**Staphylococcus epidermidis**: how to turn from commensal to be a pathogen lifestyle

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**ABSTRACT**

*Staphylococcus epidermidis* normally is a commensal inhabitant of healthy human skin and mucosa, but also a common nosocomial pathogen in immunocompromised patients, neonates, and patients with indwelling medical devices. To distinguish the pathogen and commensal strain is a big challenge when identifying this agent with its related infection. This mini-review aims to summarize recent research in this area with a special emphasis on the virulence factor of generating genotypic and phenotypic diversity in *S. epidermidis*. By living between a commensal and pathogen, *S. epidermidis* needed to establish many strategies to face different clinical environments, including the new ecological niche of biomaterials. In addition, the growing number of immunocompromised patients increased the risk for a very sensitive host. However, further exploration of the relationship between virulence factor and *in vivo* pathogenesis is still needed. According to the virulence factor of these bacteria, which are considered as a real pathogen, strict control measures should be taken for *S. epidermidis* infection.

**ABSTRAK**


**Keywords**: *Staphylococcus epidermidis* – commensal – pathogen - virulence factor - biofilm

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INTRODUCTION

*Staphylococcus epidermidis* is a coagulase-negative Staphylococcus, considered as a part of the normal mucosa and skin microflora of humans and other mammals.\(^1\)\(^2\) It is considered as a member of the Staphylococci genus, which are gram-positive bacteria belonging to the family Staphylococcaceae. They are clustering, non-motile and non-spore forming cocci, facultative anaerobes and produce catalase. Currently, there are 35 known species of the genus *Staphylococcus*, from which 15 species are indigenous to humans, while the others are non-human pathogens.\(^2\)\(^3\) Coagulase-negative staphylococci (CNS) are grouped together as *Staphylococcus saprophyticus* (*S. saprophyticus*), *Staphylococcus lugdunensis* (*S. lugdunensis*), *Staphylococcus schleiferi* (*S. schleiferi*), *Staphylococcus haemolyticus* (*S. haemolyticus*), *Staphylococcus caprae* (*S. caprae*) or *S. epidermidis* based on their inability to clot blood plasma. Coagulase-negative staphylococci are widely distributed over the surface of the human body, where they constitute the majority of the commensal bacterial skin microflora.\(^1\)

Culture analysis has revealed that *Staphylococcus* spp. are the most abundant organisms colonizing moist areas. These moist sites include the umbilicus, the axillary vault, the inguinal crease (side of the groin), the gluteal crease, the sole of the foot, the popliteal fossa (behind the knee), nares anterior, and the antecubital fossa (inner elbow).\(^1\) *Staphylococcus* occupy an aerobic niche on the skin and probably use the urea present in sweat as a nitrogen source.\(^3\) In spite of being a saprophyte and opportunistic bacterium, this bacteria is involved in balancing the epithelial microflora and serves as a reservoir of resistance genes, which might be transferred to the closely related but more virulent organisms, such as *Staphylococcus aureus* (*S. aureus*).\(^4\) Accordingly, *S. epidermidis* maintains a commonly mutualism relationship with its host and serves as a shield, preventing colonization of potentially more harmful bacteria by producing lantibiotics, which are lanthionine-containing antibacterial peptides, also known as bacteriocins that may provide an added level of protection against certain common pathogens. Additionally, acting as skin microbiome, this bacteria promote the integrity of cutaneous defence through elicitation of host immune responses.\(^4\)\(^5\) As an innocuous commensal microorganism, *S. epidermidis* was for a long time seen as an virulent species. However, today this bacterium is considered the most frequent cause of healthcare associated infections (HAIs), namely those related with indwelling medical devices. Overall, *S. epidermidis* is the most common species in HAIs, followed by *S. haemolyticus*, *S. hominis*, and *S. capitis*.\(^6\)\(^7\)\(^8\) It has not been established that adherence and biofilm formation are closely linked phenotypes for clinical isolates. In this study, the initial adhesion to different materials (acrylic and glass For example, *S. epidermidis* may be involved in prosthetic joint, vascular graft, surgical site, central nervous system shunt and cardiac device infections.\(^5\)\(^9\)\(^10\)\(^11\)

