

## Adhesion of *Staphylococcus epidermidis* to Surgical Sutures

HESHAM KHALIL<sup>1</sup>, NAJAT A. MARRAIKI<sup>2</sup>, GHADAH ABUSALIM<sup>2</sup>,  
RACHEL J. WILLIAMS<sup>3</sup> and SEAN P. NAIR<sup>3</sup>

<sup>1</sup>Department of Maxillofacial Surgery, College of Dentistry, King Saud University, Riyadh (KSA).

<sup>2</sup>Department of Botany and Microbiology, College of Science, King Saud University, Riyadh (KSA).

<sup>3</sup>Division of Microbial Diseases, Eastman Dental Institute for Oral Health Care, University College London, 256 Gray's Inn Road, London WC1X 8LD (UK).

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### ABSTRACT

#### Objective

To investigate the interaction of *Staphylococcus epidermidis* with commonly used surgical sutures and the role of some of this bacterium virulence factors in this interaction.

#### Summary Background Data

Coagulase negative staphylococci are ranked as the second most common cause of postoperative surgical site infections. Sutures have been suggested to act as adhesive surfaces that promote bacterial accumulation. Adherence of *S. epidermidis* and *S. aureus* to cardiac sutures has been suggested to be one of the explanations for these organisms being the commonest cause of early prosthetic valve endocarditis. Few *S. epidermidis* virulence factors have been identified and reported to be involved in this bacterium colonization of biomaterials and biofilm formation.

#### Methods

Different strains of *S. epidermidis* were incubated with a number of commonly used sutures and examined for their capacity to bind to these sutures. The role of some of *S. epidermidis* virulence determinants thought to be important in adhesion to foreign bodies and host extracellular matrix proteins were analyzed for their role in the adhesion of this bacterium to sutures.

#### Results

Adherence of *S. epidermidis* to sutures varied according to the type of material from which the suture was constructed and the strain of bacteria. The major adhesin responsible for binding to sutures was identified as the autolysin (AtlE) of this bacterium. *S. epidermidis* adhesion significantly increased when suture materials were coated with human plasma.

#### Conclusions

*S. epidermidis* has a propensity to adhere to surgical sutures and this could increase the risk of wound infection and complications. The results of this study demonstrate that the choice of suture material could seriously impact on the risk of infection and indicate the need for further material development. These studies also suggest that inhibitors of *S. epidermidis* autolysin (AtlE) may be useful coating agents to prevent bacterial adhesion to sutures.

**Key words:** *Staphylococcus epidermidis*, adhesion, sutures, virulence.

### INTRODUCTION

Coagulase negative staphylococci are ranked as the second most common cause of postoperative surgical site infections<sup>1</sup>. These organisms can cause serious postoperative infections especially in patients with implanted foreign devices. *Staphylococcus epidermidis* has

been found to be responsible of 50-70% of catheter related infections, 40% cardiovascular implants infections<sup>2</sup> and most cases of osteomyelitis around orthopaedic implants<sup>3</sup>. Advances in surgical procedures and aseptic techniques have resulted in a reduction in the incidence of surgical related infections, but such infections do still occur at unacceptably high incidence and are complicated

in the presence of implanted devices<sup>4</sup>. The situation becomes more difficult when applied to intra-oral wounds where asepsis is a challenge. Although sutures are considered to be an important predisposing factor in development of infections, few studies have been conducted in this area of research<sup>5,6</sup>. Keratitis following eye surgery can be caused by bacterial infiltration due to irritation of loose, exposed or broken sutures. Such infections may have serious complications including visual loss<sup>7</sup>. Comparisons between infections of wounds closed by either sutures, or tissue adhesives have shown that there are more staphylococcal bacterial counts where sutures have been used. Although tissue adhesives such as cyanoacrylate may have bactericidal effect<sup>8</sup>, it has been reported that *Staphylococcus epidermidis* infections might be promoted by adhesion to such tissue adhesives<sup>9</sup>. Fibrin sealants when used instead of sutures have shown a lower rate of infection and can promote wound healing<sup>10</sup>. Hirsham *et al.* 1984 have shown that bacteria such as *S. aureus* can penetrate sutured wounds and sutures themselves contribute to this phenomenon<sup>11</sup>.

