Published in final edited form as:

Curr Opin Infect Dis. 2010 June ; 23(3): 208–216. doi:10.1097/QCO.0b013e328337fecb.

Understanding the significance of *Staphylococcus epidermidis* bacteremia in babies and children

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Abstract

Purpose of review—This review provides an overview of *Staphylococcus epidermidis* bacteremia/sepsis and Coagulase-negative staphylococci (CoNS) infections in neonates and children.

Recent findings—The incidence of *S. epidermidis* and CoNS sepsis in neonates is still very high and preventing and treating disease remains difficult. There has been recent progress in understanding pathogenesis of *S. epidermidis* infection, interaction of *S. epidermidis* with host defenses, and risk factors for the development of *S. epidermidis* disease. For example, we have gained more insight into the development of biofilm-associated catheter infections, which are responsible for recurrent CoNS infections in hospitalized premature neonates and are especially difficult to treat owing to intrinsic resistance of biofilms to antibiotics.

Summary—Biofilm-associated catheter infections by *S. epidermidis* occur frequently in neonates and adults. *S. epidermidis* bloodstream infections are particularly problematic in neonates. Prophylaxis in the form of eradicating colonizing *S. epidermidis* may be a double-edged sword, as *S. epidermidis* colonization may be beneficial to the host. New drugs may arise from a better understanding of *S. epidermidis* virulence and analysis of risk factors may help identify neonates susceptible to bacterial sepsis. However, reducing morbidity should always begin by increasing hygiene in hospital settings to reduce the introduction of potentially harmful opportunistic pathogens such as *S. epidermidis* on indwelling medical devices or during surgery.

Keywords

Staphylococcus epidermidis; neonates; sepsis; biofilm; nosocomial infections

Introduction

Staphylococcus epidermidis is found ubiquitously on healthy human skin and mucosal surfaces [1], readily colonizing newborns [2] and remaining part of the normal microflora throughout life [3]. *S. epidermidis* belongs to a group of staphylococcal species that are unable to produce free coagulase (collectively known as coagulase-negative staphylococci [CoNS]). *S. epidermidis* is the most commonly isolated etiological agent of nosocomial infections [4•]. Critically-ill patients who are immune-compromised [5, 6] and premature neonates admitted into neonatal intensive care units (NICU)s [7, 8] are the most vulnerable to CoNS infections. *S. epidermidis* rarely causes infections in healthy tissue [9] but has a

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pronounced ability to proliferate on surfaces of indwelling medical devices after surgical insertion [10], where it forms persistent multilayered agglomerations called biofilms. As biofilms are intrinsically resistant to antibiotics [11], biofilm-associated infections are a notorious burden on the increased duration of hospital admissions [12], medical resources [13] and healthcare costs [14, 15], which are estimated at US\$ 2 billion annually in the US alone [16, 17••].

Here we review CoNS infections in neonates with a focus on *S. epidermidis* and explore recent findings that may help elucidate the complex relationship *S. epidermidis* has with its host and why *S. epidermidis* continues to be one of the most successful nosocomial pathogens.

CoNS-associated clinical sepsis in neonates

Nosocomial infection rates in neonates vary from 6% to 50% in the United States alone [18, 19] with greater incidences of infection reported internationally [20, 21]. Many nosocomial infections in neonates are catheter-related, because critically ill infants require the delivery of nutrients and drugs over long periods of time [22, 23]; and IV access, the most direct way of delivering fluids, typically involves the use of central venous catheters (CVCs). A disadvantage of long-term catheter use in neonates is that bloodstream infections (BSIs), caused primarily by CoNS such as *S. epidermidis*, are a common occurrence and responsible for significant global morbidity and deaths in very low-birth-weight infants (VLBW; < 1500g) [13, 24]. In contrast, term infants are only rarely infected [24, 25].