In contrast to *S. aureus*, *S. epidermidis* does not produce many aggressive virulence factors, and consequently the infections caused are, at least in immunocompetent patients, often low-grade and chronic. For severely immunocompromised patients, *S. epidermidis* may develop into a life-threatening pathogen triggering septicaemia, meningitis, and other serious conditions.\(^1\)\(^12\) *Staphylococcus epidermidis* infections mostly are considered as being extremely recalcitrant to therapy. This is due to high antibiotic resistance rates among nosocomial *S. epidermidis* isolates,
but treatment failure is also associated with the ability of *S. epidermidis* to form biofilms on inert surfaces of medical devices from where these sticky, multilayered aggregates of bacteria are hard, if at all possible, to completely remove.\(^{13,14}\)

Additionally, the increasing use of biomaterials in modern medicine has improved the quality of life of many patients. However, as a drawback, the occurrence of biomaterial-associated infections (BAI) is increasing and now becoming a serious health threat to patients, as well as a financial burden to the society. *S. epidermidis*, generally regarded as an opportunist pathogen, is now recognised as a real “new” pathogen, since it is the major etiologic agent of BAI.\(^{10,11,15}\) Biomaterial-associated infections is generally related to microbial biofilm formation, defined as a microbial community encased in a matrix of self-produced extracellular polymeric substances (slime). Slime affects antimicrobial resistance as well as the effectiveness of the host immune system\(^{14,16}\). Currently, no effective non-invasive technique exists to prevent or destroy biofilms associated with BAI. Systemic antibiotics predominantly attack a biofilm infection through the outermost layers of the biofilm, which are usually ineffective as bacteria continue to grow from the inner layers combined with an increased production of extracellular polymeric substances. This virulence constitutes the main reason why biomaterial implants related to an infection nearly always have to be removed.\(^{17}\) In addition, the use of antibiotics and disinfectants in hospitals puts a high selective pressure on bacteria to select for resistant and well-adapted variants.\(^{18,19}\) However, this unique pattern does not yet explain why just *S. epidermidis* and not any other bacteria, was able to conquer and occupy this novel ecological niche.

Notably, it has been shown that the genomic structure of *S. epidermidis* represents an amazingly versatile microorganism living in a grey area between commensalism and pathogenicity. *S. epidermidis* employs sophisticated regulatory networks to quickly adapt its metabolism to changing external conditions, to communicate with its neighbours in the same ecological niche, or to escape the host’s immune response.\(^{8,20}\) Genomic analyses demonstrated the presence of numerous mobile genetic elements in *S. epidermidis* genomes, including methicillin resistance-mediating SCCmec elements and insertion sequences (IS). IS elements seem to be important driving forces that keep the *S. epidermidis* genome extremely flexible and trigger heterogeneous gene expression.\(^{21}\) It is suggested that well-adaptability properties both on the regulatory and genetic level might have contributed to the evolutionary success of *S. epidermidis* as a nosocomial pathogen.\(^{8}\)

Meanwhile, due to the ubiquitous prevalence of *S. epidermidis* as a commensal bacterium, clinicians often face the challenge to decide whether an isolate represents the causative agent of an infection or an unspecific culture contamination. Nowadays, our understanding of how *S. epidermidis* becomes a commensal or pathogen is far from complete and many questions still remain. This review addresses the questions concerning how the recent mechanism of commensal and infectious lifestyles of *S. epidermidis* takes place, which more focusing on literature about virulence properties of *S. epidermidis* i.e biofilm formation, icaADBC presence and the mechanism of regulating gene expression, the role of small colony variant and methicillin resistance gene, as well as its genomic flexibility.
DISCUSSION

Biofilm formation, major pathomechanism of HAIs infection

One of the main virulence characteristics of *S. epidermidis* is related with their adhesion to substratum surfaces and subsequent biofilm formation.\(^5,10\) A biofilm is a population of cells growing on a surface and enclosed in a self-produced matrix of extracellular polymeric substance (EPS). Biofilms are notoriously difficult to eradicate and are a source of many recalcitrant infections.\(^14\) Bacterial biofilm formation comprises a number of physical, biological, and chemical processes. The relative contribution of each process changes throughout biofilm development and depends on prevailing environmental and hydrodynamic conditions.\(^22\) In general, biofilm formation can be described in five phases \(^5,23,24\) as shown in FIGURE 1.

