmation of the results was carried out using the GeneXpert multiplex PCR.

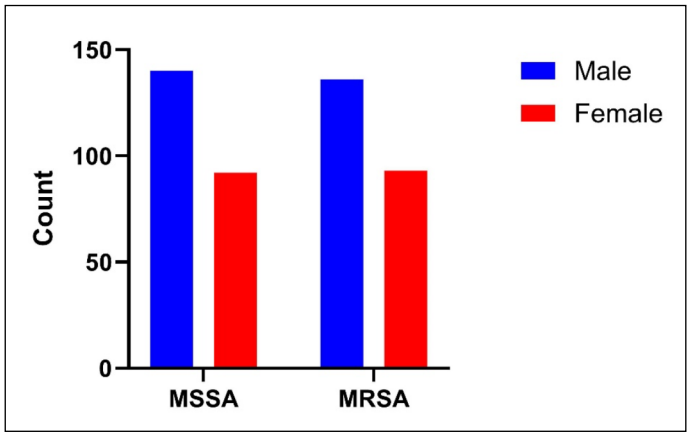

Figure 3. Distribution of infection rates among MSSA and MRSA patients according to gender. MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus.*

Invasive Devices or Procedures

Using invasive devices or procedures (Table III) revealed no significant differences in the transmission of both the MSSA and MRSA. However, invasive procedures, especially peripheral line catheters (30%), central line catheters (22%), and hemodialysis (17%), may have played an important role in SA-BSI infections. There was no noticeable distinction between the MSSA and MRSA groups.

Risk Factors for SA-BSI

Table IV displays the key risk factors implicated with SA-BSI in the following descending order: diabetes mellitus, hypertension, chronic kidney disease, and chronic heart disease: 47%, 39%, 37%, and 23%, respectively. The only statistically significant factor among the 2 groups was diabetes mellitus ($p < 0.05$). MSSA-BSI was higher in oncology patients (18%); this difference was borderline significant ($p = 0.08$).

Table I. *S. aureus* bloodstream infections (SA-BSI) associated with MRSA or MSSA.

Study variables	MSSA N = 232 (50.3%)		MRSA N = 229 (49.7%)		*p*-value
	N	%	N	%	
Sex Male Female	 140 92	 60.3 39.4	 136 93	 59.9 40.1	0.834
Ward	**MSSA N = 232 (50.3%)**		**MRSA N = 229 (49.7%)**		***p*-value**
	N	**%**	**N**	**%**	
Emergency (49%)	117	49	109	47	0.543
Medical unit (14.5%)	36	16	31	13	0.392
Paediatric unit (8.7%)	18	9	22	10	0.481
Adult ICU (8.5%)	18	8	21	9	0.586
Paediatric ICU (7.2%)	17	7	16	7	0.887
Surgical unit (4.8%)	10	4	12	5	0.640
Dialysis unit (3.7%)	8	3	9	4	0.784
Obstetrics and gynecology (1%)	4	2	1	1	0.182
Isolation unit (0.9%)	0	0	4	2	-
Day-care unit (0.6%)	1	1	2	1	0.555
Other (1.1%)	3	1	2	1	0.555
Age	46Y (± 27Y) Range (1D-100Y)		43Y (± 25Y) Range (1D-109Y)		0.699

MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus;* ICU, intensive care unit.

Table II. Bloodstream infections associated with MSSA or MRSA.

Study variables	MSSA N = 232 (50.3%)		MRSA N = 229 (49.7%)		*p*-value
	N	%	N	%	
Type of bloodstream infection					
Hospital-acquired infection	122	52.6	137	60	0.000
Community-acquired infection	110	47.4	92	40	0.000
Source of bloodstream infection					
Primary BSI	181	78	190	83	0.180
Secondary BSI	51	22	39	17	0.180
Source of secondary BSI					
Wound culture (40%)	26	40	20	40	0.977
Respiratory culture (26%)	16	24.6	14	28	0.652
Urine culture (23%)	15	23.08	11	22	0.900
Peritoneal fluid culture (3%)	3	4.62	1	2	0.449
Synovial fluid culture (3%)	0	0	3	6	-
Ear culture (2%)	1	1.54	1	2	0.847
Drain culture (1%)	1	1.54	0	0	-
Eye culture (1%)	1	1.54	0	0	-
Pleural fluid culture (1%)	1	1.54	0	0	-
HVS culture (1%)	1	1.54	0	0	-

BSI, bloodstream infection; MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus;* HVS, high vaginal swab.

