OPEN ACCESS

Review Article

Clinical characteristics of Staphylococcus epidermidis: a systematic review

Klinische Charakterisierung von Staphylococcus epidermidis: ein systematisches Review

Abstract

Staphylococci are known as clustering Gram-positive cocci, nonmotile, non-spore forming facultatively anaerobic that classified in two main groups, coagulase-positive and coagulase-negative. *Staphylococcus epidermidis* with the highest percentage has the prominent role among coagulase-negative Staphylococci that is the most important reason of clinical infections. Due to various virulence factors and unique features, this microorganism is respected as a common cause of nosocomial infections. Because of potential ability in biofilm formation and colonization in different surfaces, also using of medical implant devices in immunocompromised and hospitalized patients the related infections have been increased. In recent decades the clinical importance and the emergence of methicillin-resistant *Staphylococcus epidermidis* strains have created many challenges in the treatment process.

Keywords: coagulase-negative staphylococci, Staphylococcus epidermidis, nosocomial infections, virulence factors

Zusammenfassung

Staphylokokken sind ein Cluster Gram-positiver unbeweglicher nicht Sporen-bildender fakultativ anaerober Kokkenbakterien, die in die zwei Hauptgruppen Coagulase-positiv and Coagulase-negativ unterteilt werden. *Staphylococcus epidermidis* nimmt mit dem höchsten Anteil eine prominente Stellung unter den Coagulase-negativen Staphylokokken ein und ist die wichtigste Ursache klinisch manifester Infektionen. Auf Grund der verschiedenen Virulenzfaktoren und der besonderen Eigenschaften ist diese Species häufig Ursache nosokomialer Infektionen. Auf Grund der Fähigkeit zur Biofilmbildung und der Kolonisation auf verschiedenen Oberflächen sowie auf Grund des zunehmenden Einsatzes von Implantaten bei hospitalisierten und speziell bei immunkompromittierten Patienten ist ein Anstieg derartiger Infektionen zu verzeichnen. In den letzten Jahrzehnten stellen die klinische Bedeutung und die Entstehung von Methicillin-resistenten *Staphylococcus epidermidis*-Stämmen neue Herausforderungen an den Behandlungsprozess.

Schlüsselwörter: Coagulase-negative Staphylokokken, Staphylococcus epidermidis, nosokomiale Infektion, Virulenzfaktoren

Amirmorteza Ebrahimzadeh Namvar[1]
Sara Bastarahang[2]
Niloufar Abbasi[2]
Ghazaleh Sheikhi Ghehi[2]
Sara Farhadbakhtiarian[2]
Parastoo Arezi[2]
Mahsa Hosseini[2]
Sholeh Zaeemi Baravati[2]
Zahra Jokar[2]
Sara Ganji Chermahin[2]

1 Department of Microbiology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

2 Department of Microbiology & Biochemistry, Islamic Azad University Falavarjan Branch, Isfahan, Iran

Introduction

First time in 1882 the *Micrococcus* name was used to introduce the bacterial inflammation for determining the differences between Cocci chains and clusters by Ogston [1]. Rosenbach in 1884 named the Cocci which produced white colonies on blood agar plates as *Staphylococcus albus*, thereafter in 1891 *Staphylococcus epidermidis albus*, in 1908 *Albococcus epidermidis* and *Staphylococcus epidermidis* in 1916 were used by Welch et al. [2]. On the other hand the Kocur investigations revealed the relationship between nucleoside phosphotransferase, GC content and arginine-glutamic acid decarboxylase analysis [3], although Jeffries et al. focused on lysozyme and novobiocin susceptibility in Staphylococci and Micrococci [4]. Later, susceptibility to erythromycin (0.4 µg/ml), lysostaphin (200 µg/ml) and lysozyme (25 µg/ml) were used to differentiate the Staphylococci from Micrococci.

