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MINIREVIEW

Epidemiology and Pathogenesis of *Staphylococcus* Bloodstream Infections in Humans: a Review

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Abstract

Staphylococci are among the most frequent human microbiota components associated with the high level of bloodstream infection (BSI) episodes. In predisposed patients, there is a high risk of transformation of BSI episodes to sepsis. Both bacterial and host factors are crucial for the outcomes of BSI and sepsis. The highest rates of BSI episodes were reported in Africa, where these infections were up to twice as high as the European rates. However, there remains a great need to analyze African data for comprehensive quantification of staphylococcal BSI prevalence. The lowest rates of BSI exist in Australia. Asian, European, and North American data showed similar frequency values. Worldwide analysis indicated that both *Staphylococcus aureus* and coagulase-negative staphylococci (CoNS) are the most frequent BSI agents. In the second group, the most prevalent species was *Staphylococcus epidermidis*, although CoNS were not identified at the species level in many studies. The lack of a significant worldwide decrease in BSI episodes indicates a great need to implement standardized diagnostic methods and research etiological factors using advanced genetic methods.

K e y w o r d s: bacteremia, carriage, infection, sepsis, *Staphylococcus*

Introduction

Staphylococcus aureus is one of the most frequently isolated pathogens from the hospital or community-acquired infections. Staphylococci are a large group of bacteria in every environment; however, these bacteria can proliferate only in humans or animals. Many staphylococcal species colonize the skin and mucosal membranes, especially the perineum and pharynx. The other sites that harbor these bacteria are the gastrointestinal tract, vagina, and axilla, but carriage in those areas is less frequent (Kosecka-Strojek et al. 2018). Traditionally, staphylococci have been divided into two groups based on the production of extracellular enzyme coagulase: coagulase-positive staphylococci (CoPS) and coagulase-negative staphylococci (CoNS). The first group is represented by well-known opportunistic pathogens such as *Staphylococcus aureus*, *Staphylococcus schleiferi*, *Staphylococcus intermedius,* and *Staphylococcus pseudintermedius*, and the second group traditionally includes nonpathogenic or opportunistic pathogens; however, recently, several clinical reports have presented CoNS as dangerous pathogens, particularly for newborns or immunocompromised patients (Heilmann et al. 2019). A few species, namely *Staphylococcus hyicus*, *Staphylococcus agnetis*, and *Staphylococcus felis*, belong to the third group – coagulase-variable staphylococci. These species are usually grouped with CoPS but cannot produce clumping factors, and coagulase production tests give variable results (Becker et al. 2014). As opportunistic pathogens, staphylococci exhibit saprophytic characteristics under physiological conditions, but the bacteria become severe pathogens under additional infection-facilitating conditions.

Staphylococci are etiological agents of diseases with various localizations, manifestations and/or courses of infection. The most frequent infections are local infections, and the bacteria can cause lesions in various anatomical tissues. Overall, the infections are grouped into skin and soft tissue infections (SSTIs) with

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manifestations such as dermatitis, abscesses, furunculosis, boils, folliculitis, impetigo, or mastitis, and also includes other severe diseases such as staphylococcal foodborne disease, toxic shock syndrome, and staphylococcal scalded skin syndrome (SSSS) (Foster 2012; Tong et al. 2015). Staphylococci are also common pathogens of deep tissue infections, including foreign bodies infection. Most studies focused on *S. aureus* infections, but there is strong evidence of the CoNS involvement in severe diseases. Osteomyelitis, otitis, wound infection, endophthalmitis, urinary tract infection, meningitis, or even pneumonia may be caused by *S. epidermidis, Staphylococcus saprophyticus, Staphylococcus lugdunensis*, and *S. schleiferi* (von Eiff et al. 2002; Becker et al. 2014; Argemi et al. 2019). When staphylococci gain entry into the bloodstream, colonization becomes systemic as bacteremia and then advances to infection.

The literature was screened based on a PubMed search using the terms „staphylococci", „*Staphylococcus*" and „bloodstream infections" and/or „sepsis". The publications were then evaluated based on a citation index. Specific criteria were used to describe the worldwide occurrence of *S. aureus*, and CoNS bloodstream infections and/or sepsis, such as: only original articles were included; the data from different geographical regions/countries were analyzed; the articles with the highest number of participants and bacterial strains isolated, and those containing long-term studies or the recent data, were selected to the analysis.