Antibiotics Susceptibility Test

Table V demonstrates the antibiotic susceptibility profile of MSSA and MRSA. The results revealed that both MSSA and MRSA isolates exhibited 100% sensitivity to vancomycin. The susceptibility of MSSA to oxacillin was 100%, while all MRSA were resistant to oxacillin as expected. The susceptibility to clindamycin was 84% and 73.2% for MSSA and MRSA, respectively.

Comorbidity Analysis Reveals Disparity in Mortality Rates Among BSI Patients with MSSA and MRSA Infections

The comorbidity analysis displays that most BSI patients had one or three other diseases. The mortality rates for these patients with comorbidities were 33.2% and 26.2% for MSSA and MRSA, respectively. A considerable disparity in mortality rates was noticed among the MSSA and MRSA groups ($p < 0.05$) (Table VI).

Table III. Number of cases associated with invasive devices or procedures.

Study variables		MSSA N = 232 (50.3%)		MRSA N = 229 (49.7%)		*p*-value
		N	%	N	%	
Peripheral arterial catheter	30%	68	29.3	68	29.6	0.294
Central venous catheter	22%	43	18.5	57	25	0.151
Urine catheter	17%	33	14.2	44	15	0.253
Mechanical ventilator	10%	23	10	24	10.5	0.853
Hemodialysis	4%	7	3	12	5.2	0.313
Nasogastric tube	2%	4	1.7	3	1.3	0.613
Total parenteral nutrition	2%	3	1.2	6	2.6	0.373
Ventricular shunt	1%	2	1	2	1	0.937

MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*.

Discussion

To the best of our knowledge, this is the first study to investigate the prevalence and distribution of *Staphylococcus aureus* BSI over a four-year period, from 2017 to 2021, in the region. This study provides unique insights into the epidemiology of SA-BSI within Saudi Arabia, addressing a significant gap in regional data and offering valuable information for improving infection control strategies and patient outcomes in local healthcare settings.

Staphylococcus aureus is considered a human organism that can cause various clinical manifestations associated with infections[10]. Generally, *S. aureus* infection and/or colonization has been ranked according to their response to antibiotics as either MRSA or MSSA infections and the condition by which patients contract the infection as either HA or CA[11]. *S. aureus* ranks as the second most prevalent source of bloodstream infections, both in community and hospital settings[12]. It is a primary contributor to BSI and infective endocarditis, as well as infections in the bones and joints, skin and soft tissues, lungs and pleural cavity, and infections connected to medical devices[13]. This study explored the epidemiology and outcomes of MSSA and MRSA BSI and determined the risk factors associated with *S. aureus* bloodstream infection at KAUH. Four hundred sixty-one BSI cases were caused by *S. aureus*, 232 (50.3%) MSSA, and 229 MRSA (49.7%). According to the results obtained in this study, males were more at risk of contracting BSI mediated by MSSA and/or MRSA. Those results are similar to what has been reported in other studies[14]. Furthermore, studies[15] also highlighted an increased prevalence of MRSA infections in males. These results may provide insights into the epidemiology, risk factors, clinical characteristics, and transmission mechanisms of *S. aureus* bloodstream infections, with implications for infection prevention and control strategies in healthcare settings.

Staphylococcus aureus is one of the most common Gram-positive bacteria that induces bloodstream infections both in hospitalized patients and in the community at large[16]. It has been exhibited that hospital-acquired bloodstream infections with MRSA are more prevalent than MSSA[17]. In this investigation, we uncovered that HA-MRSA BSI was more prevalent than HA-MSSA BSI (60% *vs*. 52.6%, $p < 0.001$). In a different study, it was indicated that the high proportion of community-acquired *S. aureus* bloodstream infections provoked by MSSA highlights the prevalence of this organism as a serious cause of community-acquired infections[18]. Similarly, our study found that CA-MSSA was more prevalent than CA-MRSA (47.4% *vs*. 40%, $p < 0.001$).