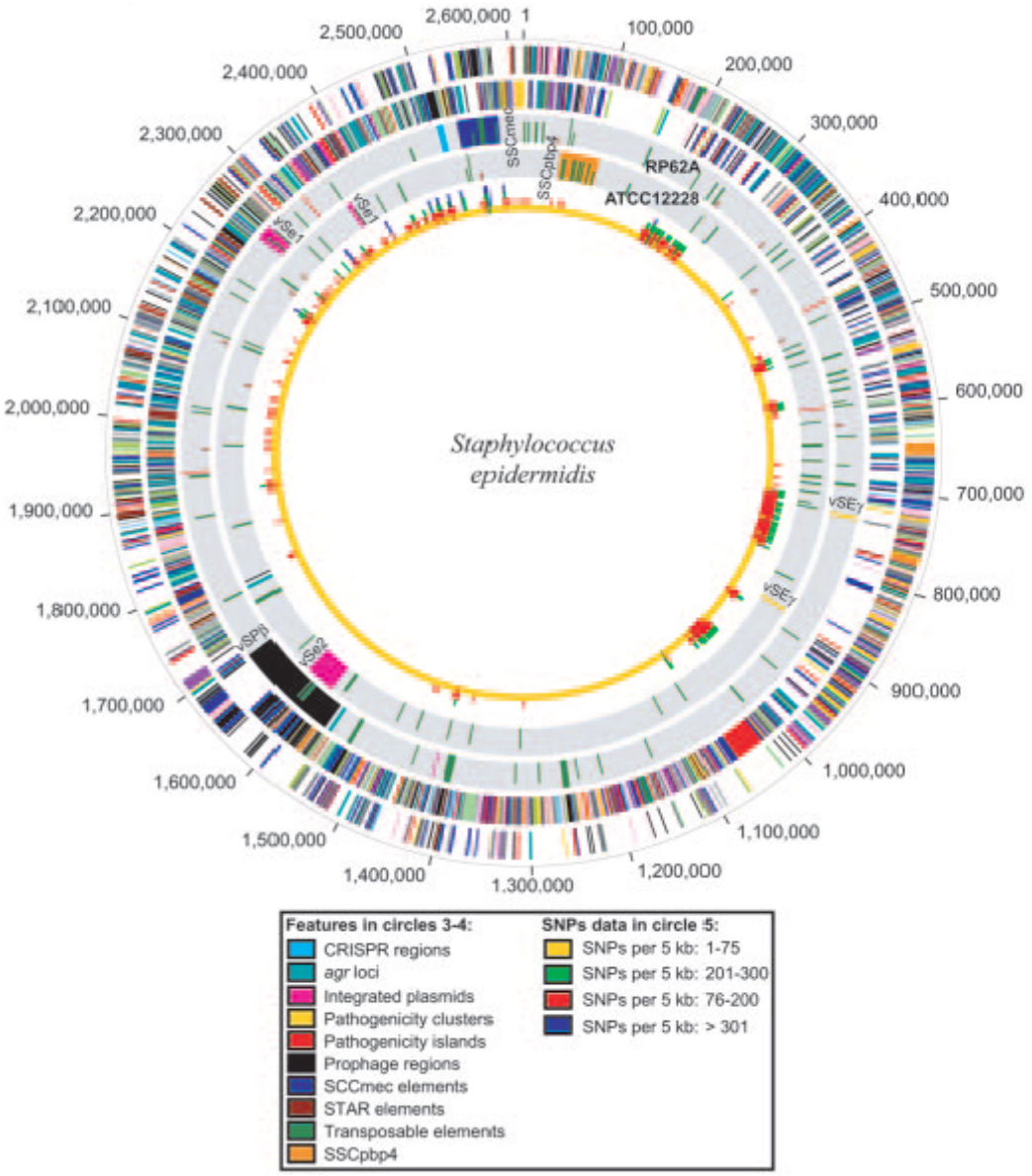

Figure 1: Circular representation of the sequenced *S. epidermidis* genome. Complete DNA sequence of *S. epidermidis* was obtained from GenBank accession numbers (AE015929).

According to Andrewes and Gordon studies *Staphylococcus* with human sources were separated to four species based on various pigments and also the ability of pathogenicity in guinea pig which were as follows: *Staphylococcus pyogenes*, *Staphylococcus epidermidis albus, Staphylococcus salivarius* and *Scurf staphylococci* [5]. Currently over than 40 species have been classified in this genus in which the *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Staphylococcus saprophyticus* are clinically prominent. Recently the classification of *Staphylococcus* and related microorganisms are based on amino acid sequences, DNA-DNA hybridization, the GC content, biochemical components, cell wall structure and molecular characterizations.

Genome structure

In recent years the complete genome of *S. epidermidis* (strain RP62A) was sequenced by using a random shotgun method which contains 6 rRNA operons, 32% (C+G) content and 2.616.530 bp chromosomal length [6]. Among of various identified plasmids that encode different resistance genes, the *vSe1* and *vSe2* in both RP62A and ATCC12228 strains are the most important ones by coding the cadmium and surface adhesion proteins [6]. On the other hand one of the virulence factors, the CAP operon, in *Bacillus anthracis* has either investigated in *S. epidermidis* [6]. The circular genome of *S. epidermidis* is illustrated in Figure 1.

Cell structure and metabolism

Due to *S. epidermidis* cell wall specificity, the teichoic acids which consist of ribitol or glycerol with phosphodiester bonds are attached to peptidoglycan by covalent connections and also the existence of glycerol teichoic acid glucosyl in structural components compare to other bacteria are momentous, so by using lysostaphyn enzyme verifying the *Staphylococcus* from *Micrococcus* is easily possible. Although this bacterium can use glucose for growing in anaerobically condition, but producing of coagulase and other agents like mannitol fermentation is negative, while in aerobically situation, the acid production is occurring from different carbohydrates (fructose, maltose, sucrose, and glycerol).

Ecology

Staphylococcus epidermidis which is known as a coagulase-negative and Gram-positive Staphylococcus, is one of the five significant microorganisms that are located on human skin and mucosal surfaces with the ability of causing nosocomial infections due to the wide usage of medical implants and devices, hence until 1980 *S. epidermidis* was considered as an opportunistic microorganism, while in accordance to various infections increasement such as cardiovascular, CNS shunts, joints, blood stream infections, etc. The mentioned bacteria is regarded as one of the main cause of nosocomial infections [7]. Later researches show that the activity of *Staphylococcus epidermidis* lipase enzyme can produce various types of esters such as geranyl, unsaturated and medium-chain esters without organic solvents; therefore this ability can be considered as an advantage in the biotechnology field of studies [8]. Investigators proved that when *S. epidermidis* has been treated with n-propanol, propanol/ethanol/chlorhexidine and alcohols this bacterium is no more alive in biofilms. Five minutes incubation in hydrogen peroxide solution in comparison to povidine-iodine reduces the mass of live cells respectively. Subsequently hydrogen peroxide (3%) and also (5%) is one of the most effective method for removing the *S. epidermidis* accumulation from surfaces by reducing the biofilms amount [9].

Virulence factors

The most significant virulence factors in *S. epidermidis* are described as below:

- Biofilms: The bacterial surface adhesive accumulation that is embedded in an extracellular matrix that creates the bacteria protection against host defense mechanisms and antimicrobial agents. Reducing the permeability, decreasing cell division and protein synthesis, anti phagocytic activity and antimicrobial barrier function are considerable specificities of biofilms. Recently is shown that *S. epidermidis* biofilm contains a large number of persistent cells that protect the microorganism against neutrophil dependent killing and complement system inactivation via deposition of C3b and immunoglobulin G [10]. Ability for biofilm formation, bacterial adaptation for surviving and pathogenicity are depending on the TCSs (two-component signal transduction systems). 17 TCSs have been distinguished in *S. epidermidis* ATCC12228 or ATCC35984. Negative regulation of biofilm formation is related to TCS *agrC*/agrA [11], [12], fibrinogen (SdrG/Fbe) and the other factors which are mediated by MSCRAMMs [13].
- PIA: The main element of extracellular matrix slime substance is PIA (polysaccharide intercellular adhesion) which is produced by *ica* gene operon products *(icaA*, *icaD*, *icaB*, and *icaC*). The *ica* gene expression is regulated by the *icaR* component and also it's noticeable that *icaD* is necessary for *icaA* activity however the partial role of *icaD* is still unknown. It should be mentioned that poly-N-acetylglucosamine (PNAG) is the same name of PIA [14].
- Bap/Bhp: One more virulence factor of *S. epidermidis* in biofilm accumulation is Bap (biofilm associated protein) which is known as a surface adhesion protein that commonly found in *S. epidermidis* strains, while in *Staphylococcus aureus* the bovine mastitis isolates are the only strains that harbor the Bap [15].
- Poly-γ-glutamic acid (PGA): According to researches since 2005 the role of this factor in phagocytosis inhibition and evading from the host immune system was discovered only in *Bacillus anthracis*, although currently this factor is acquired in *S. epidermidis*. PGA is remained from glutamic acid as a linear homopolymer which is bound to each other through the γ-carboxy group of glutamic acid and comprised of equal quantity of D- and L-glutamic acid [16].
- Toxins: The most recent pathogenicity island (SePI) in clinical *S. epidermidis* strains containing staphylococcal enterotoxin-like toxin L (SEIL) and C3 enterotoxin (SEC3), have been found [17].
- Phenol-soluble modulins (PSMs): These groups of amphipathic, α helical peptides are present in all pathogenic Staphylococci and are able to lyse the white and red blood cells, also the cytokines expression, activation of human neutrophils and inflammatory response are the other specificity of PSMs [18]. The mass spectrometry and Edman degradation are the powerful techniques for PSMs identification. By using these methods six elements of PSMs have been determined in *S. epidermidis* that the PSMδ is known as the most significant cytolysin [19].
- Delta-Toxin: Delta-toxin with cytolytic activity in blood cell lysis is responsible for hemorrhagic enterocolitis in the neonatal intensive care unit that can enhance the virulence potential of *S. epidermidis* and may lead to endemic and epidemic infections in different wards of hospitals [20].
- Clpxp: This virulence factor has a protease activity in biofilm formation in several bacteria such as *S. epider-*

midis. The Spx factor which belongs to the global regulatory system with the negative effects on biofilm and PIA production can inhibit clpP and clpX, also the responsibility of this factor is more apparent in comparison to stress response [21].