![FIGURE 1. The phases of biofilm formation in *S. epidermidis*. Graphs were modified from Vuong et al., Nuryastuti, and Bos et al.\(^5,23,24\)]
Substratum surfaces will first become covered with a conditioning film consisting of proteins and glycoproteins, such as fibronectin, vitronectin, fibrinogen, albumin, and immuno-globulins, many of which serve as binding ligands to receptors on colonizing bacteria, although adhesion can also occur to bare substratum surfaces. Biofilm formation continues with the transport of bacteria to the substratum-liquid interface, which is governed by a combination of transport mechanisms, including Brownian motion, gravity, diffusion, convection, or the intrinsic motility of a microorganism.\textsuperscript{23,24} Subsequently, in the second phase, microbial adhesion may occur which is initially of a reversible nature. Factors involved in the initial adhesion to a substratum surface include non-specific interactions originating from both the bacterial cell and substratum surfaces. These non-specific interactions are governed by physicochemical properties such as surface charge, hydrophobicity, and chemical structure of both the bacteria and substratum surface. In the third phase, reversible adhesion of bacteria changes to irreversible, amongst others due to protein-protein interactions and the production of EPS. The fourth phase in biofilm formation is surface colonization. Adhering bacteria grow and divide, forming microcolonies that are considered to be the basic organizational units of a biofilm. Entrapment of other planktonic bacteria in the EPS also occurs, resulting in a multi-layered and mature biofilm.\textsuperscript{5,23} The last step is detachment of individual bacteria or aggregates, which allows bacteria to disseminate into other areas for further surface colonization. In the clinical setting, this last step generally leads to severe systemic infections.\textsuperscript{5} As a pivotal structural component of microbial biofilms, EPS has received much attention. In general, EPS consists of polysaccharides, eDNA and proteins in a hydrated environment.\textsuperscript{26,27} Recently eDNA was found to be a major structural component of bacterial EPS where it plays a role in bacterium-surface and bacterium-bacterium interactions. The EPS produced by \textit{S. epidermidis} consists mostly of polysaccharide intercellular adhesin (PIA).\textsuperscript{26}

\textbf{icaADBC and the mechanism of regulation of expression}

Production of PIA, a key virulence factor of \textit{S. epidermidis}, is subject to on-off switching, resulting in phenotypic variability (phase variants).\textsuperscript{11,15,28} Polysaccharide intercellular adhesion production is stimulated through the action of membrane bound sensory proteins within the bacterial cell wall. Polysaccharide intercellular adhesion synthesis is catalyzed by proteins encoded within the \textit{ica} operon, a gene cluster consisting of \textit{icaADBC}. The \textit{icaA} gene product is a transmembrane protein with homology to N-acetyl-glucosaminyltransferases. The functions of \textit{icaB} and \textit{icaC} are less well defined. However, \textit{icaB} is likely to be secreted while \textit{icaC} is predicted to be an integral membrane protein. \textit{icaD} might act as a link between \textit{icaA} and \textit{icaC} and represent a novel enzyme combination. When \textit{icaA} is co-expressed with \textit{icaD}, the transferase activity increases 20 fold.\textsuperscript{11,29}

Extracellular polymeric substance production is vital, but metabolically expensive for \textit{S. epidermidis} and therefore well-regulated (FIGURE 2). Regulation of \textit{ica}-expression and biofilm formation is negatively controlled by the \textit{ica} operon regulator, \textit{IcaR} and teicoplanin-associated locus regulator, \textit{TcaR}. It is also influenced by environmental conditions that are potentially toxic for the bacterial cell. The exposure of \textit{S. epidermidis} to a high osmolarity, high temperature, detergents, urea, ethanol, the presence of sub-MIC (Minimal Inhibitory Concentration)
concentrations of certain antibiotics, glucose, iron limitation and oxidative stress have all been shown to elevate ica-expression and biofilm formation.\textsuperscript{30–32} Moreover, the global stress response factor σB, positively regulates ica-expression by negatively regulating icaR expression, while staphylococcal accessory regulator A (sarA) and regulators of sigmaB (rsbU) act similarly.\textsuperscript{33} In addition, the LuxS system involved in quorum sensing in \textit{S. epidermidis}, recently emerged as another negative regulator of biofilm formation.\textsuperscript{11}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure2}
\caption{The schematic overview of regulatory network controlling expression of ica\textit{ADBC} in \textit{S. epidermidis}. Graphs were modified from Nuryastuti.\textsuperscript{23}}
\end{figure}