The skin insertion site and the catheter hub are the most important sources of catheter colonization. From the contaminated hub, the organisms may migrate along the surface of the catheter [26] and enter the bloodstream, which causes acute late-onset sepsis infections. Clinical features of late-onset (after 72 h post-birth) CoNS-associated sepsis are not consistent between neonates and range in severity [27]. Clinical symptoms among neonates include breathing difficulties, a drop in heart-rate to less than 100 beats per minute, fever, metabolic acidosis, feeding intolerance and abdominal distension [28].

CoNS and *S. epidermidis* are extremely capable of adhering to catheters and forming biofilms [29]. In addition to intrinsically high resistance of biofilms to antibiotics, specific antibiotic resistance in *S. epidermidis* clinical isolates, in particular to methicillin (methicillin-resistant *S. epidermidis*, MRSE), is widespread and complicates treatment [30]. A positive culture, whether obtained from blood, spinal fluid, or urine, is used to determine the presence of a nosocomial infection. More stringent measures include a positive identification from the catheter hub and a peripheral vessel as well as a positive blood culture [31]. PCR may serve to substantiate conclusions. However, contamination of samples can occur at the time of sampling or during processing because of the ubiquitous presence of *S. epidermidis* on the skin of health care and laboratory personnel [32]. This may account for the large variances in identification and report of *S. epidermidis* and other CoNS between laboratories [33]. Furthermore, although CoNS are most frequently isolated from BSIs, other micro-organisms are also sometimes detected along with CoNS [34].

S. epidermidis is a highly divergent species [35]. Many isolates belong to sequence type ST2 [32, 36]. Of interest, a recent study suggested that many *S. epidermidis* isolates are shared between infants and nurses in NICUs [37], although no direct correlation has been found associating these circulating strains with ST2. Why ST2 is so prevalent is unknown.

Risk factors for infection in neonates

Several factors may contribute to increased susceptibility to infection in pre-term compared to term neonates. CoNS- and *S. epidermidis*-associated BSIs are particularly prevalent among infants weighing less than 1500 g at birth (VLBW infants) and neonates with low gestational age [13]. VLBW infants are more likely to stay longer in the NICUs and require treatment and nutrition via CVCs. Nutrition formulae that immature neonates receive when administered into NICUs (TPNs, total parenteral nutrition) contain polyunsaturated fatty acids (PFAs) [38], which provide an important alternative to glucose as sources of energy [39]. However, not all premature neonates can fully utilize PFAs and thus they may accumulate in the neonate [40]. This is of special importance because peroxidation of the lipids to form toxic hydroperoxides may occur within the TPN emulsion [41] or in activated neutrophils [42]. Historically, the use of TPNs in premature neonates has been associated with increased CoNS-associated bacteremia [12], which may be attributed to impaired functions of cells of the immune system [43]. In pre-term neonates, PFAs may further reduce the function of neutrophils, which already have decreased killing capacities [44] and reduced ability to initiate the oxidative burst in response to bacterial stimulation [45] compared to those of term neonates and adults.

Interaction of *S. epidermidis* with innate host defense

The innate immune system is a non-selective protective barrier, consisting of different types of immune cells, humoral and other proteinaceous factors (such as antimicrobial peptides, AMPs) as well as epidermal and mucosal surfaces, that protect against invading microbial pathogens [46]. When bacteria enter the bloodstream, the host innate immune system immediately responds with an influx of immune cells to the site of infection. Neutrophils are the main type of leukocyte found in blood and play a key effector role against *S. aureus* infection *in vitro* and *in vivo* [47, 48]. In addition, they are efficient at clearing developing biofilms by *S. aureus* by phagocytosis [49] but less so biofilms produced by *S. epidermidis* *in vitro* [50]. Upon phagocytosis, neutrophil bacterial killing is mediated by oxidative and non-oxidative mechanisms in the phagosome [51].