- Embp: Is an extracellular matrix binding protein which can mediate the biofilm accumulation and fibronectin attachment with an additional role in *S. epidermidis* [22], while Aps AMP and SepA protease regulation are helpful for *S. epidermidis* persistent in neutrophils [19].

Accumulation-associated protein (Aap), extracellular matrix-binding protein (Embp), poly-β-6, 1-N-acetyl-D-glucosamine (PNAG), lipase, glutamic serine protease and cysteine protease are the other significant virulence factors.

Typing methods

The existing of some specificity such as frequency isolation from several patients with similar markers and clones, virulence factors, source of epidemic infections and the pathogenesis mechanism in S. *epidermidis* as an important nosocomial infections have been led to various typing methods, for instance plasmid and restriction endonuclease enzyme analysis, DNA hybridization, RAPD, SCCmec typing, PFGE and MLST. It's noticeable that the antibiotic resistance profile, biotyping, serotyping and phage typing are the conventional methods.

- Restriction endonuclease analysis: The ability of this method is producing the nucleotide sequence complementary data for plasmid identity approving in different strains by cleaving the palindromic base sequences on specific sites [23].
- Ribotyping: This type of the southern hybridization method contains ribosomal RNA (rRNA) genes fingerprinting. Lysing the genomic DNA with restriction enzymes is the first conducted step. Electrophoresis of DNA fragments, transferring onto nylon membrane and DNA labeled probe hybridization with specific 16s and 23s rRNA are the next steps in ribotyping [24].
- Pulsed-field gel electrophoresis: Is one of the usual primary molecular typing methods which are used in Staphylococcal epidemiology outbreak infections and clinical investigations in a short period of time [25].
- Multilocus sequence typing: Presently this sensitive molecular analysis technique which is based on evaluating different alleles by seven specific housekeeping genes to study allele profiles to determining different sequence types (ST) is preferred for *S. epidermidis* typing pattern. Despite three main considered methods for MLST, the most specific one was described by Thomas in 2007 [26].
- Multiple-locus variable-number tandem repeat analysis: Another molecular typing method is MLVA with the basis of variable numbers of tandem repeats (VNTR) evaluation. Johansson for the first time used five VTR loci (se^1–se^5) in MLVA for *S. epidermidis* [27].
- RAPD: Random amplified polymorphic DNA is a type of modified PCR method in which the short random sequences are able to anneal to different locations of whole genome and can produce a wide range of amplified PCR products [28].
- SCCmec typing: Resistance to methicillin in *S. epidermidis* which is encoded with the presence of the mecA gene is related to a penicillin binding protein ($PBP2_a$). This protein in comparison with other types has a low affinity for binding to beta-lactam antibiotics [29]. The origin of this gene is still unknown, although due to the high homology (88%) of mecA in the *Staphylococcus sciuri* with other coagulase-negative Staphylococci, the existence of the same origin of this resistance gene is probable. Currently coagulase-negative Staphylococci (CoNS), especially *S. epidermidis* are considered as a capable reservoir for transferring the mec gene between the species of Staphylococci [30]. The mec operon consists of mecA, mecI and mecR1 is located on staphylococcal cassette chromosome mec (SCCmec). SCCmec typing, which classifies SCCmec elements on the basis of their structural differences, is considered as a powerful tool for epidemiological studies of Staphylococcal methicillin-resistant strains [31]. Based on sequence diversity of the mentioned areas; the SCCmec element is classified to (I to XI) different types. The SCCmec is integrated on a specific site in the Staphylococcal chromosome called attBscc (bacterial chromosomal attachment site) which is located at the 3' section of the open reading frame X (orfX) [32]. The SCCmec structure contains mec gene complex, ccr gene complex and the junkyard region [33]. The ccr gene complex region involves CCR protein and invertase-resolvase enzymes family that is responsible for mobile elements transferring. According to the ccr genes composition, ccrA-ccrB and ccrC are reported as two separate complexes [34]. The mec gene complex with two different progression lineages is evaluated that the class (A) which is known as the major part of mec complex that includes an insertion sequence IS431 and also the hyper-variable region is the important section [35]. Insertion of IS, IS1272 or IS431 elements in regulatory part of mecA gene is the origin of the differences between mec gene complexes. Due to the variety of mecI-mecR1 regional structure five main classes (A, B, C1, C2 and D) of mec gene complex have been described by IGW-SCC [36]. The J regions which were named "junkyard" despite of less functional importance have the high epidemiological efficient because of their significant role in transferring the resistance encoding genes to heavy metal and additional antibiotics [37]. The three SCCmec elements typing methods with different basis have been identified as follows:

Table 1: Biochemical and laboratory characteristics of the *Staphylococcus* spp.

Test	*S. aureus*	*S. epidermidis*	*S. haemolyticus*	*S. lugdunensis*	*S. saprophyticus*	*S. schleiferi*	*S. simulans*
Colony pigment	+	–	d	d	d	–	–
Staphylocoagulase	+	–	–	–	–	–	–
Clumping factor	+	–	–	(+)	–	+	–
Heat-stable nuclease	+	–	–	–	–	+	–
Alkaline phosphatase	+	+	–	–	–	+	(d)
Pyrrolidonyl arylamidase	–	–	+	+	–	+	+
Ornithine decarboxylase	–	(d)	–	+	–	–	–
Urease	d	+	–	d	+	–	+
β-Galactosidase	–	–	–	–	+	(+)	+
Acetoin production	+	+	+	+	+	+	d
Novobiocin resistance	S	S	S	S	R	S	S
Polymyxin B resistance	S	R	S	S/R	S	S	S
Acid (aerobically from)							
D-Trehalose	+	–	+	+	+	d	d
D-Mannitol	+	–	d	–	d	–	+
D-Mannose	+	(+)	–	+	–	+	d
D-Turanose	+	(d)	(d)	(d)	+	–	–
D-Xylose	–	–	–	–	–	–	–
D-Cellubiose	–	–	–	–	–	–	–
Maltose	+	+	+	+	+	–	(±)
Sucrose	+	+	+	+	+	–	+

Modified from Bannerman TL: Staphylococcus, micrococcus, and other catalase: positive cocci that grow aerobically. In Murray PR et al, editors: *Manual of clinical microbiology*, ed 8, Washington, DC, 2003, ASM Press.
+, 90% or more strains positive; ±, 90% or more strains weakly positive; –, 90% or more strains negative; *d*, 11% to 89% of strains positive; ( ), delayed reaction; *R*, resistant; *S*, sensitive.