The genetic and molecular basis of biofilm formation in \textit{S. epidermidis} is multi-faceted. It has been reviewed that there are two distinct mechanisms of biofilm development; through an \textit{ica}-dependent and an \textit{ica}-independent mechanism of biofilm development.\textsuperscript{11} Biofilm production by \textit{ica} operon-encoded enzymes is currently the best-understood biofilm mechanism in staphylococci,\textsuperscript{11} which is regulated by several regulatory genes such as icaR, αB, rsbU and sarA, including the reversible integration of the IS256 into those genes.\textsuperscript{28,34} Additionally, a surface protein homologous to biofilm-associated protein (Bap), accumulation-associated protein (Aap), and considerable amounts of extracellular teichoic acids (ECTA)\textsuperscript{8} have been identified to be involved in ica-independent biofilm formation in some \textit{S. epidermidis}, which is also under control of the sarA regulatory gene.\textsuperscript{11}
Recent studies imply that the multicellular organization of bacteria in a biofilm is a crucial mechanism in resisting unfavorable conditions. Heterogeneous gene expression is typically observed in clinical *S. epidermidis* strains, and it is assumed that this ability is an advantage for adaptation of staphylococci to changing environmental conditions. Phase variation involves both regulatory pathways, e.g. in response to environmental signals, as well as genetic variations, by local genomic re-arrangements, altered activity of regulatory proteins or modulation of transcription or translation of the appropriate gene through strand slip mechanisms.

Polysaccharide intercellular adhesin is the most important component of the staphylococcal slime and its production is catalyzed by proteins encoded within the *icaADBC* operon. Different *S. epidermidis* strains vary widely in the degree of PIA or slime, and biofilm they produce. The importance of the *ica* operon has been confirmed in numerous epidemiological studies, which found a higher prevalence of the *ica* genes in clinical than in control skin isolates. Clinical strains of *S. epidermidis* obtained from urinary tract infection, as well as from paediatric cancer patients receiving chemotherapy are reported to be related with *ica*-presence.

Epidemiological studies have shown that the *icaADBC* operon is a typical feature of nosocomial *S. epidermidis* strains obtained from device-associated infections. It is shown that *icaADBC* operon is mostly prevalent in strains associated with intravascular catheter-associated bacteremia and septicemia. A study of the occurrence of *ica* operon among *S. epidermidis* isolates obtained from various origins has indicated that the genetic information for biofilm formation is rarely found in isolates obtained outside of hospital settings. Interestingly, many of these studies found that invasive *S. epidermidis* strains significantly more often carried *icaADBC* than colonizing commensal *S. epidermidis* strains. Therefore, *icaADBC*-negative *S. epidermidis* strains were regarded as non-virulent and it was proposed to use *icaADBC* as a genetic marker to distinguish invasive and contaminating *S. epidermidis* in blood cultures.

**Phenotypic and genotypic instability of biofilm-forming ability**

Phenotypic variation in *ica*-presence is commonly observed in *S. epidermidis*. Ziebuhr and coworkers identified an insertional element (IS256) that was capable of inserting itself into the *ica*-locus resulting in *ica*-negative phenotypes. This disruption was shown to be reversible as precise excision from the *ica*-locus which observed at low incidence resulting in *ica*-positive phenotypes.

We and others have shown that a significant proportion (42-85%) of clinical isolates are *ica*-negative during culturing in the laboratory. In contrast to studies showing a reversible switching (phenotypic switching) between *ica*-positive and *ica*-negative phenotypes, the *ica*-locus was permanently lost in these strains. The absence of IS256 and phenotypic variation in these clinical *S. epidermidis* isolates and the inability to switch back to *ica*-positive suggested a new mechanism of switching in terms of biofilm formation involving genetic instability.