Although the mechanism behind the increased risk of wound sepsis in the presence of suture materials is not clear, it is generally thought that sutures act as adhesive surfaces that promote bacterial accumulation. Adherence of *S. epidermidis* and *S. aureus* to cardiac sutures has been suggested to be one of the explanations for these organisms being the commonest cause of early prosthetic valve endocarditis<sup>12</sup>. Bacterial cell surface properties can affect adhesion to different biomaterials<sup>13</sup>. Bacterial adhesion is often found to differ between materials with different chemical compositions or hydrophobicity<sup>14</sup>. A relationship between hydrophobicity and bacterial adhesion to biomaterials has been demonstrated for *S. epidermidis*<sup>15</sup>. The adhesion of hydrophobic strains of *S. epidermidis* to Teflon catheters is significantly higher than that of hydrophilic strains<sup>16</sup>. *S. epidermidis*, exhibits weaker interactions with host proteins when compared to *S. aureus*, therefore, hydrophobic interaction with plastic biomaterials is usually impaired by plasma proteins<sup>16</sup>. Suture use not only plays a role in infection but triggers inflammatory reactions, producing scarring and alters the process of wound healing<sup>17</sup>.

Two stages have been identified in the process of foreign body related infection and biofilm formation. These are the primary attachment of bacteria to the material and the formation of multi-layered cell clusters. Very few *S. epidermidis* virulence factors have been identified. However the role of some of these virulence factors in attachment to biomaterials has been reported in the literature. *S. epidermidis* microbial surface components recognizing adhesive matrix molecules (MSCRAMMS), such as the fibrinogen binding protein (fbe) also known as SdrG<sup>18</sup>, and fibronectin binding protein<sup>19</sup>, might be involved in indirect attachment of *S. epidermidis* to biomaterials. The *S. epidermidis* autolysin AtlE has been found to be responsible for the primary attachment of this organism to central catheters<sup>20</sup>. The polysaccharide intercellular adhesin (PIA) of *S. epidermidis* has been demonstrated to be involved in intercellular adhesion, biofilm formation and biomaterial related infection<sup>21</sup>. The GehD lipase of *S. epidermidis* has been shown to be a bifunctional molecule, acting both as lipase and a collagen adhesin<sup>22</sup>, however, the role of this adhesin in adhesion to abiotic surfaces has not been investigated.

In this study, we have examined the capacity of different strains of *S. epidermidis* to adhere to commonly used surgical sutures. The role of some *S. epidermidis* virulence factors in the capacity of this organism to adhere to surfaces was also determined. These observations could yield insights into mechanisms relevant to suture related infection and help in the prevention of such infections.

## METHODS

### Bacterial strains and growth

The *S. epidermidis* strains used in this study were: NCTC11047 (from the National Collection of Type Cultures, Central Public health Laboratory, UK), *S. epidermidis* strain 19 a fibrinogen binding isolate from a patient with peritonitis obtained from Karolinska Institute, Sweden. *S. epidermidis* strain HB and its isogenic *sdrG* deficient mutant (from Professor Tim Foster, Trinity College, Dublin, Ireland). Strain 9 and its isogenic mutants 2J24 (*gehC::ermC*), and KIC82 (*gehD::ermC*) were a gift from Professor Keith

Holland, School of Biochemistry and Molecular Biology, University of Leeds, UK). Strain O-47 and its isogenic mutant deficient in PIA and AtIE (From Professor Paul Fey, Nebraska Medical Center, University of Nebraska, Nebraska, USA). Strain RP62A is a clinical isolate. Bacteria were routinely grown in brain heart infusion broth (Oxoid, Basingstoke, United Kingdom) aerobically at 37°C with shaking.

### Suture materials

Five sutures were used in this study; these were prolene, vicryl, silk (mersilk), monocryl and polydioxanone (PDS II), all manufactured by Ethicon and obtained from Johnson and Johnson Company, UK. Prolene (Polypropylene) is a monofilament, synthetic, nonabsorbable. It is composed of an isotactic crystalline stereoisomer of polypropylene. Vicryl (Polyglactin 910) is a synthetic, absorbable suture, composed of 90 % glycolide and 10 % L-lactide. Mersilk is a nonabsorbable multifilament, composed of an organic protein. Monocryl (Poliglecaprone 25) is a synthetic, absorbable, monofilament suture prepared from a copolymer of glycolide and caprolactone. PDS II (Polydioxanone) is a synthetic, absorbable, monofilament suture made of the polyester poly dioxanone.