- The restriction enzymes digestion methods
- Multiplex PCR methods
- Methods based on real-time PCR
  The hybridization method of mecA and Tn554 probes were used for the first time for polymorphism investigation of mecA gene [38], while in other methods the J regions and mec classes in addition ccr types were studied as two separate pathways. For instance the Oliveira, Zhang, Boye, Kondo and Milheirico are the most important methods in this group [34], [39], [40], [41], [42], [43]. In the real-time PCR technique which was conducted by Francois in 2004, the ccrB was selected as the target of the study [44].

Laboratory diagnosis

Coagulase-negative Staphylococci particularly *Staphylococcus epidermidis* are the saprophytic microorganisms that isolated with high frequency from the bloodstream and the other various sources may cause the true invasive infections. Determining the differences between *S. aureus* and *S. epidermidis* infections are valuable in discrimination of highly contaminated and true bacteremia infections, hence the rigorous and rapid diagnosis of the main cause of infection in clinical microbiology laboratories is exactly essential [45]. In past decades studies based on bacterial colony identification, microbiological culture medium, Gram staining, catalase test, coagulase and phosphatase activity, nitrate reductase, DNase, TNase, acid production from carbohydrates (D-trehalose, sucrose, maltose, D-mannitol, D-xylose), tolerance to 10–15% NaCl, hemolytic activity on 5% blood sheep (Table 1), antibiotic sensitivity test to polymyxin B and novobiocin for detection of CoNs specially *S. epidermidis* isolates were more common [46], while some investigators in microbiological laboratories have identified *Staphylococcus epidermidis* with high sensitivity and specificity by using complex medium containing trehalose, mannitol, phenol and phosphate in a single agar plate [47], [48]. Currently most of typical traditional methods as mentioned above are used for detection of Staphylococci species, for instance the tube coagulase test can directly detect this enzyme from blood samples but due to common culturing and prepared dilution methods the sensitivity range of the test is reported from 62 to 100% [48], [49]. Analysis of fatty acids is another diagnostic method for determining *S. aureus* isolates, while in coagulase-negative Staphylococci this kind of identification usually fails. However despite certain *S. epidermidis* strains with phosphatase negative reaction are often misidentified with *S. hominis* [50]. Commercial kits almost known as the rapid and miniaturized systems methods for identification of *S. epidermidis* such as: API Staph-Ident, API Staph-Trac, Sceptor Gram-Positive MIC/I, Vitek GPI Card and Minitek Gram-Positive System. Rapid molecular methods for example peptide nucleic acid (PNA), fluorescence in situ hybridization (FISH), etc. prepare results in less than 2 hours. It's about more than one decade that the PNA FISH technique has been used in clinical labs, because of the limitation of PNA FISH [51], [52] additional

alternative methods are being used. In QuickFISH method the coagulase-negative Staphylococci are determined in <30 minutes with blood culture containing tubes that specific probes are the advantage of this method. In many researches despite DNA hybridization and 16s rRNA analysis, ERIC and BOX-PCR have been used as a complementary methods [53].

Staphylococcus epidermidis infections

Due to lack of information about *S. epidermidis* life cycle, many studies have been conducted for identification of the pathogenecity mechanisms and the related infections of this microorganism [54]. This bacterium is known as the major cause of medical implant device infections such as peripheral or central intravenous catheters (CVCs) [54]. In accordance to performed researches in United States, at least 5 cases of bloodstream infections of 1,000 CVC in ICU, the 22% of mentioned infections are correlated by *Staphylococcus epidermidis* [54]. On the other hand this microorganism may play a significant role in shunt, prosthetic joint, vascular graft and surgical site infections [55]. Eye keratitis and endophthalmitis of contaminated contact lens, urinary catheter infections [56]; bacteremia, mediastinitis and other infections are associated with *S. epidermidis*. Existence of *S. epidermidis* high frequency on human skin microflora, extensive colonization on epithelial cells and also various virulence factors can considered as the main reasons of these infections [57].

Antibiotic resistance

One of the most significant events in clinical microbiology is the antimicrobial resistance emergence in nosocomial pathogens. There are many various resistance mechanisms in bacteria; hence some of them may be intrinsically resistant to certain antibiotics or to more than one class of antimicrobial agents. However the mutation and acquired antimicrobial resistance genes from the other microorganism are the considerable ways of achieving the antimicrobial resistance [58]. In this circumstance, the role of exopolysaccharide matrix or ability of biofilm formation which is produced by some of the pathogenic bacteria, especially *S. epidermidis* to reduce the permeability and penetration of antibiotics is very important [59]. During the last two decades, according to significant changes of medical implant device usage, indiscriminate uses of broad-spectrum antibiotics especially the Beta-lactams family [60] in immunocompromised patients and also predisposing factors in high risk cases [61]. The emergence of *S. epidermidis* as an opportunistic pathogen is very critical. The Beta-lactam antimicrobial drugs can be inactivated by the following three mechanisms:

- Bacterial Beta-lactamase enzymes
- Change of main target of antibiotics with PBP2a
- Permeability modification.

While anti-staphylococcal penicillins such as methicillin and oxacillin were considered as the first-line therapy options, the emergence of methicillin-resistant Staphylococci have impacted the concerns in healthcare units [62]. For the first time resistance to methicillin was reported in 1961. In a study which was conducted by Guisti et al. in 1999, methicillin resistance ratio reported (48.6%) [63]. Resistance to mentioned antimicrobial groups has been increasing more and more, for instance in Finland in 1983 the resistance percent (28%) was raised up to (77%) in 1994 respectively [64]. Currently 75 up to 90 percent of *S. epidermidis* isolates from various nosocomial infections in most European and American countries are methicillin-resistant strains [65]. The gene with 30 to 50 Kb in methicillin-resistant *Staphylococcus* is related to *mec* and consists of mecA and the other genes, which is encoding the PBP2a, is responsible for methicillin-resistant strains [66]. Recently the CoNS particularly *S. epidermidis* are known as a potential source for transferring of *mec* gene among *Staphylococcus* spp. These claims are proven by following reasons:

- The SCCmec elements high frequency and diversity in CoNS
- Existence of various ccrs
- The high prevalence of MRSE in comparison to others [67].