BSIs can be classified as primary or secondary according to the source from which they arise. Primary BSI develops within the cardiovascular system, whereas secondary BSIs result from an infection in another part of the body[19]. According to published data[20], primary SA-BSI is more prevalent than secondary SA-BSI. This aligns with our findings, where primary SA-BSI occurred more often than secondary SA-BSI (80% *vs*. 20%, $p = 0.180$). Parallel to our results, it has been shown that device- and procedure-related infections are the most common sources of HA-MRSA BSIs[21]. Further, indwelling devices, including intravascular catheters, were reported as one of the most common causes of primary SA-BSI[22]. For secondary BSIs, the most frequent sources of infection were skin and soft tissue infections, joint or bone infections, infective endocarditis, and respiratory tract infections[23]. In our study, primary MRSA and MSSA BSI were most prevalent in patients with either a peripheral arterial catheter (30%) or a central venous catheter (22%). Conversely, secondary BSIs most commonly originated from soft tissue and skin infections (40%), respiratory tract infections (26%), and urinary tract infections (23%).

Over time, there has been a growth in the number of adult patients recognized with community-acquired methicillin-resistant *Staphylococcus aureus* bloodstream infections. This disease is more strongly connected with cutaneous abscess and necrotizing pneumonia and less so with endovascular infections in comparison with community-acquired methicillin-sensitive *S. aureus* BSI[24]. In our study, we noticed that patients with CA-MRSA BSI had a higher likelihood of skin and soft tissue infections, particularly cutaneous abscesses, compared to patients with CA-MSSA BSI (21% *vs*. 16%, $p = 0.317$). The present investigation determined peripheral arterial catheters as the primary risk factor, contributing to 30% of cases, while ventricular shunts were the least common, accounting for only 1%. Device-related infections accounted for 33% of SA-BSI cases. The increasing use of indwelling foreign devices, including vascular catheters, hemodialysis equipment, and orthopedic prostheses, in clinical settings is a widely recognized risk factor for SA-BSI[23]. Healthcare workers should implement CDC recommendations to prevent device- and procedure-associated infections[25].

Table IV. Risk factors involved in SA-BSI.

Co-morbidities (underlying diseases)		MSSA N = 232 (50.3%)		MRSA N = 229 (49.7%)		*p*-value
		N	%	N	%	
Diabetes mellitus	46%	95	41%	115	50%	**0.046**
Hypertension	39%	90	39%	88	38%	0.936
Chronic kidney disease	37%	84	36%	85	37%	0.839
Chronic heart disease	23%	58	25%	49	21%	0.360
Haemodialysis	20%	44	19%	49	21%	0.515
Surgery	19%	42	18%	47	21%	0.510
Oncology	18%	49	21%	34	15%	0.080
Skin infection	16%	37	16%	37	16%	0.951
Chemotherapy	11%	30	13%	20	9%	0.147
Congenital malformation	3%	10	4%	6	3%	0.322
Chronic liver disease	3%	9	4%	7	3%	0.630
Preterm infant	3%	9	4%	5	2%	0.289
Chronic lung disease	4%	7	3%	10	4%	0.442
COVID-19	4%	7	3%	12	5%	0.230
Tuberculosis	3%	5	2%	7	3%	0.543
Rheumatological	2%	4	2%	7	3%	0.349
Haemorrhage	1%	2	1%	2	1%	0.990
HIV	1%	2	1%	2	1%	0.990

SA-BSI, *Staphylococcus aureus*-bloodstream infection; COVID-19, coronavirus disease of 2019; HIV, human immunodeficiency virus; MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*.