### Adhesion assay

Sterile suture samples of two centimeter length were incubated with *S. epidermidis* strains in 4 milliliters of sterile phosphate buffered saline (PBS) (Sigma-Aldrich, UK). Incubation was at 37°C with shaking at 200 rpm for 3 hours unless otherwise specified. After incubation, non adhered bacteria were removed by washing with PBS three times. As a control, the liquid from the last wash-up was examined for bacterial colonies by plating on blood agar plates containing 5% horse blood. To remove the adherent bacteria, the samples were resuspended into two milliliters of sterile PBS containing 0.1% Triton X100 and vortexed for three minutes. The number of bacteria adhered to sutures was determined by serial dilution and plating on blood agar plates containing 5% horse blood.

### Adhesion of *S. epidermidis* plasma coated suture materials

Sutures were incubated in human plasma

overnight, washed with PBS then resuspended in 4 ml of PBS containing  $10^8$  bacteria. Tubes were incubated at 37°C for 3 hours with shaking. Sutures were washed three times with PBS and resuspended in fresh 3 ml of PBS and vortexed for 3 minutes. Adhered bacteria were enumerated by serial dilution and plating on blood agar plates.

### Statistics

Data were analyzed with a student's *t* test. Significance was defined as  $P < 0.05$ . Data are expressed as means and standard deviations of at least three experiments.

## RESULTS

### Different strains of *S. epidermidis* have different capacities to adhere to suture materials

To determine if *S. epidermidis* adheres to surgical suture materials, five different sutures were incubated with different strains of *S. epidermidis*. Fig.1 shows the capacity of three *S. epidermidis* strains to adhere to five suture materials, prolene, mersilk, monocryl, polydioxanone and vicryl. *S. epidermidis* strain NCTC11047 had a significantly greater capacity to bind to all the sutures tested when compared to strains 19 and RP62A (figure 7-1). Adhesion of *S. epidermidis* to sutures differed according to the material from which the suture was constructed. For example adhesion of *S. epidermidis* strain NCTC11047 to silk was 5.4 fold higher than to polydioxanone ( $P < 0.01$ ).

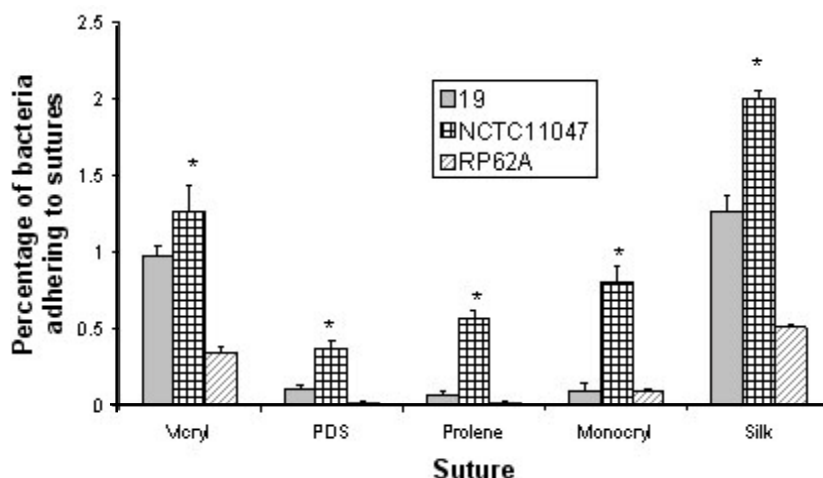
Adhesion of *S. epidermidis* strain 19 to silk was 12-fold higher than its adhesion to polydioxanone ( $P < 0.001$ ). Comparison of the adhesion of *S. epidermidis* strain 19 to all five sutures revealed that adhesion to PDS II was lowest followed by prolene, monocryl, vicryl and silk. *S. epidermidis* strains NCTC11047 and RP62A showed low adhesion to PDS II and prolene. These findings suggest that the monofilament sutures PDS II, monocryl and prolene to which less bacteria bind may present less of an infection risk than multifilament sutures such as vicryl and silk.