Resistance to quinolones such as ciprofloxacin [68], ofloxacin [69], fusidic acid and other antimicrobial agents like vancomycin is still rising. It should be noted that resistance to fusidic acid is associated with the mechanism of target site modification and protection by *fusA*, *fusE* [70], [71] and FusB family proteins *(fusB*, *fusC* and *fusD)* [72].

Prevention and treatment

Apparently *Staphylococcus epidermidis* is regarded as one of the most biomaterial-associated infection (BAI) reasons. Also extracellular polysaccharides production and biofilm formation increase the bacterial stability on different surfaces therefore the antibiotic penetration will be prevented [73]. Despite of antibiotic treatment and elimination of related infection factors the medical implant infections are extremely resistant to antimicrobial agents. Although antimicrobial prophylaxis is significant remedy to prevent (BAI) but emerging of antibiotic resistance is the concerning issue. The Archer and Tenenbaum study showed that widespread use of antibiotics in cardiac surgery patients as prophylaxis raised the resistance range of *S. epidermidis* to beta-lactam agents such as methicillin, however new strategies are required to prevent and treat the related infections [74]. The cationic antimicrobial peptides (Amps) with intercellular targets or mechanism of cell membrane destruction and also the

bactericidal peptides with domains banding lipopolysaccharides basis as BP2 decrease the *S. epidermidis* stamina in (BAI) and peri-implant tissues, on the other hand due to conducted researches the furanones complex has the potential to reduce the biofilm formation in *S. epidermidis* [75]. One of the oxazolidinone antibiotic classes is linezolid with the remarkable role against various pathogens specifically methicillin-resistant Staphylococci and glycopeptide-resistant cocci. The mentioned drugs prevent the protein producing process by inhibiting the 70s initial complex. This agent has a wide usage in bones and joints infection treatment [76]. Presently some compounds with antimicrobial effects such as, *N*-acetylcysteine (NAC), cinnamon oil and farnesol are very substantial in reducing biofilm formation and intercellular adhesions [77]. Vancomycin, linezolid, daptomycin, tigecycline, quinupristin/dalfopristin and dalbavancin are known as very important medicines for *S. epidermidis* infections treatment. Furthermore another effective drug in biofilm formation reducing is rifampicin but this factor has the disadvantage of fast spread of antibiotic resistance. It should be noted that low resistance has been observed in streptogramins, linezolid and tigecycline [78].

Conclusion

According to increasment of coagulase-negative Staphylococci importance particularly *S. epidermidis* as an agent of nosocomial infections, further clinical and experimental studies in different fields such as mechanism of transmission, ecology, virulence factors, typing methods and antimicrobial resistance mechanism are needed. However the prevention and treatment of *S. epidermidis* infections should depend on our knowledge about the reservoirs, epidemiology, and host defenses against these microorganisms.

Notes

Competing interests

The authors declare that they have no competing interests.

Acknowledgment

We thank Amirhossein Ebrahimzadeh Namvar for all supports.

References

1. Newsom SW. Ogston's coccus. J Hosp Infect. 2008 Dec;70(4):369-72. DOI: 10.1016/j.jhin.2008.10.001
2. Bannerman TL. Staphylococcus, Micrococcus, and other catalase-positive cocci that grow aerobically. In: Murray PR, Baron EJ, Jorgensen JH, Pfaller MA, Yolken RH, editors. Manual of clinical microbiology. 8th ed. Washington, DC: ASM Press; 2003. p. 384–404.
3. Komagata K, Kocur M. The nucleoside phosphotransferase test and the differentiation of staphylococci and micrococci. Spisy. 1967;40:236.
4. Jeffries L. Menaquinones in the classification of Micrococcaceae, with observations on the application of lysozyme and novobiocin sensitivity tests. Int J Syst Bacteriol. 1966;19:183-8. DOI: 10.1099/00207713-19-2-183
5. Andrewes FW, Gordon MH. Report on the biological characters of the staphylococci pathogenic for man. In: 35th Annual Report of the Local Government Board, Bd 1905-6. APP. B. H.M. Stationery Office; 1907. p. 543-60.
6. Gill SR, Fouts DE, Archer GL, Mongodin EF, Deboy RT, Ravel J, Paulsen IT, Kolonay JF, Brinkac L, Beanan M, Dodson RJ, Daugherty SC, Madupu R, Angiuoli SV, Durkin AS, Haft DH, Vamathevan J, Khouri H, Utterback T, Lee C, Dimitrov G, Jiang L, Qin H, Weidman J, Tran K, Kang K, Hance IR, Nelson KE, Fraser CM. Insights on evolution of virulence and resistance from the complete genome analysis of an early methicillin-resistant Staphylococcus aureus strain and a biofilm-producing methicillin-resistant Staphylococcus epidermidis strain. J Bacteriol. 2005 Apr;187(7):2426-38. DOI: 10.1128/JB.187.7.2426-2438.2005
7. von Eiff C, Peters G, Heilmann C. Pathogenesis of infections due to coagulase-negative staphylococci. Lancet Infect Dis. 2002 Nov;2(11):677-85. DOI: 10.1016/S1473-3099(02)00438-3
8. Chang RC, Chou SJ, Shaw JF. Synthesis of fatty acid esters by recombinant Staphylococcus epidermidis lipases in aqueous environment. J Agric Food Chem. 2001 May;49(5):2619-22. DOI: 10.1021/jf001337n
9. Presterl E, Suchomel M, Eder M, Reichmann S, Lassnigg A, Graninger W, Rotter M. Effects of alcohols, povidone-iodine and hydrogen peroxide on biofilms of Staphylococcus epidermidis. J Antimicrob Chemother. 2007 Aug;60(2):417-20. DOI: 10.1093/jac/dkm221
10. Costerton JW, Lewandowski Z, Caldwell DE, Korber DR, Lappin-Scott HM. Microbial biofilms. Annu Rev Microbiol. 1995;49:711-45. DOI: 10.1146/annurev.mi.49.100195.003431
11. Zhang YQ, Ren SX, Li HL, Wang YX, Fu G, Yang J, Qin ZQ, Miao YG, Wang WY, Chen RS, Shen Y, Chen Z, Yuan ZH, Zhao GP, Qu D, Danchin A, Wen YM. Genome-based analysis of virulence genes in a non-biofilm-forming Staphylococcus epidermidis strain (ATCC 12228). Mol Microbiol. 2003 Sep;49(6):1577-93.
12. Handke LD, Rogers KL, Olson ME, Somerville GA, Jerrells TJ, Rupp ME, Dunman PM, Fey PD. Staphylococcus epidermidis saeR is an effector of anaerobic growth and a mediator of acute inflammation. Infect Immun. 2008 Jan;76(1):141-52. DOI: 10.1128/IAI.00556-07
13. Bowden MG, Chen W, Singvall J, Xu Y, Peacock SJ, Valtulina V, Speziale P, Höök M. Identification and preliminary characterization of cell-wall-anchored proteins of Staphylococcus epidermidis. Microbiology (Reading, Engl). 2005 May;151(Pt 5):1453-64. DOI: 10.1099/mic.0.27534-0
14. Lou Q, Zhu T, Hu J, Ben H, Yang J, Yu F, Liu J, Wu Y, Fischer A, Francois P, Schrenzel J, Qu D. Role of the SaeRS two-component regulatory system in Staphylococcus epidermidis autolysis and biofilm formation. BMC Microbiol. 2011;11:146. DOI: 10.1186/1471-2180-11-146