Bacteremia, bloodstream infection, and sepsis

Bacteremia. Bacteremia is characterized by the presence of pathogens in the blood (Pai et al. 2015). Transient bacteremia is limited to one or two days, without any manifestations, and may be caused by some staphylococcal species. Furthermore, the phenomenon does not indicate any further manifestation in healthy hosts (Samet et al. 2006). The presence of bacteria in the blood is eliminated by immunological defense systems and is known in the literature as „natural bacteremia" or „physiological bacteremia".

Bloodstream infection. However, in predisposed hosts, bacteremia advances to bloodstream infection (BSI), manifesting as an inflammatory response against microorganisms or/and against their metabolites present in the body (Dayan et al. 2016). The BSI can be successfully treated or advances to sepsis (Thomer et al. 2016; Michalik et al. 2020). Sepsis is related to organ dysfunction, perfusion disturbances, or hypotension with accompanying lacticaemia, oliguria, and/or psychological disorders (Samet et al. 2006; Hotchkiss et al. 2016).

Therefore, some *S. aureus* bacteremia complications, such as endocarditis, attributable mortality, embolic stroke, or recurrent infection during the 12-week follow-up period, are circumstances associated with the increased sepsis frequency from 11% to 43%. When the inflammatory response is triggered by the massive release of pro-inflammatory Th1 cytokines, such as TNF-α, IL-1β, IL-6, and IFN-γ, a septic shock may occur (Dayan et al. 2016).

Sepsis. Sepsis is the incorrect, inflammatory response of the host organism to infection, and often, it is a result of systemic bloodstream infections. Recently, sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection (Singer et al. 2016). Untreated sepsis can lead to severe sepsis or septic shock and, consequently, multiple organ failure (Sequential Organ Failure Assessment, SOFA) and death (Stevenson et al. 2016). Sepsis is a critical clinical stage of general toxemia and organ dysfunction, and a patient's inflammatory response interferes with the functioning of vital organs, such as the heart, kidneys, lungs, or liver. Sepsis-3 recommends a new sepsis scoring system, rapid sequential assessment of organ failure (qSOFA), consisting of 3 elements: an altered mental state, respiratory rate, and systolic blood pressure (Minejima et al. 2019). Patients with suspected infection expected to have a prolonged ICU stay can be identified at the bedside with quick SOFA, i.e., alteration in mental status, systolic blood pressure ≤ 100 mmHg, or respiratory rate ≥ 22/min. Moreover, patients with septic shock can be identified with a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain MAP ≥ 65 mmHg and having a serum lactate level > 2 mmol/l (18 mg/dl) despite adequate volume resuscitation (Singer et al. 2016).

Pathogenicity of staphylococcal bloodstream infections

Antibiotic resistance. Staphylococci exhibit a wide resistance to antibiotics. One of the most dangerous features of staphylococci is their multi-resistance. Research indicates that both the CoPS and CoNS species have staphylococcal chromosome cassettes *mec* (SCC*mec*) that determine resistance to methicillin in both groups. Furthermore, the *SCCmec* elements of CoNS present extreme diversity, which causes many diagnostic problems (Hosseinkhani et al. 2018). The increase of methicillin-resistant *S. aureus* (MRSA) isolates in hospital and the community due to horizontal gene transfer across bacterial species occurred. The environmental and animal-associated CoNS may be underestimated factor for the spread of the resistance genes into more pathogenic species like *S. aureus* (Kosecka-Strojek et al. 2016; Lisowska-Łysiak et al. 2019). Methicillin and

vancomycin resistance remain the major antimicrobial resistance phenotype of concern. Although still relatively infrequent, multi-resistant CoNS with reduced susceptibility to glycopeptides are emerging pathogens of clinical concern and should be kept in mind in empirical and rational therapy of BSI (Veach et al. 1990; Natoli et al. 2009). In recent years an emerging spread of linezolid-resistant *Staphylococcus capitis* and *S. epidermidis* strains in Europe was shown (Tevell et al. 2017; Kosecka-Strojek et al. 2020). An increased resistance is the result of antibiotic pressure, which could select resistant clones among staphylococci.