### *S. epidermidis* SdrG (fbc) is involved in adhesion to suture materials

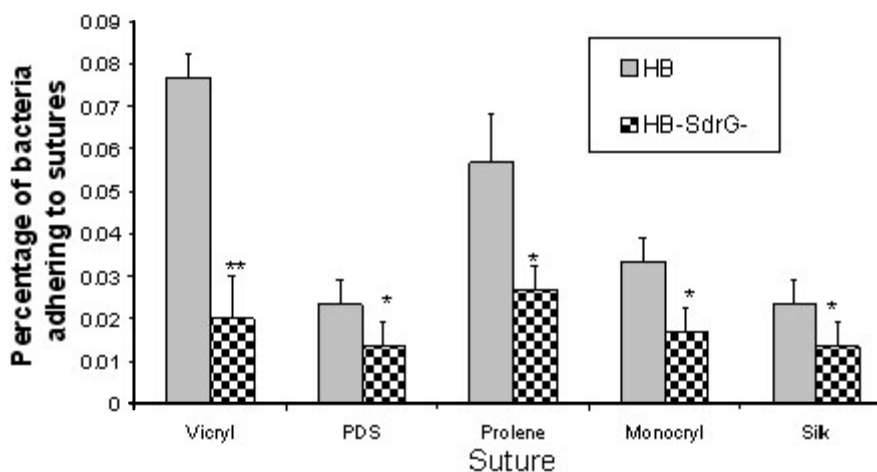
It has recently been reported that *S. epidermidis* SdrG (fbc) promotes bacterial adhesion

to fibrinogen<sup>18</sup>. To determine if this factor was involved in adhesion of *S. epidermidis* to suture materials, a *S. epidermidis* mutant disrupted in the *sdrG* gene was compared to the parent strain (HB). Fig 2 shows the levels of adhesion of *S. epidermidis* strain HB and its SdrG deficient mutant to five

different surgical sutures. There was a significant reduction in the adhesion of the mutant strain to all of the sutures. The level of adhesion was reduced by 28 to 70 % dependant on the suture material. Adhesion of the parent strain to vicryl was 70% higher than its isogenic mutant ( $P = 0.0001$ ).



**Fig. 1:** Adhesion of *S. epidermidis* strains 19, NCTC11047 and RP62A to sutures. Data are the percentage of the bacterial inoculums adhering to sutures. The results are from one representative experiment of at least three; data are the means and standard deviations of three replicate cultures. The graph shows that different strains of *S. epidermidis* have different capacities to adhere to different sutures (PDS: polydioxanone II). \* indicates  $p$  value  $< 0.05$



**Fig. 2:** The graph shows the capacity of *S. epidermidis* HB and its isogenic mutant disrupted in SdrG to adhere to sutures. The experiment is a representative of three experiments performed on different occasions. Data are the means and standard deviations of three replicate experiments. *S. epidermidis* strain HB disrupted in SdrG had a reduced capacity to adhere to sutures. \* indicates  $p$  value  $< 0.05$ , \*\*  $P$  value  $< 0.01$

### GehD lipase is involved in adhesion of *S. epidermidis* to suture materials

The genes for two lipases GehC and D from *S. epidermidis* have been cloned and sequenced<sup>23,24</sup>. The lipase GehD has been found

to be a bifunctional molecule, not only acting as lipase but also as cell surface-associated collagen adhesin<sup>22</sup>. We examined the role of the *S. epidermidis* lipases in adhesion of this bacterium to different suture materials. Fig. 3 shows the

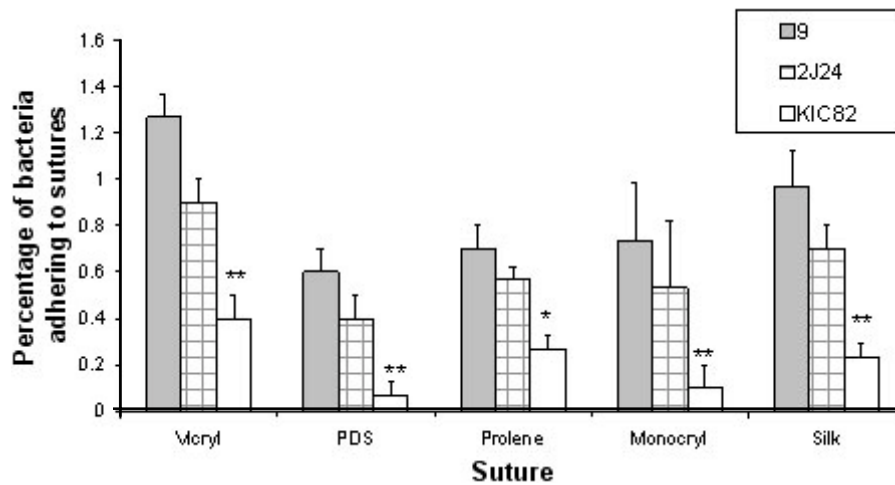


Fig. 3: The role of *S. epidermidis* lipases in adhesion to sutures. The graph shows the capacity of *S. epidermidis* strain 9, its isogenic mutants 2J24 deficient in the GehC lipase and KIC82 deficient in the GehD lipase to adhere to sutures. The experiment is a representative of three experiments performed on different occasions. Data are the means and standard deviations of three replicate experiments. The GehD mutant strain had a reduced capacity to bind to sutures \* indicates p value < 0.05, \*\* P value < 0.01