15. Tormo MA, Knecht E, Götz F, Lasa I, Penadés JR. Bap-dependent biofilm formation by pathogenic species of Staphylococcus: evidence of horizontal gene transfer? Microbiology (Reading, Engl). 2005 Jul;151(Pt 7):2465-75. DOI: 10.1099/mic.0.27865-0

16. Kocianova S, Vuong C, Yao Y, Voyich JM, Fischer ER, DeLeo FR, Otto M. Key role of poly-gamma-DL-glutamic acid in immune evasion and virulence of Staphylococcus epidermidis. J Clin Invest. 2005 Mar;115(3):688-94. DOI: 10.1172/JCI23523

17. Marraffini LA, Sontheimer EJ. CRISPR interference limits horizontal gene transfer in staphylococci by targeting DNA. Science. 2008 Dec;322(5909):1843-5. DOI: 10.1126/science.1165771

18. Vuong C, Dürr M, Carmody AB, Peschel A, Klebanoff SJ, Otto M. Regulated expression of pathogen-associated molecular pattern molecules in Staphylococcus epidermidis: quorum-sensing determines pro-inflammatory capacity and production of phenol-soluble modulins. Cell Microbiol. 2004 Aug;6(8):753-9. DOI: 10.1111/j.1462-5822.2004.00401.x

19. Cheung GY, Rigby K, Wang R, Queck SY, Braughton KR, Whitney AR, Teintze M, DeLeo FR, Otto M. Staphylococcus epidermidis strategies to avoid killing by human neutrophils. PLoS Pathog. 2010;6(10):e1001133. DOI: 10.1371/journal.ppat.1001133

20. Vuong C, Otto M. Staphylococcus epidermidis infections. Microbes Infect. 2002 Apr;4(4):481-9. DOI: 10.1016/S1286-4579(02)01563-0

21. Wang C, Fan J, Niu C, Wang C, Villaruz AE, Otto M, Gao Q. Role of spx in biofilm formation of Staphylococcus epidermidis. FEMS Immunol Med Microbiol. 2010 Jul 1;59(2):152-60. DOI: 10.1111/j.1574-695X.2010.00673.x

22. Schommer NN, Christner M, Hentschke M, Ruckdeschel K, Aepfelbacher M, Rohde H. Staphylococcus epidermidis uses distinct mechanisms of biofilm formation to interfere with phagocytosis and activation of mouse macrophage-like cells 774A.1. Infect Immun. 2011 Jun;79(6):2267-76. DOI: 10.1128/IAI.01142-10

23. Melter O, Santos Sanches I, Schindler J, Aires de Sousa M, Mato R, Kovárova V, Zemlicková H, de Lencastre H. Methicillin-resistant Staphylococcus aureus clonal types in the Czech Republic. J Clin Microbiol. 1999 Sep;37(9):2798-803.

24. Grimont F, Grimont PA. Ribosomal ribonucleic acid gene restriction patterns as potential taxonomic tools. Ann Inst Pasteur Microbiol. 1986 Sep-Oct;137B(2):165-75. DOI: 10.1016/S0769-2609(86)80105-3

25. Tenover FC, Arbeit RD, Goering RV, Mickelsen PA, Murray BE, Persing DH, Swaminathan B. Interpreting chromosomal DNA restriction patterns produced by pulsed-field gel electrophoresis: criteria for bacterial strain typing. J Clin Microbiol. 1995 Sep;33(9):2233-9.

26. Thomas JC, Vargas MR, Miragaia M, Peacock SJ, Archer GL, Enright MC. Improved multilocus sequence typing scheme for Staphylococcus epidermidis. J Clin Microbiol. 2007 Feb;45(2):616-9. DOI: 10.1128/JCM.01934-06

27. Johansson A, Koskiniemi S, Gottfridsson P, Wiström J, Monsen T. Multiple-locus variable-number tandem repeat analysis for typing of Staphylococcus epidermidis. J Clin Microbiol. 2006 Jan;44(1):260-5. DOI: 10.1128/JCM.44.1.260-265.2006

28. Bardakci F. Random amplified polymorphic DNA (RAPD) Markers. Turk J Biol. 2001;25:185-96.

29. Deurenberg RH, Stobberingh EE. The evolution of Staphylococcus aureus. Infect Genet Evol. 2008 Dec;8(6):747-63. DOI: 10.1016/j.meegid.2008.07.007

30. Aires de Sousa M, de Lencastre H. Bridges from hospitals to the laboratory: genetic portraits of methicillin-resistant Staphylococcus aureus clones. FEMS Immunol Med Microbiol. 2004 Mar 8;40(2):101-11. DOI: 10.1016/S0928-8244(03)00370-5

31. Tsubakishita S, Kuwahara-Arai K, Sasaki T, Hiramatsu K. Origin and molecular evolution of the determinant of methicillin resistance in staphylococci. Antimicrob Agents Chemother. 2010 Oct;54(10):4352-9. DOI: 10.1128/AAC.00356-10

32. Hiramatsu K, Cui L, Kuroda M, Ito T. The emergence and evolution of methicillin-resistant Staphylococcus aureus. Trends Microbiol. 2001 Oct;9(10):486-93. DOI: 10.1016/S0966-842X(01)02175-8

33. Hiramatsu K, Katayama Y, Yuzawa H, Ito T. Molecular genetics of methicillin-resistant Staphylococcus aureus. Int J Med Microbiol. 2002 Jul;292(2):67-74. DOI: 10.1078/1438-4221-00192

34. Chongtrakool P, Ito T, Ma XX, Kondo Y, Trakulsomboon S, Tiensasitorn C, Jamklang M, Chavalit T, Song JH, Hiramatsu K. Staphylococcal cassette chromosome mec (SCCmec) typing of methicillin-resistant Staphylococcus aureus strains isolated in 11 Asian countries: a proposal for a new nomenclature for SCCmec elements. Antimicrob Agents Chemother. 2006 Mar;50(3):1001-12. DOI: 10.1128/AAC.50.3.1001-1012.2006