Virulence determinants and other invasion/evasion determinants. Staphylococci exhibit a strong capacity to infect human hosts by using specific strategies to enable the adherence, invasion, persistence, and evasion of the host's immunity mechanisms. However, the infection ability is not similar for all species within the *Staphylococcus* genus. In general, CoNS isolates present lower levels of virulence determinants than CoPS, but the factors involved in colonization support invasion in the host (Becker et al. 2014). It is especially true in extremely immature infants, in whom more than 80% of late-onset sepsis (diagnosed after 72 hours of life) is caused by CoNS (Lauterbach et al. 2016; Wójkowska-Mach et al. 2019). However, despite the relatively low level of virulence, immature infants with sepsis caused by these pathogens present a wide range of clinical symptoms (Lauterbach et al. 2016). It was shown that *S. lugdunensis* was responsible for sepsis and endocarditis on the 1st day of life in a term newborn, which underwent lotus birth (Ittleman and Szabo 2018). In contrast, *S. aureus* strains often exhibit a vast arsenal of toxins and enzymes involved in staphylococcal pathogenesis. Toxins can lead to a weak response of the human organism because they can degrade certain host cells, manipulate the innate and adaptive immune response, and degrade intercellular junctions, contributing to the *S. aureus* proliferation (Oliveira et al. 2018).

Toxins. One of *S. aureus* toxicity mechanisms is damage to host cell membranes caused by hemolysins, bicomponent leukocidins, or phenol-soluble modulins (Herrera et al. 2016). However, it has been proven that CoNS also secrete toxins and enzymes. Based on CoNS strains whole-genome sequencing (WGS) performed by Argemi et al. (2019), the presence of proteases, lipases, and hemolysins genes in *S. epidermidis*, *S. capitis*, and *Staphylococcus caprae* was shown. Moreover, enterotoxin genes in *S. epidermidis* and *Staphylococcus haemolyticus* genomes were shown (Nanoukon et al. 2018; Argemi et al. 2019). Other toxins produced by *S. aureus* are usually infection-specific, such as enterotoxins or toxic shock syndrome toxin. Furthermore, bacteria-host interactions depend on extracellular enzymes, and the largest group of enzymes includes proteases. This category consists of serine proteases, the metalloprotease aureolysin, and staphopains that are engaged in the evasion of complement-mediated killing, host tissue destruction, immunoglobulin degradation, and deregulation of fibrinolysis (Miedzobrodzki et al. 2002; Sabat et al. 2008; Kalińska et al. 2012; Martínez-Garcia et al. 2018).

Biofilm formation. Biofilm formation is an additional factor associated with CoPS and CoNS infections (Grzebyk et al. 2013; Argemi et al. 2019). Biofilm formation is one of the staphylococcal survival strategies within host organisms. The presence of staphylococcal biofilms is a key factor involved in bacterial resistance to various groups of antibiotics. Bacterial biofilms are defined as communities of bacterial colonies attached to the host surface and surrounded by exopolymeric matrix substances strictly regulated by numerous proteins engaged in the biofilm life cycle. It was shown that biofilms could evade the host immune response, which leads to the persistence of staphylococci. Bhattacharya et al. (2018) proved that *S. aureus* biofilms could release leukocidins, which affect extracellular trap formation and allow evasion of neutrophil-mediated killing. Biofilm production has also been proven for CoNS species, including *S. lugdunensis* that produces adhesins and other biofilm promoters (Argemi et al. 2017). Staphylococcal pathogenesis is a process that involves an array of extracellular proteins, biofilm, and cell wall components that are coordinately expressed in different phases of infection. The expression or suppression of two divergent loci, accessory gene regulator (*agr*) and staphylococcal accessory regulator (*sar*) are recognized as critical regulators of virulence in staphylococci (Arya and Princy 2013).

Risk factors present in humans: predisposed patients. Several studies have shown that host risk factors may significantly enhance the effects of BSIs, including mortality. The high-risk group of staphylococcal infections contains mostly patients with indwelling medical devices. The highly predisposed groups also contain premature newborns or elderly patients or multimorbid, chronically ill, or immunosuppressed patients. A large group of the patients infected is also those with inserted foreign plastic bodies, such as implants and venflons.