Kwiecinski and Horswill[26] conveyed that patients with *S. aureus* bloodstream infection (BSI) had encountered numerous comorbidities, such as diabetes, kidney disease, heart disease, malignancy, immunosuppression, MRSA colonization, and the existence of indwelling medical devices, as well as intravenous drug use. Similarly, in our study, we found that the most common risk factors associated with *S. aureus* BSI were diabetes mellitus (46%), hypertension (39%), kidney disease (37%), heart disease (23%), hemodialysis (20%), and postoperative infection (19%). Patients with diabetes face a 4.4 times higher risk of developing bloodstream infections compared to those without diabetes, making them more vulnerable to sepsis of unknown origin. People with diabetes are at a raised risk of MRSA colonization compared to those without diabetes. Diabetes may heighten a patient's vulnerability to *S. aureus* BSI due to other medical conditions and consequences, such as elevated tissue glucose levels and reduced oxygen supply, which often impair the immune system[27]. In addition, Sohail et al[28] highlighted that patients with MRSA had a significantly higher frequency of diabetes mellitus than those with MSSA. In our study, the risks of acquiring MSSA and MRSA-BSI were similar, with no significant differences observed across all risk factors except for diabetes mellitus ($p < 0.046$), which was statistically significant ($p \leq 0.019$).

A published study[29] emphasized that 45% of admitted patients with MRSA infections encountered colonization before the development of bloodstream infections (BSI). In our study, only 55 patients (24%) were colonized with MRSA before developing BSI ($p < 0.001$). Regarding the mortality rate, the overall mortality of *S. aureus*-related BSI was 35.3%, with higher rates in MRSA cases (39.9%) in comparison with MSSA (30.7%)[30]. These findings vary from ours, where the overall 30-day mortality rate was 29.7%, with a higher rate among individuals with MSSA than those with MRSA (33% and 26%, respectively) ($p < 0.001$). A previous study[14] noted that the rate of *S. aureus* BSI-related mortality was higher in men than in women within 28 days (19.3% *vs*. 13.2%). Similarly, in our study, the 30-day mortality rate was 1.7 times higher in men than in women (63% *vs*. 37%).

Table V. Antibiotic sensitivity profile of MRSA and MSSA isolates.

Antibiotics	MSSA N = 232	MRSA N = 229
Oxacillin	232/232 (100%)	0/229 (0%)
Clindamycin	195/232 (84%)	167/229 (73.2%)
Vancomycin	232/232 (100%)	229/229 (100%)

MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*.

Another study[31] documented that the prevalence of hospital-acquired BSI-related mortality was higher than community-acquired BSI. In our study, the mortality rates from hospital-acquired BSI were higher in MRSA patients. In comparison, death rates from community-acquired BSI were higher in MSSA patients, with this difference being statistically significant ($p \leq 0.05$).

According to a study, the connection of *S. aureus* bloodstream infection (SA-BSI) in diabetic patients with mortality has raised[32]. In this study, the total death rate for SA-BSI patients with diabetes was 55.5% (49.4% MSSA *vs*. 63.3% MRSA), with no significant difference ($p \geq 0.102$). Immunosuppression was another risk factor associated with high mortality rates due to SA-BSI. A study noted that the mortality rate because of *S. aureus* in immunocompromised patients, such as those undergoing chemotherapy, living with HIV, or having a dysfunctional immune system, was 20%[33]. In our study, the death rate among chemotherapy patients was 10%. Nevertheless, the fatality rate was significantly higher among individuals undergoing chemotherapy with MSSA (12, 15.6%) in comparison with those with MRSA (2, 3.3%), showing a six-fold difference.

Based on the report, the antibiotics of choice to treat MSSA bloodstream infections are anti-staphylococcal penicillins, including nafcillin, oxacillin, or dicloxacillin[34]. Alternative antibiotics include first-generation cephalosporins like cefazolin, both of which were found to be highly effective in treating MSSA. These outcomes align with our study, where cloxacillin was recognized as the drug of choice for treating MSSA BSI, as MSSA is susceptible to all beta-lactam antibiotics. It has been noted that MRSA is naturally resistant to oxacillin and most beta-lactam antibiotics[35]. Our study discovered similar results, with MRSA showing resistance to all beta-lactam antibiotic groups, including those typically used for MSSA, such as oxacillin and cephalosporins. One exception is the newer generation of cephalosporins, such as cefazolin and ceftobiprole. Recent reports[36] indicated that the UK guidelines for treating MRSA-related BSI recommend intravenous vancomycin as the first-line antibiotic. When vancomycin is contraindicated, linezolid can be used as an alternative first-line treatment. In this study, 100% of MRSA was found to be sensitive to vancomycin, and we employed linezolid either as an alternative to vancomycin or as an oral antibiotic for discharged patients.