35. Ito T, Katayama Y, Asada K, Mori N, Tsutsumimoto K, Tiensasitorn C, Hiramatsu K. Structural comparison of three types of staphylococcal cassette chromosome mec integrated in the chromosome in methicillin-resistant Staphylococcus aureus. Antimicrob Agents Chemother. 2001 May;45(5):1323-36. DOI: 10.1128/AAC.45.5.1323-1336.2001

36. International Working Group on the Classification of Staphylococcal Cassette Chromosome Elements (IWG-SCC). Classification of staphylococcal cassette chromosome mec (SCCmec): guidelines for reporting novel SCCmec elements. Antimicrob Agents Chemother. 2009 Dec;53(12):4961-7. DOI: 10.1128/AAC.00579-09

37. Malachowa N, DeLeo FR. Mobile genetic elements of Staphylococcus aureus. Cell Mol Life Sci. 2010 Sep;67(18):3057-71. DOI: 10.1007/s00018-010-0389-4

38. Leski T, Oliveira D, Trzcinski K, Sanches IS, Aires de Sousa M, Hryniewicz W, de Lencastre H. Clonal distribution of methicillin-resistant Staphylococcus aureus in Poland. J Clin Microbiol. 1998 Dec;36(12):3532-9.

39. Zhang K, McClure JA, Elsayed S, Louie T, Conly JM. Novel multiplex PCR assay for characterization and concomitant subtyping of staphylococcal cassette chromosome mec types I to V in methicillin-resistant Staphylococcus aureus. J Clin Microbiol. 2005 Oct;43(10):5026-33. DOI: 10.1128/JCM.43.10.5026-5033.2005

40. Boye K, Bartels MD, Andersen IS, Møller JA, Westh H. A new multiplex PCR for easy screening of methicillin-resistant Staphylococcus aureus SCCmec types I-V. Clin Microbiol Infect. 2007 Jul;13(7):725-7. DOI: 10.1111/j.1469-0691.2007.01720.x

41. Kondo Y, Ito T, Ma XX, Watanabe S, Kreiswirth BN, Etienne J, Hiramatsu K. Combination of multiplex PCRs for staphylococcal cassette chromosome mec type assignment: rapid identification system for mec, ccr, and major differences in junkyard regions. Antimicrob Agents Chemother. 2007 Jan;51(1):264-74. DOI: 10.1128/AAC.00165-06

42. McClure JA, Conly JM, Elsayed S, Zhang K. Multiplex PCR assay to facilitate identification of the recently described Staphylococcal cassette chromosome mec type VIII. Mol Cell Probes. 2010 Aug;24(4):229-32. DOI: 10.1016/j.mcp.2010.01.001

43. Milheiriço C, Oliveira DC, de Lencastre H. Multiplex PCR strategy for subtyping the staphylococcal cassette chromosome mec type IV in methicillin-resistant Staphylococcus aureus: 'SCCmec IV multiplex'. J Antimicrob Chemother. 2007 Jul;60(1):42-8. DOI: 10.1093/jac/dkm112

44. Francois P, Renzi G, Pittet D, Bento M, Lew D, Harbarth S, Vaudaux P, Schrenzel J. A novel multiplex real-time PCR assay for rapid typing of major staphylococcal cassette chromosome mec elements. J Clin Microbiol. 2004 Jul;42(7):3309-12. DOI: 10.1128/JCM.42.7.3309-3312.2004

45. Bates DW, Goldman L, Lee TH. Contaminant blood cultures and resource utilization. The true consequences of false-positive results. JAMA. 1991 Jan;265(3):365-9. DOI: 10.1001/jama.1991.03460030071031

46. Renneberg J, Rieneck K, Gutschik E. Evaluation of Staph ID 32 system and Staph-Zym system for identification of coagulase-negative staphylococci. J Clin Microbiol. 1995 May;33(5):1150-3.

47. Kloos WE, Jorgensen JH. Staphylococci. In: Lennette EH, Balows A, Hausler WJ Jr, Shadomy HJ, editors. Manual of clinical microbiology. 4th ed. Washington, D.C.: American Society for Microbiology; 1985. p.143-53.

48. Lagacé-Wiens PR, Alfa MJ, Manickam K, Karlowsky JA. Thermostable DNase is superior to tube coagulase for direct detection of Staphylococcus aureus in positive blood cultures. J Clin Microbiol. 2007 Oct;45(10):3478-9. DOI: 10.1128/JCM.01477-07

49. Sturm PD, Kwa D, Vos FJ, Bartels CJ, Schülin T. Performance of two tube coagulase methods for rapid identification of Staphylococcus aureus from blood cultures and their impact on antimicrobial management. Clin Microbiol Infect. 2008 May;14(5):510-3. DOI: 10.1111/j.1469-0691.2008.01966.x

50. Ieven M, Verhoeven J, Pattyn SR, Goossens H. Rapid and economical method for species identification of clinically significant coagulase-negative staphylococci. J Clin Microbiol. 1995 May;33(5):1060-3.

51. Oliveira K, Procop GW, Wilson D, Coull J, Stender H. Rapid identification of Staphylococcus aureus directly from blood cultures by fluorescence in situ hybridization with peptide nucleic acid probes. J Clin Microbiol. 2002 Jan;40(1):247-51. DOI: 10.1128/JCM.40.1.247-251.2002

52. Perry-O'Keefe H, Rigby S, Oliveira K, Sørensen D, Stender H, Coull J, Hyldig-Nielsen JJ. Identification of indicator microorganisms using a standardized PNA FISH method. J Microbiol Methods. 2001 Dec;47(3):281-92. DOI: 10.1016/S0167-7012(01)00303-7

53. Wieser M, Busse HJ. Rapid identification of Staphylococcus epidermidis. Int J Syst Evol Microbiol. 2000 May;50 Pt 3:1087-93.

54. Rogers KL, Fey PD, Rupp ME. Coagulase-negative staphylococcal infections. Infect Dis Clin North Am. 2009 Mar;23(1):73-98. DOI: 10.1016/j.idc.2008.10.001

55. McCann MT, Gilmore BF, Gorman SP. Staphylococcus epidermidis device-related infections: pathogenesis and clinical management. J Pharm Pharmacol. 2008 Dec;60(12):1551-71. DOI: 10.1211/jpp/60.12.0001

56. Warren JW. Catheter-associated urinary tract infections. Int J Antimicrob Agents. 2001 Apr;17(4):299-303. DOI: 10.1016/S0924-8579(00)00359-9

57. Otto M. Staphylococcus epidermidis--the 'accidental' pathogen. Nat Rev Microbiol. 2009 Aug;7(8):555-67. DOI: 10.1038/nrmicro2182

58. Garza-González E, Morfín-Otero R, Llaca-Díaz JM, Rodriguez-Noriega E. Staphylococcal cassette chromosome mec (SCC mec) in methicillin-resistant coagulase-negative staphylococci. A review and the experience in a tertiary-care setting. Epidemiol Infect. 2010 May;138(5):645-54. DOI: 10.1017/S0950268809991361