We showed that the presence of the *ica*-locus in clinical isolates represents a disadvantage for growth in laboratory conditions. In line with this, it was recently suggested that the presence of the *icaADBC* operon represents a disadvantage when *S. epidermidis* colonizes the skin.
Strains that have a high level of PIA production have a significant growth disadvantage under commensal conditions and are therefore outcompeted by strains with more moderate or absent PIA production. Whereas PIA production enables staphylococci to survive and grow under hostile, infection related conditions (biofilms), during commensal colonization (as well as during planktonic growth), PIA production can be considered a burden that can easily be subsided. It is important to conclude that the ability to express different slime-producing phenotypes could provide staphylococci with a greater degree of flexibility for colonizing a range of different environments. Too much or no PIA production is only favourable under specific conditions while the ability to regulate PIA production allows the organism to adapt to all conditions, both commensal and infectious.

Other studies have found, in *S. epidermidis*, IS256 detection is attributed to the epidemic biofilm-forming clonal lineages, and the element has been shown to trigger heterogeneous biofilm expression by reversible transposition into biofilm-associated genes and regulators. IS256 was shown to cause phase variation of *icaADBC* operon expression by alternating insertion in and precise excision from the PIA synthesis-mediating gene locus. While switch-off of PIA production through IS256 insertions occurs with a frequency of approximately $10^{-6}$ per cell and generation, restoration of PIA-dependent biofilm formation by precise IS256 excision was found to be an extremely rare event ($10^{-11}$ per cell and generation).

The role of small colony variant (SCV)

Small colony variants are naturally occurring subpopulations of bacteria demonstrating distinctive phenotypic characteristics and pathogenic traits. Phenotypically, SCVs have a slow growth rate, atypical colony morphology associated with the formation of pinpoint or ‘fried egg’ colonies and unusual biochemical features. It was most extensively studied for staphylococci, especially for *S. aureus* as well as *S. epidermidis*. SCVs were recorded as being $<1$ mm in size (less than 1/10 of the normal cell size), with reduced pigmentation and haemolytic activity as described in literature. The tiny size of SCVs on solid agar is often due to auxotrophy for haemin and/or menadione, two compounds involved in the biosynthesis of electron transport chain components, which is associated with defects in electron transport and, consequently, altered membrane potential. The abnormal membrane potential, in turn, may confer on these variants innate resistance to aminoglycosides, since the ability of these antibiotics to gain access to intracellular target sites depends on the proton motive force. More importantly, some reports have linked bacterial SCVs to several recurring infections that are intractable to conventional treatment antibiotic regimes.

Small colony variants have been associated with long-lasting, chronic, and recurrent infections, and it was suggested that this property was linked to the ability of SCVs to survive intracellularly, thereby being protected from the host immune system and the action of antibiotics. Both biofilm formation and the SCV phenotype may contribute to the recurrence and persistence of staphylococcal infections; bacteria are either embedded in large, adherent biofilms on the surfaces of implanted foreign bodies or may persist intracellularly in phagocytes, such as epithelial or endothelial cells, and thus evade the host immune system. Additionally, it was proved that in vitro experiment using menadione auxotrophs of *S. aureus* and haemin auxotrophs of *S. epidermidis*. 
resulted in the upregulation of alternative sigma factor B, which plays a central role in the augmentation of icaADBC expression and PIA production.\textsuperscript{43,47}

**Methicillin resistance gene**

In addition to biofilm formation, nosocomial *S. epidermidis* isolates are characterized by their pronounced resistance against commonly used antibiotics including methicillin. Methicillin resistance is, similar with *S. aureus*, mediated by the meca gene encoding a penicillin binding protein with reduced affinity to β-lactam antibiotics.\textsuperscript{48} However, in contrast to methicillin-resistant *S. aureus* (MRSA), attention paid to methicillin resistant *S. epidermidis* (MRSE) in hospital settings is not adequate enough, meaning they are not dealt with by using intense hygienic measures as those for MRSA. As a result, methicillin resistance rates among nosocomial *S. epidermidis* isolates and other CoNS are extremely high and regularly exceed those of MRSA.\textsuperscript{48–50} It has been reported approximately 80\% of *S. epidermidis* isolates from device-associated infections are considered as MRSE, and also found to be multiresistant; whereas commensal strains obtained from the community are mostly methicillin-sensitive *S. epidermidis*.\textsuperscript{10}