The essential patients' factors that determine bloodstream infections and complications are age, presence of comorbidities, and appropriate initial antibiotic treatment (Ayau et al. 2017). Bloodstream infections occur in elderly patients over 75 years old, resulting in increased mortality (Gasch et al. 2013). A 9-year study performed by Ayau et al. (2017) underlined risk factors that increased the probability of mortality, such as age, cancer, heart disease, neurological disease, nursing

home residence, and Charlson score greater than 3. In fact, cancer itself increases the 30-day mortality, but Bello-Chavolla et al. (2018) reported additional risk factors, including hematologic malignancy, hyperglycemia, abdominal source of infection, and endocarditis, based on studies conducted on patients with cancer. Malignancy was also confirmed to be a key factor associated with poor outcomes of infection in other studies (Papadimitriou-Olivgeris et al. 2019).

Epidemiology: Worldwide distribution of staphylococcal bloodstream infections

Staphylococcal bloodstream infections are currently a challenging issue for clinicians, diagnosticians, and microbiologists, primarily due to their high frequency worldwide. Studies on bloodstream infection episodes differ slightly from each other because of the high number of patients and the number of institutions involved in providing the data. Interestingly, all of these studies confirmed a high number of staphylococci isolated from blood samples, ranging from 23.9 to 79.2% (Table I). In many cases, *S. aureus*, usually MRSA isolates, and CoNS were the predominant species involved in BSI episodes. However, most importantly, staphylococcal bloodstream infections affect the whole world, not only developing countries. It is imperative to analyze the data to implement standard diagnostic methods, to compare the results among various countries, to evaluate existing preventive measures, and to plan effective infection prevention and control programs or establish new programs, including the use of advanced genetic methods (Dik et al. 2016; Sabat et al. 2017; Kosecka-Strojek et al. 2019). This study compares staphylococcal bloodstream infections in the world. The evaluation of *S. aureus* and CoNS as etiological agents of BSI of the cited publications was made under the following criteria: the studies included patients with symptoms of BSI/sepsis; pathogens grew on at least one percutaneous blood culture and a culture of the catheter tip; bacteria have been identified as *S. aureus* or CoNS species using commercial/automated identification tests; susceptibility testing was performed, and CoNS species from positive blood samples were included in comprehensive data for analysis except where specified in the laboratory records as contaminants.

Europe. The epidemiology of BSI episodes in Europe was analyzed in detail. The European Centre for Disease Prevention and Control (ECDC 2008; 2018) presented that CoNS were the most numerous bloodstream infections pathogens isolated in Europe. Moreover, the biggest groups of infected patients consisted of neonates and children, and the probability of serious complications such as long-term adverse neurological outcomes or mortality remained high for these infections (Zingg et al. 2017). Deptuła et al. (2018) reported that catheter-related BSI episodes in Poland occurred in 48.9% of the patients analyzed, and the predominant pathogens were CoNS. These results suggest a strong need for the construction of functional incidence-based surveillance programs in Poland to reduce BSI episodes. The Neonatology Surveillance Network (PNSN) prepared one of these programs and focused on late-onset BSI (LO-BSI) in very-low-birth-weight infants. The study showed that CoNS were the most common cause of LO-BSI (Wójkowska-Mach et al. 2014). Both studies confirmed that it is necessary to implement a national program for infectious disease monitoring and prevention.

Another study in Germany focused on pediatric BSI was based on 20 years of sample collection at a tertiary care hospital. This study conducted a complex observation of a large group of BSI episodes. The results showed an increasing number of CoNS to be responsible for these infections (Hufnagel et al. 2008). Similar results were published by Buetti et al. (2017), which were based on a 7-year surveillance study in Switzerland, although the major pathogen isolated was *Escherichia coli*. These findings were confirmed by other studies performed in Switzerland when staphylococci caused a big group of BSI episodes, but the major isolated pathogens were Gram-negative rods (Papadimitriou-Olivgeris et al. 2019).