Table VI. The mortality rate of comorbidities.

Number of comorbidities/patients	MSSA N = 232 (50.3%)		MRSA N = 229 (49.7%)		*p*-value
	N	%	N	%	
0 (11%)	21	9.1	30	13.1	0.166
1 (27%)	68	29.3	59	25.8	0.394
2 (26%)	66	28.4	55	24.0	0.280
3 (21%)	48	20.7	49	21.4	0.852
4 (9%)	18	7.8	22	9.6	0.481
5 (5%)	9	3.9	13	5.7	0.365
6 (1%)	2	0.9	1	0.4	0.570
Mortality rate	77	33.2	60	26.2	**0.000**

The number of comorbidities per patient: 0 - no comorbidities; 1 - one comorbidity; 2 - two comorbidities; 3 - three comorbidities; 4 - four comorbidities; 5 - five comorbidities; 6 - six comorbidities. MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*.

Limitations

This study is limited to a single center and relies exclusively on the analysis of clinical data from that center.

Conclusions

In conclusion, this is the first study investigating *Staphylococcus aureus* bloodstream infections in Saudi Arabia at King Abdulaziz University over a four-year period, from 2017 to 2021. This study highlights the epidemiology, risk factors, and clinical outcomes of *Staphylococcus aureus* bloodstream infections at King Abdulaziz University Hospital. We found that both methicillin-susceptible *S. aureus* and methicillin-resistant *S. aureus* significantly contribute to the burden of bloodstream infections, with HA-MRSA being more common than HA-MSSA and CA-MSSA being more common than CA-MRSA. The study identified important risk factors, including diabetes, peripheral arterial catheters, and indwelling devices, which are strongly associated with the occurrence of SA-BSI. Men, in particular, were at higher risk of acquiring these infections, and the 30-day all-cause mortality rate was substantial, with MSSA-related mortality outpacing MRSA-related mortality. These findings enforce the need for enhanced infection control measures, especially in the use of medical devices, and highlight the importance of targeted therapies for both MSSA and MRSA infections. The study also highlights the function of vancomycin and linezolid as effective treatment options for MRSA-BSI, with newer cephalosporins potentially offering alternative therapeutic strategies.

Conflict of Interest

The authors declare no conflict of interest in relation to this study.

Authors' Contributions

A. Albuhairy contributed to the conceptualization, data interpretation, and manuscript drafting and writing. D. Attallah was responsible for data collection and analysis. S. Qashqari, R. Kaki, S. Harakeh, K. Alkuwaity, T. Abujamel, T. Altorki, J. Mokhtar, H. Momin, O. Alharbi, M. Ismail, M. Mufrrih, A. Sait, and I. Abu provided critical reviews and revisions of the manuscript. M. Al-Rabia contributed through supervision, idea development, and manuscript feedback, while B. Saleh and T. Ekhmimi assisted in manuscript preparation and editing. A. Elfadil provided conceptualization and overall supervision of the study. K. Ibrahem was responsible for critical review, manuscript formatting, and revision. Each author has read and approved the final version of the manuscript.

AI Disclosure

This study utilized artificial intelligence (Chat GPT) and assisted technologies in various aspects of the research process. Specifically, AI tools were employed for data analysis and interpretation, as well as for generating figures and visualizations. These tools were instrumental in enhancing the research's efficiency and accuracy. However, the authors made all final decisions regarding the study design, data interpretation, and manuscript preparation.

Funding

No external or internal funding was received for the conduct of this research or the preparation of this manuscript.

