Staphylococcus epidermidis: why is it so successful?

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Introduction

Coagulase-negative staphylococci (CoNS), particularly *Staphylococcus epidermidis*, are among the most frequently isolated microorganisms in clinical microbiology laboratories. The vast majority of infections assumed to be caused by CoNS comprise a significant consequence of hospitalization [1]. Reports on surveillance data taken from the National Nosocomial Infections Surveillance System during the late 1980s and early 1990s have indicated that CoNS are among the five most commonly reported pathogens in hospitals conducting hospital-wide surveillance. In addition, CoNS were the most frequently reported pathogens in nosocomial bloodstream infections [2,3].

One of the major problems facing the laboratory is distinguishing clinically significant, pathogenic strains of CoNS from contaminant strains because of their prevalence on human skin and mucous membranes and their relatively low virulence. Currently, out of more than 30 coagulase-negative species, 12 species are mainly found in specimens of human origin [1,4].

In clinical microbiology it is very important to differentiate CoNS on the basis of their novobiocin susceptibility. The most important group of the novobiocin-susceptible CoNS comprises five species and is designated the *S. epidermidis* group. Within this group, *S. epidermidis* sensu stricto is the most commonly isolated species, followed by *S. haemolyticus* and *S. hominis* [1,4].

Several possible virulence factors have been described for strains of novobiocin-susceptible CoNS, especially *S. epidermidis*. For example, some products of *S. epidermidis*, particularly peptidoglycan, induce the release of tumor necrosis factor-α, interleukin-1β and interleukin-6 by human monocytes [5,6]. The quantity of tumor necrosis factor-α that is released depends particularly on the size of the peptidoglycan molecule, as well as the presence of human serum. In addition, at least some coagulase-negative staphylococcal strains express a specific receptor for human transferrin, based on a common cell wall protein with a molecular mass of 42 kDa [7]. The increasing importance of CoNS may be in part due to the growing appreciation of this group of organisms as opportunistic pathogens and to reports describing new virulence factors. Furthermore, CoNS have become the leading causative agent of hospital-acquired infections, particularly as the patient population changes.

Groups of patients particularly susceptible to infections due to Staphylococcus epidermidis

Several groups of patients are especially susceptible to *S. epidermidis* infections; in these patients, either *S. epidermidis* or other coagulase-negative, novobiocin-susceptible staphylococcal species may be the predominant cause of the infectious disease.

One group comprises intravenous drug users, particularly heroin users, who frequently develop right-sided endocarditis, with *S. epidermidis* being the most frequently isolated causative organism. It has been postulated that heroin is injected intravenously in the form of microcrystals and causes microlesions of the tricuspid valvular endothelium. Repeated episodes of *S. epidermidis* bacteremia with large inocula, as a result of non-sterile injections, could then lead to tricuspid valve endocarditis [4]. However, these hypotheses have not yet been finally confirmed by experimental studies.

The second group, which is increasing in numbers, consists of immunocompromised patients. In premature newborns the opsonophagocytosis system is still not adequately developed and is thus unable to handle peri- or postpartum infectious challenges, including those of pathogens with relatively low virulence, particularly bacteria such as the CoNS. *S. epidermidis* is the leading cause of septicemia in premature newborns if the onset occurs later than 24–48 h after birth [8]. Patients with neutropenia after cytostatic and/or immunosuppressive therapy are also susceptible to septicemia caused by *S. epidermidis*. Most of these patients suffer from leukemia, but patients with other malignant diseases may also be at risk if the number of functioning granulocytes is too low [1,4]. The main sources of infection are the skin and mucous membranes of the oral cavity, nose and urogenital tract, and the point of entry is very often an intravascular catheter [1,9].

The most important group of particularly susceptible patients are those with indwelling or implanted foreign polymer bodies. These devices are increasingly used—permanently or transiently—in diagnostic and therapeutic procedures. The most important complication associated with the presence of foreign bodies is infection, and the most frequently isolated bacteria are CoNS, particularly *S. epidermidis* [9,10]. A battery of virulence factors involved in the pathogenesis of polymer-associated staphylococcal infection has been defined and characterized in recent years (see below).

Furthermore, there is growing evidence that some other, more chronic associated clinical syndromes may also be at least partly associated with *S. epidermidis*. These 'chronic polymer-associated syndromes' with

possible involvement of *S. epidermidis* are the 'aseptic' loosening of hip prostheses or other joint prostheses [11], the fibrous capsular contracture syndrome after mammary augmentation with silicone prostheses [12], and the late-onset endophthalmitis after implantation of artificial intraocular lenses following cataract surgery [13]. In different studies, identical clones, characterized by molecular typing methods, have been isolated at different times and/or from various multiple sites.