On the other hand, an increase in the presence of CoNS was observed, but a minority of studies identified bacteria to the species level. One of these studies was performed in Sweden and showed the CoNS were related to newborns' sepsis from 1987 to 2014. The authors presented that *S. epidermidis* (67.4%) was the most frequent pathogen, followed by *S. haemolyticus* (10.5%), and *S. capitis* (9.6%) (Ehlersson et al. 2017). The epidemiological study in France was partially consistent with previously mentioned research and showed that *E. coli* was the primary pathogen in 36% of BSI episodes, followed by *S. aureus* (16%), and CoNS (8%). The other investigation from France showed the median rate of CoNS in sepsis (12.2%), and all of these strains belonged to *S. capitis* species (Butin et al. 2017). However, studies in the United Kingdom, Greece, Netherlands, and Romania confirmed that CoNS were predominant pathogens in BSI episodes and sepsis (Cailes et al. 2018; Zlatian et al. 2018; Gkentzi et al. 2019; Zonnenberg et al. 2019).

Asia. A study designed in Japan by Takeshita et al. (2017) showed that the major pathogens isolated from BSIs were CoNS (736 cases, 23%), but *S. aureus* isolates were also among the most commonly isolated strains. These results were comparable to those observed in Europe (Takeshita et al. 2017). The authors also focused on 30-day mortality associated with the species and the

Table I
Worldwide distribution of staphylococcal bloodstream infections. The gray areas consist of the primary pathogen isolated in studies provided according to adequate reference.

No.	Continent	Country	No. of institutions	Years of isolation	Total number of BSI episodes	*Staphylococcus*	*Staphylococcus* (%)	*S. aureus*	*S. aureus* (%)	CoNS	CoNS (%)	Reference
1	Africa	Ghana	1	2010–2013	1,763	507	28.8	76	4.3	431	24.4	Labi et al. 2016
2	Africa	Egypt	1	2013–2015	65	26	40,1	6	9.3	20	30.8	Seliem and Sultan 2018
3	Africa	Ethiopia	1	2016–2017	88	38	43.0	16	18.0	22	25.0	Sorsa et al. 2019
4	Africa	Zambia	1	2013–2014	103	13	12.0	6	6.0	7	6.0	Kabwe et al. 2016
5	Asia	Japan	5	2012–2013	3,284	1,030	32.2	294	9.2	736	23.0	Takeshita et al. 2017
6	Asia	South Korea	55	2013–2014	717	349	48.7	81	11.3	268	37.4	Lee et al. 2015
7	Asia	Arab States	4	2013–2015	785	289	36.85	17	2.2	272	34.65	Hammoud et al. 2017
8	Asia	China	1	2015–2016	133	64	60.3	8	7.5	56	52.8	Jiang et al. 2016
9	Asia	Nepal	1	2017	56	50	89,2	11	19.6	39	69,6	Thapa et al. 2019
10	Asia	India	1	2012–2014	183	87	47.4	42	22.9	45	24.5	Bandyopadhyay et al. 2018
11	Asia	Taiwan	1	2008–2013	2,090	485	23.2	57	2.7	428	20.5	Chen et al. 2016
12	Australia	Australia	23	2008–2012	9,418	3,160	36.4	1,429	18.0	1,731	18.4	Si et al. 2016
13	Australia	Australia	1	2005–2016	203	115	40.3	46	16.1	69	24.2	Worth et al. 2018
14	Australia	Australia	1	2005–2016	146	79	54.1	26	17.8	53	36.3	Gowda et al. 2017
15	Europe	Turkey	1	2003–2009; 2010–2016	925	542	58.6	46	5.0	496	53.6	Mutlu et al. 2019
16	Europe	Switzerland	20	2008–2014	1,823	535	30.0	300	17.0	235	13.0	Buetti et al. 2017
17	Europe	Switzerland	1	2014–2017	404	78	19.3	68	16.8	10	2.5	Papadimitriou-Olivgeris et al. 2019
18	Europe	Poland	nd	2012–2015	329	150	45.6	53	16.1	97	29.5	Deptuła et al. 2018
19	Europe	Germany	1	1985–1995; 1997–2006	1,646	650	79.2	241	28.1	409	51.1	Hufnagel et al. 2008
20	Europe	Romania	1	2016–2017	170	81	47.65	63	37.06	18	10.59	Zlatian et al. 2018
21	Europe	Holland	1	2008–2014	93	84	90.4	70	75.3	14	15.1	Zonnenberg et al. 2019
22	Europe	France	1	2011–2012	201	28	12.2	0	0.0	28	12.2	Butin et al. 2017
23	Europe	United Kingdom	30	2005–2014	3,903	2,466	65.0	233	8.0	2,233	57.0	Cailes et al. 2017
24	Europe	Greece	16	2012–2015	459	140	30.4	2	0.4	138	30.0	Gkentzi et al. 2019
25	North America	USA	1	2002–2012	8,196	4,254	51.9	721	8.8	3,533	43.1	Larru et al. 2016
26	North America	USA	1	2006–2017	92	39	42.4	7	7.6	32	34.8	Wagstaff et al. 2019
27	North America	USA	10	2015–2018	5,066	1,500	29.0	1,115	22.0	355	7.0	Khare et al. 2019
28	North America	USA	1	2013–2017	97	29	29.9	17	17.5	12	12.4	Black et al. 2019
29	South America	Brazil	28	2016	47	17	36.2	6	12.8	11	23.4	Braga et al. 2018
30	South America	Latin America	32	2001–2013	3,066	1,625	53.0	267	8.7	1,358	44.3	Escalante et al. 2018