Informed Consent

The Ethics Committee granted a waiver for individual patient consent, allowing the study to proceed without direct patient interaction, while patient isolates used for infection diagnosis are, as standard practice in hospitals, managed in compliance with strict ethical guidelines.

Ethics Approval

The study was approved by the research Ethics Committee at King Abdulaziz University Hospital (KAUH) under approval number HA-02-J-008, dated September 5, 2012.

ORCID ID

Ali M. Albuhairy: 0009-0006-3595-3575
Safinaz Talla't Qashqari: 0009-0005-0605-7520
Reham Kaki:0000-0002-4620-8726
Steve Harakeh: 0000-0001-7512-8787
Bandar Hasan Saleh: 0000-0002-3205-2986
Khalil Alkuwaity: 0009-0005-5689-7683
Jawahir A. Mokhtar: 0000-0001-7563-6941
Turki Abujamel: 0000-0001-9503-8770
Dalya Attallah: 0009-0006-0082-1177
Tarfa A. Altorki: 0009-0001-0374-2187
Mohammed W. Al-Rabia: 0000-0002-1578-1810
Karem Ibrahem: 0009-0005-9473-3591
Abdelbagi Elfadi: 0000-0002-4070-6257
Mohammed Mufrrih: 0000-0002-6834-2379
Ahmad M Sait: 0000-0002-1698-5444
Mazen A. Ismail: 0000-0001-6237-1841
Ohood S Alharbi: 0000-0002-8720-5054
Hattan Jamal Momin: 0009-0000-1790-2842
Ibrahim Mohammed Abu: 0000-0002-8800-5388
Tariq Ekhmimi: 0009-0008-9840-8069

Acknowledgments

We sincerely appreciate the invaluable support provided by the staff of the Clinical Microbiology Laboratory at King Abdulaziz University Hospital, whose assistance in supplying the necessary bacterial isolates was instrumental to this study. We also extend our deep gratitude to the research ethics committee at King Abdulaziz University Hospital for their dedicated time and effort in approving and supporting

our research. Their guidance and expertise have been crucial in advancing our work.

Availability of Data and Materials

The raw data supporting the findings of this study are available from the corresponding author upon reasonable request

