

Staphylococcus epidermidis: A Commensal Emerging As A Pathogen With Increasing Clinical Significance Especially In Nosocomial Infections

M Rasheed, M Awole

Citation

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Abstract

S. epidermidis lives naturally on the skin and mucous membranes.

While at one time the appearance of *S. epidermidis* in clinical material could be dismissed as contamination, it is now one of the most important agents of nosocomial infections especially in immunocompromised individuals, neonates and patients with internal prosthetic devices. In these patients, the infection result from a compromise in both general and local defense mechanism, and inability to clear staphylococci from infected device because of a biofilm on the foreign body surface. Distinguishing, clinically significant pathogenic strains from contaminant strains is one of the major challenges facing clinical microbiologists. Because many isolates are multiply antibiotic resistant, their infections are difficult to treat and can even be fatal.

A detailed characterization of isolates of *S. epidermidis* strains through speciation, genetics and antibiotic susceptibility may be necessary to distinguish infecting from contaminating isolates and to plan suitable therapy.

INTRODUCTION

Coagulase negative staphylococci (CNS) constitute a major component of the normal skin and mucosal microflora₁.

They are commonly isolated in clinical specimens and many are identified as important agents of hospital acquired infections especially in immunocompromised individuals, neonates and patients with internal prosthetic devices_{2,3}.

CNS were considered as harmless skin commensal and dismissed as culture contaminants, but in recent years, they are increasingly being recognized as important human pathogens₁.

Among all CNS, *Staphylococcus epidermidis* strains represent the most frequent cause of nosocomial sepsis and the most common agents of infections with implanted medical devices₄.

MOLECULAR MECHANISM OF BIOFILM FORMATION

A characteristic of many pathogenic strains of *S. epidermidis*

is the production of slime resulting in biofilm formation₅. The slime is predominantly a secreted teichoic acid, normally found in the cell wall of the staphylococci₆. This ability to form a biofilm on the surface of a prosthetic device is probably a significant determinant of virulence for these bacteria₇. Biofilm may serve to protect the organism from host phagocytic mechanism and improve the local nutritional environment₈.

Recently, the genetic control of the slime production has begun to be elucidated, first in the *S. epidermidis* and then in *Staphylococcus aureus*. Synthesis of the capsular polysaccharide is mediated by the *ica* operon (intercellular adhesion gene cluster)₉.

It appears that bacterial adherence is a complex multistep process that is influenced by the host, the device and the microbe. The adherence process is sub divided into the following stages: attachment, adhesion and aggregation₈.

The primary attachment of *S. epidermidis* to a polystyrene surface is related to a cell surface protein exhibiting

vitronectin binding activity¹⁰.

The later phases of adherence, in which organisms adhere to one another and elaborate biofilm, are mediated by polysaccharide intercellular adhesin (PIA), which is synthesized by products of the chromosomal *ica* gene locus, which comprises intercellular adhesion genes (*ica A*, *ica D*, *ica B*, and *ica C*) organized, in an operon^{11,12, 13,14}.

Mutants lacking PIA are less virulent in an animal model for foreign body infection and immunization with purified PIA is protective¹⁵.

Sub inhibitory concentrations of tetracycline and the semi synthetic streptogramin antibiotic quinupristin-dalfopristin were found to enhance *ica* expression 9 to 11 fold, whereas penicillin, oxacillin, chloramphenicol, clindamycin, gentamycin, ofloxacin, vancomycin and teicoplanin had no effect on *ica* expression. A weak (2.5 fold) induction of *ica* expression was observed for sub inhibitory concentrations of Erythromycin¹⁶.

S. epidermidis strains from clinical materials appears to differ from saprophytic strains by the presence of the *ica A* and *ica B* genes, their capacity for phase variation, their abilities to adhere to polymer and autoaggregate and in their colony morphology on congo red agar¹⁷.