nd – no data

group of pathogens. They concluded that the highest mortality rates were exhibited by hospital-acquired BSI (HA-BSI) pathogens, followed by community-onset healthcare-associated BSI (CHA-BSI), and the most dangerous species were CoNS and *Klebsiella pneumoniae*. The study from South Korea showed that CoNS were the most frequent pathogens engaged in neonatal sepsis (Lee et al. 2015). Studies in India proved a high staphylococci frequency in BSI episodes, however, gram-negative rods were mostly isolated in majority from blood samples (Bandyopadhyay et al. 2018). On the other hand, CoNS became the major isolated pathogen in neonatal sepsis in China, Nepal, Taiwan, Turkey and the Arab States, which proves widespread staphylococcal-caused sepsis in Asia (Jiang et al. 2016; Chen et al. 2017; Hammoud et al. 2017; Thapa and Sapkota 2019; Mutlu et al. 2020). These findings strongly correlate with European data.

North America and South America. In the USA research performed by Larru et al. (2016) presented similar results as European or Asian studies. The most commonly isolated pathogens were CoNS and *S. aureus*, and these pathogens were associated with healthcare-acquired BSI. Moreover, the authors confirmed that all the CoNS were evidenced as pathogens and not as contaminants. Another study from the USA showed a significant majority of *S. aureus* strains involved in neonate sepsis (Khare et al. 2020). The predisposed patients' characteristics were also comparable to those observed in Europe. These studies showed that the most endangered group consists of children and infants, especially with prolonged hospitalization.

Interestingly, children hospitalized since birth exhibited a significantly low prevalence of hospital-onset *S. aureus* bacteremia (Burke et al. 2009). For comparison with the USA, Latin American countries were also analyzed for staphylococcal bloodstream infections. Arias et al. (2017) presented a paper summarizing the results for nine South American countries, from Mexico to Argentina. This study did not evaluate the number of coagulase-negative staphylococci but showed many MRSA strains found in BSI samples from these countries. Notably, the highest number of participants with MRSA-associated BSI was reported in Brazil. Other studies confirmed that the prevalence of intensive-care unit-acquired infections was higher in Brazilian hospitals than in European countries and in the USA (Braga et al. 2018). On the other hand, the highest rates of CoNS (44.3%) were present in NEOCOSUR studies on five Latin American countries: Argentina, Chile, Paraguay, Peru and Uruguay (Escalante et al. 2018).

Africa. The World Health Organization (WHO) reported that, to date, information regarding bloodstream infections in Africa is scarce due to the lack of research (Bagheri Nejad et al. 2011). However, it was estimated that the incidence of bloodstream infections (up to 14.8%) in developing countries in Africa was up to twice as high as the average European prevalence (7.1%) (ECDC 2008). The studies cited were not correlated with each other with respect to the microbiological data; the major BSI-associated pathogens presented, such as *Pseudomonas aeruginosa*, *E. coli*, *K. pneumoniae*, *Enterobacter* spp., and *S. aureus,* varied among papers (Bagheri Nejad et al. 2011). Besides, the most recent investigations showed a significant increase in CoNS prevalence in BSI episodes in Africa. Labi et al. (2016) showed a high number of positive blood culture samples (21.9%) among neonates, and the significant pathogens were CoNS. Nanoukon et al. (2017) obtained similar results in Benin, where *S. haemolyticus* and *S. epidermidis* were identified as the most frequently isolated pathogens. Similar results were also obtained in Egypt and Malawi (Mashaly and El-Mahdy 2017; Musicha et al. 2017). CoNS were confirmed as a major pathogen isolated in further investigations on smaller groups of patients, mostly neonates in Egypt and Ethiopia (Seliem and Sultan 2018; Sorsa et al. 2019). In contrast, a study from Zambia reports that the most frequent pathogen isolated from neonates with sepsis was *Klebsiella* sp. (Kabwe et al. 2016).