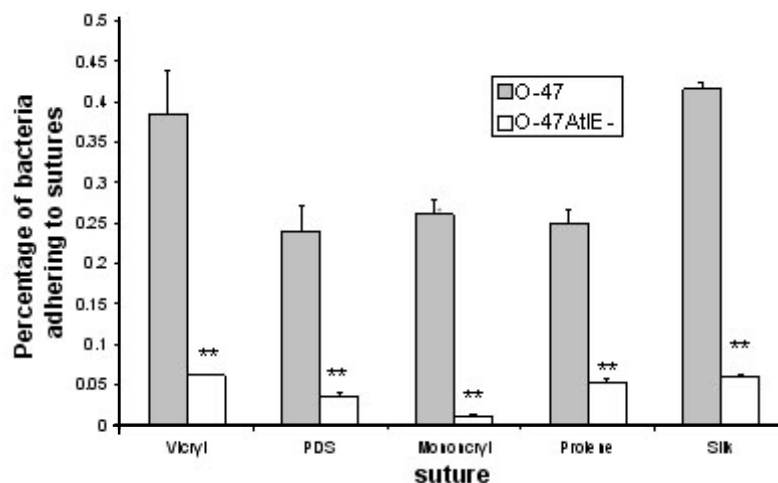


Fig. 4: The role of the *S. epidermidis* autolysin AtIE in adhesion to sutures. The graph shows the capacity of *S. epidermidis* strain O-47 and its isogenic mutant deficient in the autolysin AtIE to adhere to sutures. The experiment is a representative of three experiments performed on different occasions. Data are the means and standard deviations of three replicate experiments. \*\* indicates p value < 0.01

adhesion of *S. epidermidis* strain 9, and its isogenic mutants 2J24, deficient in *GehC* lipase and KIC82 deficient in *GehD* lipase. The *gehD* mutant was significantly less adherent to sutures when compared to wild type strain. Reduction of adhesion ranged from 68% for vicryl ( $P = 0.0006$ ) to 88% for PDS ( $P = 0.001$ ). There was no significant reduction of the adhesion of the *gehC* mutant to sutures compared to the parental strain.

### ***S. epidermidis* autolysin AtlE plays a role in bacterial adhesion to suture materials**

*S. epidermidis* autolysin AtlE can mediate primary attachment of *S. epidermidis* to polymer surfaces<sup>25</sup>. In this experiment we examined the role of the autolysin AtlE in the adhesion of *S. epidermidis* to different surgical sutures. Fig. 4 shows adhesion of *S. epidermidis* strain O-47 and an isogenic mutant deficient in the autolysin AtlE to

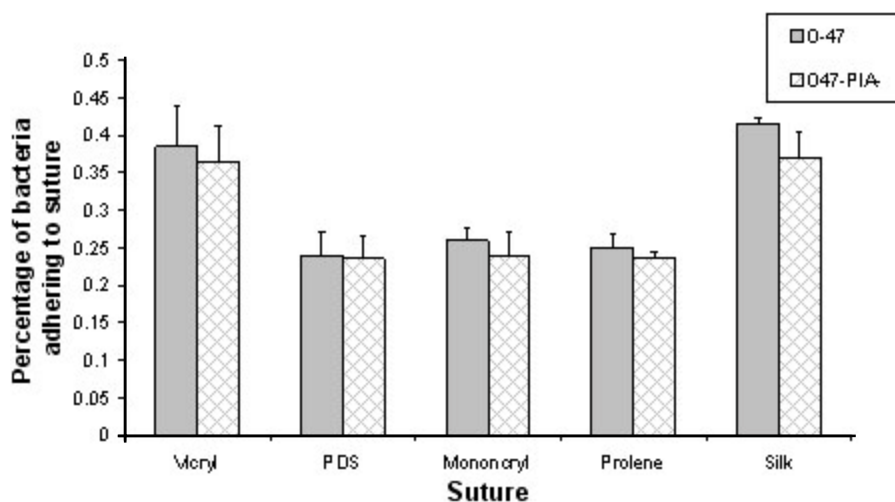


Fig. 5: aThe role of *S. epidermidis* polysaccharide intercellular adhesin (PIA) in adhesion to sutures. The graph shows the capacity of *S. epidermidis* strain O-47 and its isogenic mutant deficient in PIA to adhere to sutures. The experiment is a representative of three experiments performed on different occasions. Data are the means and standard deviations of three replicate experiments