INFECTIONS BACTEREMIA

S. epidermidis and other CNS are the most frequently reported pathogens in nosocomial blood stream infections¹.

According to the Centers for Disease Control and Prevention's National Nosocomial infection surveillance system; *S. epidermidis* is responsible for 33.5% of nosocomial blood stream infections¹⁸.

These bacteremias are largely due to intravascular associated infection. Unfortunately, nosocomial bacteremia due to *S. epidermidis* is a rapidly increasingly problem^{5, 19, 20}.

A study has demonstrated that the isolation of CNS was attributed to the colonization of the implanted catheter since the same microorganism had been isolated from the blood of patients during the preceding weeks, some of them with multiple positive cultures²¹.

It is known that mucosal damage of the alimentary tract and concurrent colonization of mucous membranes are risk

factors for *S. epidermidis* infections²². Colonization of the gut and skin with antibiotic resistant *S. epidermidis* can follow the intensive use of oral and systemic antimicrobials²³.

Bacteremia originating from these sites can result from a compromise in both general and local defense mechanism in severely immunocompromised patients.

S. epidermidis frequently contaminate blood cultures making their interpretation a major concern for clinicians and for microbiologists. Although, criteria such as, sepsis symptoms, the number of positive blood cultures from separate venipuncture or access site and the similarity of their antibiotic resistance profiles, are often considered⁵.

A large proportion of nosocomial isolates of CNS are resistant to multiple antibiotics, including penicillinase resistant penicillins²⁴.

Localized infections with positive blood cultures are associated with higher mortality rate than localized infections without positive blood cultures²⁵.

INFECTIONS ASSOCIATED WITH MEDICAL DEVICES

S. epidermidis is the most prominent cause of intravascular catheter associated infection¹⁹.

In one study it was demonstrated that two clones of *S. epidermidis* were predominantly involved in colonization and subsequent infection in neutropenic hemato-oncologic patients in a setting with a high incidence of Catheter Related Infection (6.0/1000 catheter days), and a very high catheter removal rate for CRI, 70%, despite prompt treatment with vancomycin. They seem to have persisted for a period of at least 5 years in the hematology department²⁶.

At insertion, these clones constituted 13% CNS isolated from air samples and 44% CNS isolated from skin cultures.

After insertion, their combined prevalence increased to 53% in catheters not associated with CRI and 74% in catheters associated with CRI.

A likely source of *S. epidermidis* strains involved in CRI appeared to be the skin flora in 75% of cases²⁶.

As 94% of these two predominant strains were ciprofloxacin resistant and all patients received selective antimicrobial prophylaxis with ciprofloxacin, these strains possessed a

selective advantage.

Perhaps sub inhibitory concentration of ciprofloxacin is able to promote adherence of these two *S. epidermidis* clones, as has been described recently for *S. aureus* ²⁷.

However, in earlier studies, adherence of a variety of CNS strains was reduced after incubation with sub inhibitory concentration of ciprofloxacin²⁸.

Migration of skin organisms at the insertion site into the cutaneous catheter tract with colonization of the catheter tip is the most common route of infection for peripherally inserted, short-term catheters ^{29,30}.

Some catheter materials have surface irregularities that enhance the microbial adherence. Additionally, certain catheter materials are more thrombogenic than others, a characteristic that also might predispose to catheter colonization and catheter related infection²⁹.

Teflon or polyurethane catheters have been associated with fewer infectious complications than catheters made of polyvinyl chloride or polyethylene³¹.

Contamination of the catheter hub contributes substantially to intraluminal colonization of long-term catheters and implicated as an additional entry point leading to catheter related sepsis justifying local use of antibiotics in preventive control measures^{29, 32}.

Rarely, catheter might become hematogenously seeding from another focus of infection ^{29, 30}.

It might be possible to eradicate methicillin resistant CNS at the site of catheter implantation by using antiseptics and to prevent ingress of CNS by a combination of occlusive dressings and careful handling of catheters and insertion sites with gloved hands²².