TLRs are a group of receptors that recognize universal, highly conserved microbial antigens (pathogen-associated molecular patterns [PAMPs]). TLR activation leads to the up-regulation of immune defense systems that include phagocytosis and cytokine release [52]. In particular, TLR2 plays a key role in the recognition of Gram-positive pathogens by detecting Gram-positive cell wall components, such as lipoproteins [53]. On the other hand, hyper-stimulation of TLR2 through administration of Pam2Cys (a TLR2 agonist) decreases neutrophil levels *in vivo*, which leads to more severe sepsis in mice with multiple pathogens including *S. aureus* [54•].

TLR2 has also been reported to recognize specific *S. epidermidis* antigens, namely phenol soluble modulins (PSMs) [55] and poly-N-acetylglucosamine (PNAG; also known as polysaccharide intercellular adhesin; PIA) [56]). However, these findings need to be confirmed using defined genetic deletion strains, as it is possible that contaminating lipopeptides or other substances were the underlying cause of the detected pro-inflammatory effects. Accordingly, recent findings indicate PSMs are recognized predominantly by a receptor other than TLR2 (A. Peschel, personal communication).

While the level of TLR2 activation during staphylococcal sepsis may have a crucial role in determining the outcome of disease, the functional consequences of neonatal TLR activation in immune cells are very different from those in adults, as demonstrated by decreased production of TLR2-dependent cytokines [57]. In addition, neonatal immune cells are less capable of producing multiple cytokines simultaneously in response to TLR stimulation

[58]. In neonates, there is enhanced TLR2 expression on monocytes and granulocytes over the course of neonatal sepsis [59]. In addition, phagocytosis of *S. aureus* and *S. epidermidis* causes neutrophil apoptosis *in vitro* [50]. A combination of these factors may explain why neutropenia is observed during sepsis in sick VLBW infants [60].

Lipoteichoic acid (LTA), a highly conserved epitope in the staphylococcal cell wall that has antiphagocytic properties [61, 62], induces the cytokine cascade through stimulation of TLR2 [63]. However, LTA is also responsible for inhibition of pro-inflammatory cytokine production in keratinocytes in a TLR2 dependent manner [64•]. Skin damage will undoubtedly occur when catheters are being inserted and TLR2-dependent inhibition of pro-inflammatory cytokine production would allow *S. epidermidis* to adhere, proliferate and migrate along catheters with minimum interference from host defenses.

A shorter secreted form of LTA, known as “lipid S” from *S. epidermidis*, has been described [65] with significant pro-inflammatory properties [66]. However, it appears that during the biochemical characterization of “lipid S”, data were misinterpreted and “lipid S” signals and pro-inflammatory capacity are attributable to PSM-mec, a recently discovered phenol soluble modulin (PSM) [67•].

Mannose-binding lectin (MBL) is a pattern recognition receptor that recognizes carbohydrate moieties on the surface of a wide range of microorganisms [68]. It is thought to be a primary host defense mechanism against CoNS species [69]. Although MBL affinity to *S. epidermidis* is significantly reduced compared to that of *S. aureus* [68], the MBL and classical complement pathways are indispensable for mediating rapid PMN-phagocytic killing of *S. epidermidis* in suspension [70, 71•]. Furthermore, deficiencies in complement factor C3 and IgG, essential factors for activation of the complement cascade, have been related to greater risk for CoNS-associated sepsis in neonates [72]. Whether there is an association between low circulating MBL levels and increased risk of infection in neonates [73, 74] remains to be addressed.

***S. epidermidis* and acquired host defense**

Bacterial infiltration first activates neutrophils and other phagocytes to produce cytokines. Eventually, a more specific acquired immune response is induced by T cells, which have an important role in determining the type of immune response against the invading pathogen.