Thus, in the cutaneous ecosystem, CoNS generally function as commensal or saprophytic organisms. However, if the barrier function of the skin is impaired by any trauma or during surgery, especially in association with the insertion or implantation of a foreign body, these organisms can gain entry to the host. Depending upon their ability to adhere to host or foreign body surfaces, breach or avoid the host immune system, multiply, and produce an inflammatory response in the host, they may then develop the lifestyle of a pathogen [1].

New aspects of the pathogenesis of polymer-associated infections due to Staphylococcus epidermidis

Most important in the pathogenesis of *S. epidermidis* infection associated with foreign bodies such as orthopedic devices, intravascular catheters, cerebrospinal fluid shunts, prosthetic heart valves, continuous ambulatory peritoneal dialysis (CAPD) catheters and cardiac pacemakers [10] is the colonization of the polymer surface by formation of a biofilm. Such biofilms are composed of multilayered cell clusters embedded in an extracellular slime substance (ESS), which consists mainly of cell wall teichoic acids and host products [10]. Biofilm formation proceeds in two steps: rapid adherence of *S. epidermidis* cells to the polymer surface is followed by a more prolonged accumulation phase involving cell proliferation and intercellular adhesion. Adherence to biomaterials depends on the characteristics of the bacterial cell surface and on the nature of the polymer material and is influenced by non-specific physicochemical forces such as polarity, van der Waal's forces and hydrophobic interactions [10]. Initial adherence and cell surface hydrophobicity have been associated with bacterial surface proteins [14]. The staphylococcal surface proteins SSP-1 and SSP-2 are organized as fimbria-like polymers and have been described as mediating *S. epidermidis* adherence to polystyrene [15]. Recently, the surface-associated autolysin AtlE of *S. epidermidis* has been found to contribute to primary attachment of bacterial cells to a polymer surface [16]. Implanted material rapidly becomes coated with plasma and connective tissue proteins such as fibronectin, fibrinogen, and vitronectin [17,18] and some of these host factors could serve as specific receptors for colonizing bacteria [19,20]. The autolysin AtlE also has vitronectin-binding activity, suggesting not only a function in the early stages of adherence involving direct interactions between bacteria and naked polymer surfaces, but also a contribution to later stages of adherence involving specific interactions with vitronectin deposited on the polymer surface [16]. Aside from proteins, a polysaccharide structure, capsular polysaccharide/adhesin (PS/A), has been attributed to cellular adherence to biomaterials [21].

Following the primary attachment to the polymer surface, the bacteria multiply and form multilayered cell clusters, which process requires intercellular adhesion. Recently, the specific polysaccharide intercellular antigen (PIA) involved in intercellular adhesion and biofilm accumulation has been detected. Purification and structural analysis of PIA revealed that it is a linear β-1,6-linked glucosaminoglycan mainly composed of at least 130 2-deoxy-2-amino-D-glucopyranosyl residues, of which 80–85% are *N*-acetylated [22]. Most recently, the genes (*icaABC*) mediating cell clustering and PIA synthesis in *S. epidermidis* have been cloned and sequenced [23]. Moreover, additional factors are obviously essential for accumulative growth of *S. epidermidis*, such as the 140-kDa extracellular protein AAP (accumulation-associated protein), which is absent in an accumulation-negative but PIA-positive mutant [24]. How this antigen acts in accumulation has still to be explored. There is substantial evidence that biofilm-encased *S. epidermidis* is protected against host response mechanisms such as opsonophagocytosis and against antibiotic action [25]. This could explain the facts that even an immunocompetent host cannot eliminate the infectious focus on the foreign body and that antibiotic therapy also fails in most cases.

Emergence of glycopeptide-resistant strains

A large proportion of nosocomial isolates of CoNS are resistant to multiple antibiotics, including penicillinase-resistant penicillins [26]. Given the extremely high frequency of these isolates, vancomycin has been recommended empirically for the treatment of infections produced by these microorganisms. Until recently, CoNS have displayed uniform susceptibility to glycopeptides. However, the emergence of strains with decreased levels of susceptibility to vancomycin and especially teicoplanin has been reported in several studies [27,28]. One study revealed that 14 of 32 clinical isolates of CoNS exhibiting either decreased levels of susceptibility or true resistance to teicoplanin belonged to the species *S. epidermidis* [29]. The in vivo development of resistance to glycopeptides among CoNS strains limits the therapy of infections by these microorganisms. Thus, there is a need for resistance

surveillance of nosocomial isolates of CoNS, especially of the clinically increasing significant species *S. epidermidis*.

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