Australia. The rate of healthcare-associated BSIs in Australia is lower than reported elsewhere in the world, which was confirmed by a study in Queensland on 23 public hospitals and by research conducted by the Victorian Healthcare Associated Infection Surveillance System (VICNISS) Coordinating Centre in Victoria (Si et al. 2016; Gowda et al. 2017; Worth et al. 2018). Papers showed that the most frequently reported pathogens responsible for BSI episodes were CoNS, from 18.4 to 24.2%, and *S. aureus,* from 15.2 to 16.1%.

The distribution of all of the aforementioned staphylococcal bloodstream infections is presented in Table I.

S. aureus is one of the most frequent bloodstream infection agents

According to the ECDC report, *S. aureus* is one of the major agents causing bloodstream infections in Europe. Based on the studies conducted in 25 European countries, the ECDC estimated the dynamic changes in *S. aureus* clones associated with BSI episodes. The report states that the *S. aureus* BSI infection mortality rate was 19.4% of the episodes' total number. Moreover, as expected, the MRSA all-cause mortality (24.4%) was higher than that of MSSA infections (17.1%).

***Spa* types related to *S. aureus* from BSI in Europe.** ECDC also estimated 20 of the most frequent MRSA and MSSA *spa* types. The first group included the

5 most frequent *spa* types, namely, t032 (ST22, 17.9%), t003 (ST225, 8.8%), t008 (ST8, 8.4%), t002 (ST5, 7.7%), and t067 (ST125, 4.4%). Interestingly, the significant increase in incidence was related to the multilocus variable number of tandem repeats analysis type (MLVA type) ST22, and this lineage constituted 36% of the top-ranking isolates in 2011. This MRSA clone was first identified in England and was further detected in Ireland, Germany, Hungary, Portugal, and Northern Italy. The fifth most abundant *spa* type t067 was firstly described in Spain (Grundmann et al. 2014). In comparison, the rates of MSSA *spa*-type frequency were lower than those of MRSA isolates, and the 7 most popular types were t091 (ST7, 5.3%), t084 (ST15, 4.7%), t002 (ST5, 4.6%), t015 (ST45, 3.7%), t008 (ST8, 3.7%), t012 (ST30, 3.4%), and t0127 (ST1, 3.2%) (Grundmann et al. 2014). Two *spa* types (t008 and t002) were present in both MRSA and MSSA infections, which was probably a result of the high overall global frequency of these types, according to Ridom SpaServer (www.spaserver.ridom.de).

***Spa* types related to *S. aureus* from BSI in Poland.** *S. aureus*, a key pathogen in BSI episodes, was also identified in a study conducted by our group (Ilczyszyn et al. 2016). This study, performed on neonates and children in Poland, showed the most frequent MRSA genotype to be *spa* type t003-CC5, which is consistent with the data presented by ECDC. Among MSSA strains, the most frequent genotypes belonged to the following *spa* types: t091-CC7, t037-CC30, t008-CC8, and t240-CC10. Additionally, some of the observed genotypes exhibited age-related patterns, and the *spa* type t003, *spa*-CC 002, and CC5 were strongly associated with invasive infections in infants and young children (Ilczyszyn et al. 2016).

***Spa* types related to *S. aureus* from BSI outside Europe.** A study in China, performed for five years, examined *S. aureus* BSI samples and identified the most frequent *S. aureus* spa types and virulence factors. According to these data, the most frequent MRSA *spa* type in China was t030/t037, belonging to MLVA type ST239. These isolates also harbored SCC*mec* III cassette, which represents the hospital-acquired strains, and an *agr* system I. In comparison, the most frequent Chinese MSSA isolates presented the t318 type ST188 and also harbored *agr* I (Liu et al. 2018).