In an *S. aureus* sepsis mouse model, high levels of T-helper (Th) 2 polarizing cytokines such as IL-4 and IL-10 were detected [75]. Th2 cells play a prominent role in neutralizing extracellular microorganisms by stimulating B-cells for antibody production [76]. Thus, antibody-mediated responses may also be important in controlling *S. epidermidis* and CoNS sepsis infections. Interestingly, whole blood from term neonates can be as efficient at producing cytokines compared to that of adults in response to *in vitro* stimulation with *S. epidermidis* [77•]. Generally, production of cytokines is significantly lower as a response to *S. epidermidis* compared to *S. aureus* [78, 79•]. However, in chronic *S. epidermidis* biofilm-associated infections, a cellular immune response may be initiated as indicated by the production of high levels of IL-1 β , IL-12 and gamma interferon (IFN- γ) by human leukocytes in an *in vitro* biofilm model [80].

The importance of T cells in controlling *S. epidermidis* infection was recently evaluated in an *in vivo* catheter infection mouse model [81•]. Nu/Nu mice (athymic and T-cell deficient but B-cell and natural killer cell positive) were most susceptible toward *S. epidermidis* biofilm infections. These data support the notion that patients with immune deficiencies may be more prone to recurrent *S. epidermidis* biofilm-associated infections [82, 83].

***S. epidermidis* pathogenesis**

There is increased recent interest in the mechanisms by which *S. epidermidis* can persist and cause infection. Unlike its close relative *S. aureus*, *S. epidermidis* produces only a fraction of secreted virulence factors such as toxins and degradative exoenzymes [4]. *S. epidermidis* invasive strains appear to be predominantly of ST2; and some genetic factors seem to be correlated with invasiveness, such as the insertion element IS256 and the *ica* genes encoding the PNAG/PIA immune evasion and biofilm exopolysaccharide [84, 85]. The insertion element IS256 is believed to contribute to genetic adaptation that may have a role during infection [86]. Many of the virulence factors of *S. epidermidis* have been recently reviewed [4]. Therefore, the following sections will specifically address virulence factors with a putative role in *S. epidermidis* neonatal infection.

Putative virulence determinants involved in neonatal sepsis

Necrotizing enterocolitis is a highly fatal disease which occurs in 5–10% in VLBW neonates [87]. Clinical symptoms of necrotizing enterocolitis include apnea, desaturations, bradycardia, lethargy and temperature instability and complications with the patient's gastrointestinal tract [88]. How bacteria induce necrotizing enterocolitis still remains elusive. It has been suggested that other virulent microorganisms may damage the intestinal epithelium [87], which would allow *S. epidermidis* and CoNS to disseminate into the blood [89]. Furthermore, production of delta-toxin was implicated in neonatal necrotizing enterocolitis [90]. *S. epidermidis* delta-toxin (also known as PSM γ) is a 24 amino acid long peptide transcribed within RNAIII, the small regulatory RNA molecule that is required for virulence determinant regulation by the *agr* quorum-sensing system [91, 92]. The recent discovery that delta-toxin is but one member of a larger family of similar peptides with frequent cytolytic potential, the PSMs [93, 94], will require a more detailed investigation of the pathogenic potential of delta-toxin and other PSMs in necrotizing enterocolitis and other diseases. This includes the very recently identified PSM-mec, which is encoded on a transferable genetic element [67], in contrast to all other PSMs, which are encoded on the core *S. epidermidis* genome.

S. epidermidis and many other CoNS are protected from attacks by the immune system by specific extracellular polymers. First, the *ica*-encoded exopolysaccharide PNAG/PIA [95, 96] was shown to inhibit neutrophil phagocytosis and activity of AMPs, thus contributing significantly to *S. epidermidis* immune evasion [97, 98], in addition to its role as a structural component of the biofilm matrix. Second, poly- γ -DL-glutamic acid (PGA) has a similar function in immune evasion [99].

Putative virulence determinants involved in neonatal catheter-associated infections

Biofilm formation, a multi-stage process that occurs in four phases; attachment (adhesion), accumulation, maturation and detachment [100], is an important virulence determinant during catheter-associated infection. Bacteria that form biofilms on medical catheters are known to be notoriously difficult to eradicate [11, 101] and it has been estimated that biofilms are associated with 65% of nosocomial infections [11].