ENDOCARDITIS

Coagulase negative staphylococci, usually *S. epidermidis*, previously a minor cause of native valve endocarditis, are an important cause of prosthetic valve endocarditis and nosocomial infective endocarditis. Nosocomial native valve infections generally result from infected intravascular devices; the affected valve may or may not have been previously abnormal^{33,34}.

S. epidermidis, are the predominant cause of nosocomial prosthetic valve endocarditis, can be acquired in the theatre

(or shortly thereafter) at the time of the original valve replacement and presents within weeks or more often diagnosed within 60 days after surgery (early onset) and the cause of 3 to 8% of native valve endocarditis cases, usually in the setting of prior valve abnormalities^{34, 35, 36}.

The vast majority of CNS causing PVE, when speciated were *S. epidermidis*.

In contrast, when infection involves native valves, only 50% of isolates were *S. epidermidis* ^{35, 36}.

Prosthetic infection can also be acquired from an infected intravascular device.

Nosocomial staphylococci tend to be multiple resistant.

Community acquired endocarditis, which may involve native (usually) or prosthetic valves, is increasingly recognized. Most patients with native valve infection have a pre-existing cardiac abnormality.

The organism must derive from the patient's skin but predisposing skin lesions are seldom detected. The infection often mimics *S. aureus* endocarditis with rapidly destructive valvular disease, neurological manifestation and concomitant vertebral osteomyelitis.

The commonest pathogen is *S. epidermidis*, but there are increasing reports of other species, particularly *S. lugdunensis*, which seems to be especially virulent. These community acquired strains are frequently penicillin sensitive³⁷.

Some cases of endocarditis following implantation of a prosthetic valve were recently shown to be attributable to polyclonal *S. epidermidis* populations³⁸. Therefore, the detection in samples from the same patient of *S. epidermidis* strains with different antibiograms does not necessarily indicate contamination of the samples during collection.

Complications, such as dehiscence of the valve or obstruction, are relatively common.

Blood cultures are usually positive and diagnosis is occasionally difficult. Antibiotic treatment of prosthetic valve endocarditis due to *S. epidermidis* is often inadequate and additional surgical intervention is required in most cases ^{39, 40}.

URINARY TRACT INFECTIONS

S. epidermidis is the predominant species cultured from the

urine in significant numbers (10⁴ cfu/ml), accounting for 80-90% of non *S. saprophyticus* CNS isolates.

It is cultured almost exclusively from the urine of hospitalized patients with complications of the urinary tract. About half of them have an indwelling urinary catheter.

Both males and females are equally affected and most patients are 50 or more years of age. In at least half of the cases, the organisms are multiple drug resistant⁴¹.

EYE INFECTIONS

S. epidermidis is commonly cultured from the conjunctive and lid margins of normal subjects⁴².

Because of its ubiquitous nature and relatively low virulence, *S. epidermidis* has received so far little attention for its role in ocular infections. However, in different studies

S. epidermidis has been reported to play a significant role in several ocular external diseases such as chronic blepharitis and suppurative keratitis^{43, 44}.

Given the high level broad spectrum activity against most bacteria and the reduced frequency of ocular toxic effects, ciprofloxacin is currently considered the drug of choice in the therapy for bacterial keratitis⁴⁵.

However, there is growing evidence for ciprofloxacin resistant ocular strains of *S. epidermidis*⁴⁶.

Vancomycin and teicoplanin are antistaphylococcal antibiotics, to which resistance is rarely seen, and should be considered the drugs of last resort for the therapy of nosocomial gram positive infections⁴⁷. The multiple resistance of *S. epidermidis* is a recognized problem. It might possibly represent a response to prolonged treatment.

PEDIATRICS

Major advances in perinatal and neonatal care units have significantly improved survival of very low birth weight infants. However late onset nosocomial neonatal septicaemia, after more than 72 hours post delivery, by CNS, the most common organism accounting for more than 50% cases, show multiple antibiotic resistance including resistance to methicillin^{48, 49}.

