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Mini Review

The role of *Staphylococcus epidermidis* in neonatal sepsis: Guarding angel or pathogenic devil?

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ABSTRACT

Neonatal late-onset sepsis (LOS) is a serious problem in neonatal intensive care. Coagulase-negative staphylococci, especially *Staphylococcus epidermidis*, have emerged as the predominant pathogen of LOS in very low birth weight (VLBW) infants, accounting for up to 77.9% of neonatal LOS in industrialized countries and 46.5% in some developing regions. VLBW neonates with indwelling medical devices are most susceptible for *S. epidermidis* sepsis, the incidence rate of which is approximately 25%. However, *S. epidermidis* primarily plays a commensal role on human host and is of evolutionary importance to newborns, by inhibiting virulent pathogens and educating the innate immune system. Recent advances in molecular microbiology show that *S. epidermidis* is a bacterial species equipped with remarkable genetic flexibility, and can employ a multitude of mechanisms to become adapted to the changing environment. Extrinsic factors in the neonatal ward, such as the interruption of skin barrier by medical devices and the selective pressure due to antibiotics, contribute to the conversion of *S. epidermidis* from a member of the skin microflora to an infectious agent. Furthermore, neonates are predisposed for *S. epidermidis* infections due to their distinct immunological characteristics. A better understanding of the dichotomy of *S. epidermidis* and the underlying mechanisms may inspire new anti-infectious strategies.

Introduction

Advances in neonatal intensive care have dramatically reduced the mortality rate of premature infants during the last two decades [Sweet et al., 2013]. However, the increasing survival of preterm infants is complicated by a growing burden of short-term and long-term problems associated with nosocomial infections [Marchant et al., 2013]. The last two decades have seen coagulase-negative staphylococci (CONS), especially *Staphylococcus epidermidis*, emerge as the predominant pathogen responsible for neonatal late-onset sepsis mainly in industrialized countries [Bizzarro et al., 2005; Marchant et al., 2013]. *S. epidermidis* is permanently present in the nosocomial environment and can disseminate widely among hospitals in different regions, adding to the morbidity, mortality and medical cost [Strunk et al., 2007; Power Coombs et al., 2013]. The evolving paradigm of *S. epidermidis* sepsis is a significant change from the traditionally held view, which envisioned *S. epidermidis* as a harmless skin inhabitant. Interdisciplinary collaborations at the interface of microbiology and immunology have generated new insights into the nature of *S. epidermidis*, showing that *S. epidermidis* mostly engages itself in a beneficial way in host defense and immune maturation, but may adopt an infectious lifestyle under certain circumstances [Cogen et al., 2008; Otto, 2009]. A thorough and comprehensive understanding of how *S. epidermidis* successfully establishes itself as the most widespread pathogen in the nosocomial environment may help to expand our armamentarium of anti-infectious strategies.

Clinical aspects of *S. epidermidis* neonatal sepsis

Neonatal sepsis is one of the leading causes of neonatal death [Qazi and Stoll, 2009]. Early-onset sepsis (EOS), reflecting trans-placental, or more frequently, ascending infections from the maternal genital tract, occurs within 72 h of age [Behrman et al., 2004]. In contrast, late-onset sepsis (LOS) is associated with the postnatal healthcare environment and usually presents after 72 postnatal hours, with the peak incidence between the 15th and

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Table 1
Regional differences in the proportion of neonatal LOS attributable to CONS.

Region	Birth year of cohort	No. of infants with LOS	Proportion (%) of LOS caused by CONS	Reference
Developed countries				
USA	2002–2008	3797	53.2	Boghossian et al. (2013)
England	2006–2008	416	54.0	Vergnano et al. (2011)
Netherland	2003–2006	318	77.9	van den Hoogen et al. (2010)
Australia	1992–2004	220	64.4	Lahra et al. (2009)
Developing regions				
Hebei (China), Malaysia, Hong Kong and Thailand	2006–2009	782	42.2	Al-Taiar et al. (2013)
Taiwan	2004–2011	713	39.9	Tsai et al. (2013)
Kuwait	2005–2009	949	35.5	Hammoud et al. (2012)
Turkey	2003–2010	86	46.5	Ozkan et al. (2013)

LOS: late-onset sepsis; CONS: coagulase-negative staphylococci

17th day of life [Stoll et al., 2002; Hira et al., 2007; Boghossian et al., 2013]. Current data shows that there is a shift from EOS to LOS, and CONS is now responsible for more than 50% of LOS in industrialized countries [Lahra et al., 2009; van den Hoogen et al., 2010; Vergnano et al., 2011; Boghossian et al., 2013]. The corresponding proportion is 35–46.5% in some developing regions (Table 1) [Hammoud et al., 2012; Tsai et al., 2013; Al-Taiar et al., 2013; Ozkan et al., 2013]. Although only few studies have particularly focused on *S. epidermidis*, it is possible to make data extrapolation due to the fact that *S. epidermidis* is most frequently identified among CONS species [Marchant et al., 2013]. The incidence of neonatal LOS due to CONS is inversely associated with infant maturity, and very low birth weight (VLBW) preterm infants (BW <1500 g) were found to be most susceptible [Boghossian et al., 2013; Tsai et al., 2013], with an incidence rate of approximately 25% [Boghossian et al., 2013]. Besides immaturity, well defined risk factors for LOS include prolonged hospital stay, repeated and prolonged invasive procedures such as central venous catheters and percutaneous central lines, intravenous lipids, late enteral feeding, prolonged duration of antibiotic use and mechanical ventilation, highlighting the impact of the nosocomial environment on the occurrence of CONS sepsis [Hira et al., 2007; Boghossian et al., 2013; Ozkan et al., 2013]. VLBW infants with indwelling medical devices are most susceptible for *S. epidermidis* sepsis, and the associated risk was up to 7 times higher than controls [Boghossian et al., 2013].