Latin American research divided the most numerous MRSA strains into three clades (A, B, and C) based on phylogenetic reconstruction. Strains in clade A belonged to ST5, ST105, and ST1011, and a majority of these strains harbored the gene cassette SCC*mec* I or II (HA-MRSA). Clade B consisted of the MLS types ST8, ST88, ST97, and ST72, accompanied by SCC*mec* IV variants. The last clade included Argentinian strains belonging to ST30 (Arias et al. 2017).

Non-*S. aureus* staphylococci as bloodstream infection agents

Human skin is colonized by various staphylococcal species, although the most invasive is *S. aureus*, followed by *Staphylococcus auricularis*, *S. capitis*, *S. epidermidis*, *S. haemolyticus*, *Staphylococcus hominis*, *S. saprophyticus*, *Staphylococcus simulans* and *Staphylococcus warneri* (Yu et al. 2017). The CoNS are among the most commonly isolated microorganisms from blood samples. Compared to *S. aureus* strains, which are classified as invasive pathogens, the clinical significance of CoNS needs to be proven. It is essential to estimate whether the presence of CoNS represents true bacteremia or sample contamination. Many of the studies conducted have not estimated the real impact of CoNS associated with blood infections, mainly because these species are less frequent overall; have not identified these bacteria at the species level; or have not distinguished the species' differences. However, several studies have shown that CoNS can cause serious bloodstream infections (Grzebyk et al. 2013; Li et al. 2016; Szczuka et al. 2016). Therefore, host-specific capabilities and strain-specific features need to be reconsidered for an improved understanding of the course of every particular infection, as under favorable conditions, CoNS species may become highly pathogenic (Becker et al. 2014).

CoNS as BSI agents in Europe. A study performed in Belgium showed that most isolated bloodstream infection-associated CoNS strains belonged to *S. epidermidis*, and 77% of these strains were identified as methicillin-resistant *S. epidermidis* (MRSE). All of these strains presented resistance to a wide range of antibiotics, especially erythromycin (*ermA*, *ermC*, and *msrA*), aminoglycosides (*aacA-aphD* and *aadC*), tetracycline (*tetK*), and mupirocin (*mupA*). Molecular typing of these strains assigned 85% of the MRSE strains to clonal complex (CC) 2, consisting of the ST2, ST5, ST59, and ST88 MLVA types (Deplano et al. 2016). Another study on *S. warneri* strains from Poland showed their wide range of pathogenicity factors. These strains were able to adhere to host cells, produce biofilms, invade and destroy epithelial cells, which strongly facilitated bacterial persistence (Szczuka et al. 2016). This finding warrants reconsideration of the role of CoNS in bloodstream infections.

CoNS as BSI agents in the USA. In studies conducted in the USA, many CoNS isolates (n = 602) were found in blood samples from years 2013–2014. The most frequently isolated strains belonged to *S. epidermidis*, *S. lugdunensis*, *S. hominis*, and *S. capitis* (Sader et al. 2016). A high number of blood samples was also analyzed in Japan by Yamada et al. (2017), and 314 methicillin-resistant CoNS (MRCoNS) strains were found. Among the Japanese strains, the predominant strains

belonged to *S. epidermidis* (78.6%), *S. haemolyticus* (14.3%), and *S. capitis* subsp. *ureolyticus*. A high number of CoNS-associated BSI episodes and increasing resistance rate should also be confirmation of the danger based on the presence and spread of these bacteria.

Conclusions

Staphylococci are among the most frequent pathogens causing bloodstream infections, which can advance to sepsis and are often observed in patients with indwelling medical devices or neonates. A high number of *S. aureus* and CoNS-related BSI episodes in high-risk patients had evidenced a significant challenge for clinicians. Many institutions widely document BSI episodes, and there has not been a worldwide decrease in these episodes. It is vital to improve existing prevention and control programs based on analysis of the data to implement standard diagnostic methods and conduct research on etiological factors, including via the usage of advanced genetic methods.

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Authors' contributions

JM and MKS brought the idea of the project. KL-Ł and MKS performed the literature research and data analysis. KL-Ł, JM and MKS drafted the work. RL provided clinical consultation of the data. All authors critically revised the work.

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Conflict of interest

The authors do not report any financial or personal connections with other persons or organizations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

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