The meca gene and its regulators are located on large DNA elements that are termed staphylococcal cassette chromosome mec (SCCmec). In addition to the methicillin resistance determinant, SCCmec carry a set of recombinases and a wide variety of mobile DNA elements such as transposons, insertion sequences or integrated plasmids.\textsuperscript{1,15} To date, five major SCCmec types have been identified, all of them can be distributed over the *S. epidermidis* genome. Interestingly, SCCmec have been shown to be transferable among staphylococcal species. These genes are now regarded as mobile elements in which extensive recombination and gene shuffling takes place.\textsuperscript{15,51} Obviously, they do not only serve as shuttles for the transfer of methicillin resistance but can also carry other staphylococcal genes. MRSE is often associated with additional antibiotic resistance, such as erythromycin (encoded by *erm* genes), ciprofloxacin, clindamycin, aminoglycosides (encoded in *aacA/aphD* gene) or trimethoprim-sulphamethoxazole.\textsuperscript{15} The recent findings of genomic research strongly suggest that *S. epidermidis* and other coagulase-negative staphylococci represent the gene pool for the ongoing generation of novel SCC types from which methicillin resistance in *S. aureus* might originate.\textsuperscript{1,12} Accordingly, it would be meaningful and reasonable to control MRSE and MR-CoNS by appropriate hygiene measures in a similar manner for MRSA, in order to lower MRSA burden in medical facilities, due to their role as reservoirs for the spread of resistance genes within microbial communities.

**Genomic flexibility**

It was demonstrated that clonal diversification in *S. epidermidis* is mainly based on genetic recombination, which is in contrast to *S. aureus*, a species known to evolve preferentially by point mutations.\textsuperscript{21,41} Multilocus sequence typing (MLST) analysis of a representative collection of clinical *S. epidermidis* isolates revealed a high degree of genetic diversity within the species, but the most widespread clone was ST2 or ST27 (sequence types). Especially, clonal complex ST2 isolates were found to be highly flexible with respect to methicillin resistance and prone to take up these mobile genetic elements.\textsuperscript{21} Possibly, the successful spread of ST2 may be due to the fact that all ST2 isolates contain IS256 insertion sequences and *ica* genes, two factors that may have determinants to enhance transmissibility, persistence, or
invasiveness in S. epidermidis. In addition, most ST2 isolates show in vitro capacity to form biofilms.\(^{15,21}\)

Instability of genetic material is often an indication of mobility, and in this respect it is also conceivable that the ica operon represents mobile DNA that has been lost in the commensal strain. S. epidermidis isolates ST 2(ST27) represent an ideal genetic background for biofilm and resistance genes, resulting in well-adapted strains which are then selected in the hospital environment and causes device-related infection and bacteraemia. The presence of multiple copies of IS256 in the ST27 genome might support this adaptation process by an ongoing generation of novel phenotypic and genotypic variants. Therefore, the combination of biofilm formation, antibiotic resistance, and genetic flexibility may explain why ST2 has become the dominant clonal variant within medical facilities.\(^{8,41}\)

**Clinical manifestation of related infection**

*Staphylococcus epidermidis* and other CoNS have for a long time been dismissed as culture contaminations which is mainly due to the fact that CoNS are primarily ubiquitous commensals of the human skin and mucosa. It is still a great challenge for the clinical microbiology laboratory to distinguish infecting strains from contaminants. In suspected *S. epidermidis* infections, where the pathogen is also a skin commensal that could contaminate skin swab or blood specimen if aseptic techniques are not followed, the same indistinguishable microorganism must be cultured from at least two separate specimens in order to differentiate a relevant infection from skin contamination.\(^{52}\) In contrast, for virulent species such as *S. aureus* or gram negative bacteria, a single positive clinical specimen may be sufficient to determine the presence of a recent infection.\(^{33,54}\) However, some groups of the population are prone to be infected with this microorganism. These higher risk groups include preterm neonates, immunocompromised individuals and patients with indwelling medical devices.\(^{1,5,10}\)