For the most part, there is a significant association of *S. epidermidis* clinical isolates and biofilm formation [32, 102]. PNAG/PIA is important for biofilm production *in vitro* and *S. epidermidis* strains lacking PNAG/PIA are significantly impaired in most animal models of biofilm-associated infection [103–105]. However, not all *S. epidermidis* clinical isolates from biofilm-associated infections, and even less from neonate BSIs, possess *ica* genes

[106–110]. In some *ica*-negative *S. epidermidis* strains, the cell surface-located accumulation-associated protein (Aap) [111•] is involved in biofilm formation [112]. Domains within the Aap fibril-like structure [113] are thought to interact with components of PNAG/PIA thus forming a protein polysaccharide biofilm network [114]. Furthermore, PNAG/PIA-independent biofilms were documented in clinical staphylococcal isolates [115]. However, such protein-dependent biofilms are more readily disrupted indicating that both PNAG/PIA and proteins contribute to efficient *S. epidermidis* biofilm formation.

The production of biofilms on catheters can lead to chronic infection. Bacteria embedded in biofilms are more resistant to antibiotics compared with their planktonic free-floating counterparts [101]. Furthermore, biofilms are responsible for reduced IgG and complement deposition for neutrophil-dependent killing of *S. epidermidis* [71]. Moreover, as the biofilm matures, small clusters of cells may detach from the mature biofilm forming the basis for continual seeding of bacteria into the bloodstream. Accordingly, in neonates with implanted CVCs, infections frequently relapse after treatment, most likely owing to the presence of biofilms [116, 117], while neonates with CoNS late-onset sepsis can be treated relatively quickly using antibiotics [118].

Regulation of virulence in *S. epidermidis*

The quorum sensing regulator *agr* modulates the expression of many *S. epidermidis* genes, including several virulence factors, in response to cell density [119–121]. Since delta-toxin is transcribed within RNAIII [91, 92], the primary intracellular effector of *agr*, production of delta-toxin is directly linked to *agr* activity. PSMs other than delta-toxin are controlled by direct binding of the AgrA response regulator to their promoter regions, resulting in similarly strict control of PSM production by *agr* [122, 123]. Production of PSM-mec is also *agr*-regulated, but it is unknown whether this occurs by direct binding of AgrA to the *psm-mec* promoter [67].

Regulation of PNAG/PIA synthesis is subject to a range of regulatory influences [124] involving several different global virulence regulators [125, 126] and the putative quorum-sensing system *luxS* [127], but not *agr* [121]. Thicker and more compacted biofilms are formed by *agr* and *luxS* mutants when compared to the corresponding isogenic wild-type strains [127–129]. For *agr*, this is thought to be due to the inability of cells to detach from the mature biofilm, possibly as a result of abolished PSM production [94].

Antibiotic resistance

Frequent antibiotic resistance, in particular to methicillin (methicillin-resistant *S. epidermidis*, MRSE), makes *S. epidermidis* an important threat in nosocomial infections. The factor responsible for methicillin-resistance is the *mecA* gene, which is located on mobile genetic elements called the staphylococcal chromosome cassette *mec* (SCC*mec*) [130]. Many *S. epidermidis* isolates possess the SCC*mec* type IV element [131]. Due to its relatively small size [132], SCC*mec* type IV is thought to be advantageous for spreading promiscuously among strains in the absence of antibiotic pressure [133]. PSM-mec is encoded within SCC*mec* types II and III [134] and is one of the few *S. epidermidis* virulence determinants that can be easily passed from strain to strain [67].

The *mecA* gene is found in more than 90% of *S. epidermidis* infection isolates, indicating an extremely high incidence of MRSE [135]. Despite such high frequency of methicillin resistance, a majority of acute cases of CoNS- and *S. epidermidis*-associated sepsis in neonates can be treated with antibiotics such as vancomycin [24, 118] without the need of catheter removal [136]. However, relapse of infection is common in patients who retain the same catheter [116, 117]. Importantly, biofilm formation significantly decreases the activity

of vancomycin and other antibiotics [117, 137]. This resistance to antibiotics by *S. epidermidis* may be brought on by failure of some antibiotics to penetrate the full depth of the biofilm or reduced growth and metabolism rates, which affects cell wall synthesis inhibitors and antibiotics that act on metabolic processes [11].