References

1) Zheng C, Chen Q, Pan S, Li Y, Zhong L, Zhang X, Cui W, Lin R, Zhang G, Zhang S. Staphylococcus aureus bloodstream infection in a Chinese tertiary-care hospital: a single-center retrospective study. Chin Med J 2023; 136: 1503-1505.
2) World Health Organization. Global antimicrobial resistance and use surveillance system GLASS report 2021. Available at: https://www.who.int/publications/i/item/9789240027336.
3) Shoaib M, Aqib AI, Muzammil I, Majeed N, Bhutta ZA, Kulyar MF, Fatima M, Zaheer CF, Muneer A, Murtaza M, Kashif M, Shafqat F, Pu W. MRSA compendium of epidemiology, transmission, pathophysiology, treatment, and prevention within one health framework. Front Microbiol 2023; 13: 1067284.
4) Gherardi G. Staphylococcus aureus infection pathogenesis and antimicrobial resistance. Int J Mol Sci 2023; 24: 8182.
5) Na P, Yang L, Zhang H, Xu Y, Bao X, Sheng S, Liang Y, Liu B, Lyu Y, Li H, Ma F, Pan H, Wang X. Oral vaccination with engineered probiotic Limosilactobacillus reuteri has protective effects against localized and systemic Staphylococcus aureus infection. Microbiol Spectr 2023; 11: e0367322.
6) Nikolic P, Mudgil P. The cell wall, cell membrane, and virulence factors of Staphylococcus aureus and their role in antibiotic resistance. Microorganisms 2023; 11: 259.
7) Ioannou P, Zacharioudaki M, Spentzouri D, Koutoulakou A, Kitsos-Kalyvianakis K, Chontos C, Karakonstantis S, Maraki S, Samonis G, Kofteridis DP. A retrospective study of Staphylococcus aureus bacteremia in a tertiary hospital and factors associated with mortality. Diagnostics 2023; 13: 1-13.
8) Abou-Zeid F, Mourani SC, Kazma JM, Gharamti A, Yasmin M, Jabak S, Baban T, Sidani N, Kanafani ZA. Epidemiology of methicillin-resistant and methicillin-sensitive Staphylococcus aureus infections in Lebanon. Microbes Infect Chemother 2023; 3: e1692-e1692.
9) Bahnasy AA. Staphylococcus aureus bacteremia. Saudi Med J 2000; 21: 171-174.
10) Vincelot M. Understanding severe Staphylococcus aureus infections: recalibration of the focus towards host genetic factors. 2023; 1-17. Available at: https://studenttheses.uu.nl/handle/20.500.12932/43648.
11) Alsallameh MSS, Alhameedawi AK, Abbas HM, Khalid, Duaa K, Suhair A. A review on methicillin-resistant Staphylococcus aureus public health risk factors, prevention, and treatment. Egypt Pharm J 2023; 22: 177-187.
12) Kimmig A, Hagel S, Weis S, Bahrs C, Löffler B, Pletz MW. Management of Staphylococcus aureus bloodstream infections. Front Med 2021; 7: 1-8.
13) Alshomrani MK, Alharbi AA, Alshehri AA, Arshad M, Dolgum S. Isolation of Staphylococcus aureus urinary tract infections at a community-based healthcare center in Riyadh. Cureus 2023; 15: 1-8.
14) Zheng C, Chen Q, Pan S, Li Y, Zhong L, Zhang X, Cui W, Lin R, Zhang G, Zhang S. Staphylococcus aureus bloodstream infection in a Chinese tertiary-care hospital: a single-center retrospective study. Chin Med J (Engl) 2023; 136: 1503-1505.
15) Renggli L, Gasser M, Buetti N, Kronenberg A; Swiss Centre for Antibiotic Resistance. Increase in methicillin-susceptible Staphylococcus aureus bloodstream infections in Switzerland: a nationwide surveillance study (2008-2021). Infection 2023; 51: 1025-1031.
16) Abraham L, Bamberger DM. Staphylococcus aureus bacteremia: contemporary management. Mo Med 2020; 117: 341-345.
17) Li Z, Zhuang H, Wang G, Wang H, Dong Y. Prevalence, predictors, and mortality of bloodstream infections due to methicillin-resistant Staphylococcus aureus in patients with malignancy: systemic review and meta-analysis. BMC Infect Dis 2021; 21: 74.
18) Yarovoy JY, Monte AA, Knepper BC, Young HL. Epidemiology of community-onset Staphylococcus aureus bacteremia. West J Emerg Med 2019; 20: 438-442.
19) Ben-David D, Vaturi A, Wulffhart L, Temkin E, Solter E, Carmeli Y, Schwaber MJ; National HA-BSI Prevention Working Group; Members of the National HA-BSI Prevention Working Group. Impact of intensified prevention measures on rates of hospital-acquired bloodstream infection in medical-surgical intensive care units, Israel, 2011 to 2019. Euro Surveill 2023; 28: 2200688.
20) Benenson S, Ben-Yosef Y, Schwartz C, Cohen MJ, Oster Y. Sources of primary bloodstream infections in internal medicine patients - a cohort study. Eur J Intern Med 2023; 113: 69-74.
21) Ham DC, See I, Novosad S, Crist M, Mahon G, Fike L, Spicer K, Talley P, Flinchum A, Kainer M, Kallen AJ, Walters MS. Investigation of Hospital-Onset Methicillin-Resistant Staphylococcus aureus Bloodstream Infections at Eight High Burden Acute Care Facilities in the United States, 2016. J Hosp Infect 2020: S0195-6701(20)30182-1.
22) Kimmig A, Hagel S, Weis S, Bahrs C, Löffler B, Pletz MW. Management of Staphylococcus aureus bloodstream infections. Front Med 2021; 7: 1-8.
23) Hindy JR, Quintero-Martinez JA, Lee AT, Scott CG, Gerberi DJ, Mahmood M, DeSimone DC,

Baddour LM. Incidence trends and epidemiology of Staphylococcus aureus bacteremia: a systematic review of population-based studies. Cureus 2022; 14: 1-14.