59. Hall-Stoodley L, Costerton JW, Stoodley P. Bacterial biofilms: from the natural environment to infectious diseases. Nat Rev Microbiol. 2004 Feb;2(2):95-108. DOI: 10.1038/nrmicro821

60. Smith AJ, Robertson D, Tang MK, Jackson MS, MacKenzie D, Bagg J. Staphylococcus aureus in the oral cavity: a three-year retrospective analysis of clinical laboratory data. Br Dent J. 2003 Dec;195(12):701-3; discussion 694. DOI: 10.1038/sj.bdj.4810832

61. Koll BS, Brown AE. The changing epidemiology of infections at cancer hospitals. Clin Infect Dis. 1993 Nov;17 Suppl 2:S322-8. DOI: 10.1093/clinids/17.Supplement_2.S322

62. Bogado I, Limansky A, Sutich E, Marchiaro P, Marzi M, Putero J, Viale A. Molecular characterization of methicillin-resistant coagulase-negative staphylococci from a neonatal intensive care unit. Infect Control Hosp Epidemiol. 2002 Aug;23(8):447-51. DOI: 10.1086/502083

63. De Giusti M, Pacifico L, Tufi D, Panero A, Boccia A, Chiesa C. Phenotypic detection of nosocomial mecA-positive coagulase-negative staphylococci from neonates. J Antimicrob Chemother. 1999 Sep;44(3):351-8. DOI: 10.1093/jac/44.3.351

64. Martins A, Cunha Mde L. Methicillin resistance in Staphylococcus aureus and coagulase-negative staphylococci: epidemiological and molecular aspects. Microbiol Immunol. 2007;51(9):787-95. DOI: 10.1111/j.1348-0421.2007.tb03968.x

65. Diekema DJ, Pfaller MA, Schmitz FJ, Smayevsky J, Bell J, Jones RN, Beach M; SENTRY Partcipants Group. Survey of infections due to Staphylococcus species: frequency of occurrence and antimicrobial susceptibility of isolates collected in the United States, Canada, Latin America, Europe, and the Western Pacific region for the SENTRY Antimicrobial Surveillance Program, 1997-1999. Clin Infect Dis. 2001 May;32 Suppl 2:S114-32. DOI: 10.1086/320184

66. Hiramatsu K. Molecular evolution of MRSA. Microbiol Immunol. 1995;39(8):531-43. DOI: 10.1111/j.1348-0421.1995.tb02239.x

67. Hanssen AM, Sollid JU. Multiple staphylococcal cassette chromosomes and allelic variants of cassette chromosome recombinases in Staphylococcus aureus and coagulase-negative staphylococci from Norway. Antimicrob Agents Chemother. 2007 May;51(5):1671-7. DOI: 10.1128/AAC.00978-06

68. Kotilainen P, Nikoskelainen J, Huovinen P. Emergence of ciprofloxacin-resistant coagulase-negative staphylococcal skin flora in immunocompromised patients receiving ciprofloxacin. J Infect Dis. 1990 Jan;161(1):41-4. DOI: 10.1093/infdis/161.1.41

69. Høiby N, Jarløv JO, Kemp M, Tvede M, Bangsborg JM, Kjerulf A, Pers C, Hansen H. Excretion of ciprofloxacin in sweat and multiresistant Staphylococcus epidermidis. Lancet. 1997 Jan 18;349(9046):167-9. DOI: 10.1016/S0140-6736(96)09229-X

70. Besier S, Ludwig A, Brade V, Wichelhaus TA. Molecular analysis of fusidic acid resistance in Staphylococcus aureus. Mol Microbiol. 2003 Jan;47(2):463-9. DOI: 10.1046/j.1365-2958.2003.03307.x

71. Norström T, Lannergård J, Hughes D. Genetic and phenotypic identification of fusidic acid-resistant mutants with the small-colony-variant phenotype in Staphylococcus aureus. Antimicrob Agents Chemother. 2007 Dec;51(12):4438-46. DOI: 10.1128/AAC.00328-07

72. O'Neill AJ, McLaws F, Kahlmeter G, Henriksen AS, Chopra I. Genetic basis of resistance to fusidic acid in staphylococci. Antimicrob Agents Chemother. 2007 May;51(5):1737-40. DOI: 10.1128/AAC.01542-06

73. Waldvogel FA, Bisno AL, editors. Infections associated with indwelling medical devices. Washington, D.C.: ASM Press; 2000.

74. Archer GL, Tenenbaum MJ. Antibiotic-resistant Staphylococcus epidermidis in patients undergoing cardiac surgery. Antimicrob Agents Chemother. 1980 Feb;17(2):269-72. DOI: 10.1128/AAC.17.2.269

75. Lönn-Stensrud J, Landin MA, Benneche T, Petersen FC, Scheie AA. Furanones, potential agents for preventing Staphylococcus epidermidis biofilm infections? J Antimicrob Chemother. 2009 Feb;63(2):309-16. DOI: 10.1093/jac/dkn501

76. Mogenet I, Raetz-Dillon S, Canonge JM, Archambaud M, Bonnet E. Successful treatment of Staphylococcus epidermidis hip prosthesis infection with oral linezolid. Ann Pharmacother. 2004 Jun;38(6):986-8. DOI: 10.1345/aph.1D354

77. Gomes F, Leite B, Teixeira P, Cerca N, Azeredo J, Oliveira R. Farnesol as antibiotics adjuvant in Staphylococcus epidermidis control in vitro. Am J Med Sci. 2011 Mar;341(3):191-5. DOI: 10.1097/MAJ.0b013e3181fcf138

78. Hellmark B, Unemo M, Nilsdotter-Augustinsson A, Söderquist B. Antibiotic susceptibility among Staphylococcus epidermidis isolated from prosthetic joint infections with special focus on rifampicin and variability of the rpoB gene. Clin Microbiol Infect. 2009 Mar;15(3):238-44. DOI: 10.1111/j.1469-0691.2008.02663.x

Corresponding author:
Amirmorteza Ebrahimzadeh Namvar
Department of Microbiology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran, Phone: +989376793243
amirmorteza.namvar@gmail.com

Please cite as
Namvar AE, Bastarahang S, Abbasi N, Ghehi GS, Farhadbakhtiarian S, Arezi P, Hosseini M, Baravati SZ, Jokar Z, Chermahin SG. Clinical characteristics of Staphylococcus epidermidis: a systematic review. GMS Hyg Infect Control. 2014;9(3):Doc23.
DOI: 10.3205/dgkh000243, URN: urn:nbn:de:0183-dgkh0002436

This article is freely available from
http://www.egms.de/en/journals/dgkh/2014-9/dgkh000243.shtml

Published: *2014-09-30*