The most important clinical manifestation associated with CoNS, particularly *S. epidermidis* is biomaterial-associated infections (BAI), which include a unique, complex constellation of many factors that have to be considered for their successful management.\(^{33}\) The increasing use of foreign materials in almost all fields of modern medicine is associated with a risk of bacterial infection.\(^{10}\) Morbidity and mortality of biomaterial-associated infections may vary according to the underlying patient condition, the microbial strain(s) that are implicated, and the type of device. Biomaterial-associated infections contribute significantly to the increasing problem of nosocomial infections. While a variety of microbial strains have been involved as causative organisms in biomaterial-associated infections, staphylococci, particularly *S. epidermidis*, account for the majority of infections related to both temporarily inserted and permanently implanted biomaterials.\(^{5,10}\)

The presence of a biomaterial significantly compromises the host’s ability to cope with infectious microorganisms. These microorganisms can reach a biomaterial implant in several ways and at different times post-implantation. Airborne microorganisms, inevitably present in the operating theater, can reach a biomaterial implant surface as early as before the implantation. Also during insertion of a biomaterial implant, microorganisms from the commensal microflora of the skin can contaminate a biomaterial implant. Perioperative contamination is believed to be the most common cause of biomaterial associated infection.\(^{10,18,33}\)

Bacteria that adhere to implanted medical
devices or damaged tissue can encase themselves in a hydrated matrix of extracellular polymeric substances, a slimy layer, and start growing into a biofilm. Bacteria organized in biofilms are at least 10-1000 times more resistant to antibiotics and can cope much better with unfavorable external conditions as the host immune system than their planktonic counterparts. The biofilm mode of growth represents a benefit for staphylococcal strains enabling them to colonize inert surfaces of medical devices. Antibiotic resistance of bacteria in the biofilm mode of growth contributes to the chronic nature of these infections, which are notoriously difficult to resolve. The mechanisms of bacterial resistance in biofilms are different from the now familiar plasmids, transposons, and mutations that convey innate resistance to individual bacterial cells. In biofilms, resistance seems to depend on multicellular strategies resulting in an impaired penetration of antibiotics to the target organisms and a decreased immune response.

Biomaterial-associated infections comprise local (e.g., exit site) and systemic infections. Originating from bacteremia or other systemic spread of causative organisms and depending on the nature and localization of the biomaterial inserted, sepsis, endocarditis, meningitis, joint sepsis, vertebral abscesses, and other local manifestations due to metastatic seeding may result. These comprise infections commonly associated with prosthetic vascular grafts, prosthetic heart valves, cardiac devices, and coronary stents. Moreover, local inflammation signs include erythema, warmth, swelling, tenderness, and purulent drainage, which characterize exit-site infections.

It has been shown that Staphylococcus epidermidis was the most frequent agents of central venous catheter (CVC) and umbilical catheter-associated BSIs (Blood Stream Infection) in neonatal ICUs. The coagulase-negative staphylococci (CoNS) group may cause further invasive infections in preterm infants, such as infective endocarditis, meningitis, and necrotizing fasciitis. Additionally, S. epidermidis is also considered as the main cause of septicemia in febrile patients who suffer from chemotherapy-induced neutropenia, which is accounting for approximately 20 to 40% of cases.

**CONCLUSION**

So far it is still a great challenge for clinicians to distinguish S. epidermidis strains that may cause infection from those that live on the skin. However, the virulence properties identified in this paper, such as the presence of biofilm formation phenotype including icaADBC operon, IS256, mecA, SCV properties, together with patient characteristics, might be used to consider the pathogenesis of infection caused by S. epidermidis. Nevertheless, up to date, the clues to distinguish between infectious and commensal strains of S. epidermidis are not clear yet. It is well understood the adhesion to host tissue is considered crucial during both these lifestyles.

By living on the verge of commensalism and pathogenicity, S. epidermidis has elaborated many strategies to overcome different clinical environments, including the new ecological niche of biomaterials. In addition, the growing number of immunocompromised patients increases the risk for a very sensitive host. The formation of biofilms, the acquisition of resistance characteristics and the enormous flexibility of the genome of staphylococci are characteristics that help their survival in specific environments and are the main reasons why staphylococci have become the most successful pathogens in clinical setting. With respect to their possible role as true pathogens, S. epidermidis infection should be
taken more seriously with adequate prevention applications for future infection control and hygiene measures.

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