Future treatments and prophylactic measures against *S. epidermidis*

As *S. epidermidis* is found ubiquitously on human skin, it is of no surprise that infection is commonly due to self-contamination during the catheter insertion procedure or from the skin of hospital workers [37]. Thus, improved education of personnel in healthcare practices, such as increased frequency of hand disinfection [138, 139] has led to a reduction in the relative risk of infections [140, 141]. The use of novel technologies to prevent bacteria from adhering onto indwelling catheters and prostheses may help reduce the incidence of disease.

There are currently no anti-staphylococcal vaccines. Most efforts are targeted at *S. aureus*, owing to the higher severity of *S. aureus*-induced disease. Active immunization strategies against *S. epidermidis* may be problematic for several reasons, for example the fact that it is a ubiquitous human commensal. One effort aimed predominantly at CoNS, passive immunization with a vaccine consisting of monoclonal antibodies against LTA, has recently undergone clinical trials in VLBW neonates [142•]. Unfortunately, this vaccine, Pagibaximab, showed no significant reduction in incidence in CoNS infection between treated and control neonate patients, under the current immunization protocols. However, administration of the vaccine was safe and changes in Pagibaximab administration are planned for future trials. Antibodies to LTA would help antagonize its anti-phagocytic property [61]. In the future, passive immunization with neutralizing antibodies against PSMs may be worth considering in addition to using PGA or PNAG/PIA for passive or active immunization strategies.

Inhibition of the quorum sensing system *agr* would prevent the production of PSMs and other virulence determinants, but there are caveats [143]. First, there are different subgroups of *S. epidermidis* that use different signals [144] and thus one anti-quorum sensing therapeutic may not function against all *S. epidermidis*. Second, *S. epidermidis* strains with *agr* deletions produce thicker and more compact biofilms [129]. Although dissemination of bacteria may be impacted as a result of *agr* inhibition, the possibility of enhanced biofilm on catheters by *S. epidermidis* cannot be excluded.

Continued use of chemical antiseptics, such as chlorhexidine, may serve to prevent staphylococcal contamination [145] but new antibiotics that can target novel bacterial processes, which are not involved in metabolism, would be more valuable in circumventing known antibiotic resistance mechanisms by staphylococci. All these measures would be a great benefit against catheter-associated infections in neonates. Notably, therapeutic strategies against *S. epidermidis* infection must omit the complete eradication of *S. epidermidis* as it is an important part of human microflora on the skin.

Conclusion

S. epidermidis and CoNS sepsis infections in neonates remain a significant burden to public healthcare especially with the emergence of antibiotic resistance. Realistically, eradicating *S. epidermidis* and CoNS is neither possible nor desirable. However, understanding the mechanisms of *S. epidermidis* pathogenesis will help give rise to new anti-staphylococcal therapies. Although the newly discovered PSMs will need to be evaluated in more detail for their toxic potential, *S. epidermidis* in general appears to lack the production of aggressive virulence factors. Rather, further strategies to inhibit biofilm formation will need to be explored to limit chronic catheter-related infections in neonates. Targeting other *S.*

epidermidis virulence factors, such as those involved in adherence, immune evasion, or quorum sensing, requires careful consideration as the outcome may not always be beneficial for the host. This also applies to modulating the neonatal innate immune system to help control infection as neonates show different responses to adults. In addition, there still is a need to understand neonatal immune responses to pathogenic bacteria before such informed decisions can be made.

Acknowledgments

This study was supported by the Intramural Research Program of the National Institute of Allergy and Infectious Diseases (NIAID), U.S. National Institutes of Health (NIH).

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