Clinical signs of neonatal sepsis are generally nonspecific and inconspicuous. Temperature instability, lethargy or irritability, increased frequency of apnea, bradycardia or tachycardia, jaundice and feeding intolerance are the most frequently recorded symptoms [Healy et al., 2004]. So far, confirmation of the clinical diagnosis of neonatal sepsis largely depends on microbiological detection of bacteria isolated from the blood culture. Some physicians ask for at least two positive blood cultures in order to differentiate between a true infection and a contamination since *S. epidermidis* ubiquitously colonizes on human skin and mucosa [Bizzarro et al., 2005; Abd El Hafez et al., 2011]. Biomarkers such as C-reactive protein and other inflammatory mediators may be helpful in identifying *S. epidermidis* sepsis [Kasper et al., 2013].

It should be noted that *S. epidermidis*, although not as virulent as its close relative *S. aureus*, can also lead to infants' death and is associated with long-term adverse outcomes. Case fatality ranges from 1.5% to 4.8% among institutions, and a mortality rate of up to 10.2% has been reported in VLBW infants [Makhoul et al., 2005; Hira et al., 2007; Tiskumara et al., 2009; Al-Taiar et al., 2013]. The incidence of meningitis and neonatal necrotizing enterocolitis (NEC) was about 0.4–7.3% and 2.3–11.5% respectively [Isaacs, 2003; Tiskumara et al., 2009; Anderson-Berry et al., 2011]. Rare but life-threatening morbidities such as osteomyelitis, hepatic abscess and small bowel perforation have also been noted [Moens et al., 2003; Holland et al., 2003; Pampinella et al., 2013]. In addition, infants with *S. epidermidis* sepsis were more likely to have bronchopulmonary dysplasia (BPD), neurodevelopmental and growth impairment [Anderson-Berry et al., 2011; Stoll et al., 2004] (Fig. 1), adding a serious burden on the affected infants and the family as well as public health. In light of the clinical significance of *S. epidermidis*, clinicians and scientists share a common interest in uncovering the nature of this nosocomial pathogen, thereby laying the foundation for possible preventive and therapeutic strategies.

The beneficial function of *S. epidermidis* on neonates

S. epidermidis normally maintains a benign relationship with the host and primarily has not evolved to become a pathogen [Otto, 2009]. In contrast to the abundant information on the infectious role of *S. epidermidis*, our understanding of the beneficial role of *S. epidermidis* on neonates is considerably limited. *S. epidermidis* colonizes on the skin immediately after birth, and rapidly dominates the microflora of various body sites within the first month of life [Capone et al., 2011]. Although the skin microbiome undergoes dramatic changes within body sites and with age throughout life, *S. epidermidis* remains the most frequently isolated species from skin, underpinning its evolutionary importance to the human host [Grice et al., 2009].

S. epidermidis exerts beneficial effects on the host by directly killing pathogens via self-produced antimicrobial substances and stimulating human innate immune system, such as Toll like receptors (TLRs) and the NF-κB signaling pathway [Cogen et al., 2008]. Live *S. epidermidis* was shown to induce the expression of human β-defensin-2 (hBD-2) and hBD-3 in keratinocytes via TLR-2 [Wanke et al., 2011]. Bacterial-conditioned medium (BCM) from *S. epidermidis* could enhance the expression of hBD-3 and RNase-7 in keratinocytes via TLR-2 and epidermal growth factor receptor (EGFR) signaling [Wanke et al., 2011]. The immune response of keratinocytes to *S. aureus* was also amplified through the abrogation of nuclear factor-κB (NF-κB) signaling suppression [Wanke et al., 2011]. Additionally, Table 2 demonstrates that certain factors secreted by *S. epidermidis* can support and prime the immune system of the host in the defense against harmful pathogens such as *S. aureus* [Otto et al., 2001; Lai et al., 2009; Bierbaum and Sahl, 2009; Iwase et al., 2010; Cogen et al., 2010; Lai et al., 2010; Li et al., 2013]. The beneficial role of *S. epidermidis* on the host immune system is further supported by recent findings. It is shown that the abundance of staphylococci in the skin microbiome peaked in the first few months of life and declined as the infant aged [Capone et al., 2011]. This suggests that the predominant colonization of staphylococci on neonatal skin may promote the early immune response, and the subsequent decline may be an orchestrated host-microbe interaction to facilitate the diversity and development of the human microbiome [Capone et al., 2011]. Erythema toxicum neonatorum, a common rash which develops in up to 70% of all healthy newborns,

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