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

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.
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 lysostaphin 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-acetylglicosamine (PNG) 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 staphylococal 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 PSMθ is known as the most significant cytolsin [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-
Multiple-locus variable-number tandem repeat analysis (MLVA) is one of the usual 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 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 (se1–se5) 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). 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 attBsc (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 mec-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:
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 cultivating 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 pathogenicity 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 ccr
• 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 furanone 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-acetyl-cysteine (NAC), cinnamon oil and farnesol are very substantial in reducing biofilm formation and intercellular adhesions [77]. Vancomycin, linezolid, dapptomycin, 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 increasement 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.

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