CNS are ubiquitous and every human is colonized soon after birth: during invasive procedures these organism may then gain entry to the blood and result in sepsis⁵⁰.

There is a clear co-relation between very low birth weight and the risk of a nosocomial infection with CNS⁵¹.

The intensive use of antibiotics in an NICU setting with highly susceptible patients causes selection of multiresistant clones of CNS, which subsequent becomes endemic⁵².

S. epidermidis distinct clones can become endemic in NICUs as long as a decade and nosocomial transmission plays an important role in *S. epidermidis* bacteremia⁵³.

Quantitative biofilm production significantly greater in strains isolated from either the blood or skin of neonates with *S. epidermidis* bacteremia⁵⁴.

DRUG RESISTANCE

Over the last decades, there has been an enormous increase and emergence of CNS strains particularly *S. epidermidis*, *S. haemolyticus* and *S. hominis*, resistant to the antibiotic methicillin, especially in nosocomial settings⁵⁵. Methicillin resistance/multiple drug resistance has been documented more often in disease causing strains of *S. epidermidis* than in skin colonizing strains⁵⁶.

Most of these strains harbor *mec A*, the gene encoding the penicillin-binding protein PBP2a, which has decreased affinity for beta lactam antibiotics⁵⁷.

Methicillin sensitive *S. epidermidis* strains should be treated with oxacillin or cefazolin or clindamicin. Methicillin resistance is equivalent to resistance to oxacillin, which is commonly used and extremely effective anti-staph drug, in fact the drug of choice. Methicillin resistant *S. epidermidis* strains should be treated with vancomycin⁵⁸.

Detection of resistance to oxacillin in staphylococci is important to guide the therapy and prevent the patient from being unnecessarily treated with vancomycin, which is an antimicrobial agent that presents therapeutic complications, high costs and may lead to the selection of resistant mutants⁵⁹.

In an article of Jukka Hyvarinan et al, the percentage of *S. epidermidis* isolates resistant to the 20 tested antibiotics was oxacillin (58%), penicillin (82%), amoxicillin/clavulanic acid (34%), cephalothin (4%), cefuroxime (31%), cefotaxime (20%), imipenem (46%), gentamycin (46%), tobramycin (57%), netilmicin (16%), ciprofloxacin (23%), ofloxacin (21%), erythromycin (36%), fusidic acid (27%), clindamycin (34%), chloramphenicol

(19%), rifampin (4%), vancomycin (0%), co-trimoxazole 62%, trimethoprim (53%)⁶⁰.

CONCLUSION

Immunocompromised patients are particularly at risk of CNS infections, as are individuals with indwelling catheters or prosthetic devices.

Because many isolates are multiply antibiotic resistant, their infections are very serious and can even be fatal.

The surfaces and materials such as floors and walls of the hospital rooms, stethoscopes, Beds, tables for nursing elements, oxygen tube extreme and oxygen masks⁶¹, may play an important role in the spread of infectious agents including antimicrobial resistant strains of *S. epidermidis*, so the regular use of disinfectant for their cleaning is advisable.

The early and precise detection of these organisms in hospital environments and in high risk patients such as cardiac surgery patients, preterm newborns or immunocompromised patients, can prevent the contamination of prosthetic devices or indwelling catheters, and may represent a substantial help for the early treatment.

CORRESPONDENCE TO

Rasheed M.U Lecturer, School of Medical Laboratory Technology Medical Faculty, Jimma University, P.O Box NO.378 Jimma, Ethiopia. Mobile: 00251 911 052 572 Phone No. 00251 47 111 8567-Residence 00251 47 111 1875-Office Email id: hmzrshd@yahoo.co.in

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<http://hopkins-abxguide.org/>,

abxfeedback@hopkinsabxguide.org

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Author Information

M.U. Rasheed, MSc, RM(ASM)

Lecturer, School of Medical Laboratory Technology, Medical Faculty, Jimma University

Mohammed Awole, M.Sc.

Head, School of Medical Laboratory Technology, Medical Faculty, Jimma University