24) Wang JL, Chen SY, Wang JT, Wu GH, Chiang WC, Hsueh PR, Chen YC, Chang SC. Comparison of both clinical features and mortality risk associated with bacteremia due to community-acquired methicillin-resistant Staphylococcus aureus and methicillin-susceptible S. aureus. Clin Infect Dis 2008; 46: 799-806.
25) Coia JE, Wilson JA, Bak A, Marsden GL, Shimonovich M, Loveday HP, Humphreys H, Wigglesworth N, Demirjian A, Brooks J, Butcher L, Price JR, Ritchie L, Newsholme W, Enoch DA, Bostock J, Cann M, Wilson, APR. Joint Healthcare Infection Society (HIS) and Infection Prevention Society (IPS) guidelines for the prevention and control of meticillin-resistant Staphylococcus aureus (MRSA) in healthcare facilities. J Hosp Infect 2021; 118: S1-S39.
26) Kwiecinski JM, Horswill AR. Staphylococcus aureus bloodstream infections: pathogenesis and regulatory mechanisms. Curr Opin Microbiol 2020; 53: 51-60.
27) Vanderschelden A, Lelubre C, Richard T, Lali SE, Cherifi S. Outcome of methicillin-sensitive Staphylococcus aureus (MSSA) bacteremia: impact of diabetes. Eur J Clin Microbiol Infect Dis 2019; 38: 2215-2220.
28) Sohail MU, Mashood F, Oberbach A, Chennakkandathil S, Schmidt F. The role of pathogens in diabetes pathogenesis and the potential of immunoproteomics as a diagnostic and prognostic tool. Front Microbiol 2022; 13: 1-15.
29) Neradova K, Fridrichova M, Jakubu V, Pomorska K, Zemlickova H. Epidemiological characteristics of methicillin-resistant Staphylococcus aureus isolates from bloodstream cultures at University Hospital in the Czech Republic. Folia Microbiol 2020; 65: 615-622.
30) Horváth A, Dobay O, Sahin-Tóth J, Juhász E, Pongrácz J, Iván M, Fazakas E, Kristóf K. Characterisation of antibiotic resistance, virulence, clonality and mortality in MRSA and MSSA bloodstream infections at a tertiary-level hospital in Hungary: a 6-year retrospective study. Ann Clin Microbiol Antimicrobials 2020; 19: 1-11.
31) Lam, JC, Gregson, DB, Robinson, S, Somayaji, R, Conly, JM, Parkins, MD. Epidemiology and outcome determinants of Staphylococcus aureus bacteremia revisited: a population-based study. Infection 2019; 47: 961-971.
32) Bello-Chavolla OY, Bahena-Lopez JP, Garciadiego-Fosass P, Volkow P, Garcia-Horton A, Velazquez-Acosta C, Vilar-Compte D. Bloodstream infection caused by S. aureus in patients with cancer: a 10-year longitudinal single-center study. Support Care Cancer 2018; 26: 4057-4065.
33) Greenberg JA, David MZ, Hall JB, Kress JP. Immune dysfunction prior to Staphylococcus aureus bacteremia is a determinant of long-term mortality. PLoS One 2014; 9: 1-6.
34) Righi E, Carnelutti A, Vena A, Bassetti M. Emerging treatment options for acute bacterial skin and skin structure infections and bloodstream infections caused by Staphylococcus aureus: a comprehensive review of the evidence. Infect Drug Resist 2022; 15: 2137-2157.
35) Sharma AD, Gutheil WG. Synergistic combinations of FDA-approved drugs with ceftobiprole against methicillin-resistant Staphylococcus aureus. Microbiol Spectr 2023; 11: e03726-22.
36) Brown NM, Goodman AL, Horner C, Jenkins A, Brown EM. Treatment of methicillin-resistant Staphylococcus aureus (MRSA): updated guidelines from the UK. JAC Antimicrob Resist 2021; 3: 1-18.