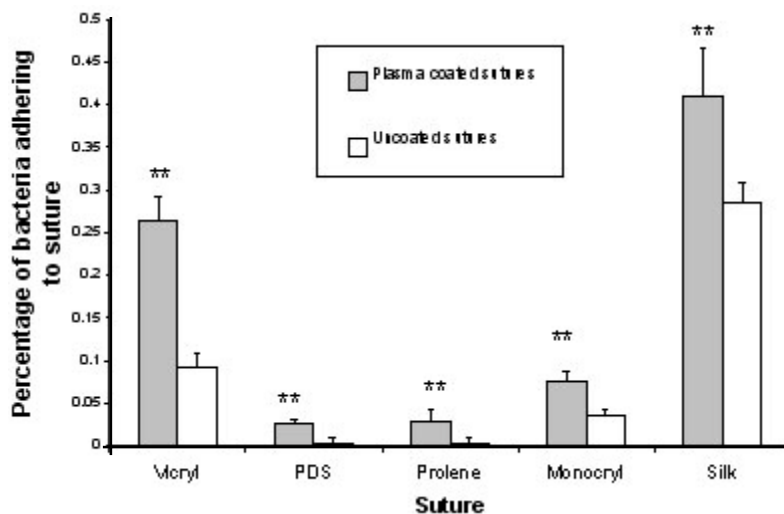


Fig. 6: Adhesion of *S. epidermidis* to plasma coated sutures. The graph shows the capacity of *S. epidermidis* strain 19 to adhere to sutures incubated with human plasma overnight. Data are the means and standard deviations of three replicate cultures. (\*\*) indicates  $p$  value  $< 0.01$

five different sutures. Deletion of AtlE significantly reduced adhesion of *S. epidermidis* to all of the sutures tested. The reduction of adhesion ranged from 75% for PDS ( $P = 0.00009$ ) to 95% for monocryl ( $P = 0.008$ ).

#### ***S. epidermidis* polysaccharide intercellular adhesin (PIA) is not involved in adhesion to suture materials**

Polysaccharide intercellular adhesin (PIA) has been shown to be important in biofilm formation and catheter related infection<sup>20</sup>. In this experiment we investigated the role of PIA in adhesion of *S. epidermidis* to sutures. Fig. 5 shows that disruption of PIA production in *S. epidermidis* did not have a significant effect on the adhesion of bacteria to sutures.

#### **Coating sutures with human plasma increases *S. epidermidis* adhesion**

Foreign devices are covered with body fluids immediately after implantation. These materials can affect bacterial adhesion to the implanted device<sup>26</sup>. We have examined the adhesion capacity of *S. epidermidis* to plasma coated sutures. Incubation of sutures with human plasma overnight has significantly increased adhesion of *S. epidermidis* to these sutures (Fig. 6). For example adhesion of *S. epidermidis* to vicryl and Silk was increased by 43% and 128% respectively ( $P = 0.02$  and  $P = 0.0008$ ).

### **DISCUSSION**

The purpose of this study was to examine the capacity of *S. epidermidis* to adhere to different surgical suture materials and to determine if any of the known adhesin molecules produced by this organism were involved in the process. It is evident from these studies that *S. epidermidis* strains have different capacities to adhere to surgical suture materials. Furthermore the material from which the suture was constructed had a significant impact on the adhesion of *S. epidermidis*. It has been accepted that bacterial adhesion to surfaces is a prerequisite step in foreign body infections<sup>2</sup>. Sutures are commonly used materials in surgical practice and can be classified in to two types according to their ability to be absorbed by host tissue, absorbable and non-absorbable. They are used either in elective

surgery where asepsis is performed prior to any incision, or in contaminated wounds where asepsis control is difficult. Non-absorbable sutures are usually removed after seven days in order to allow wound healing. The absorption time for some sutures such as polydioxanone can be as long as 180 days<sup>27</sup>. In this study, we evaluated the ability of *S. epidermidis* to adhere to some of the most commonly used surgical sutures. We found variation in the capacity of different strains of *S. epidermidis* to adhere to different suture materials. Bacterial adhesion is often found to differ between materials with different chemical compositions and/or hydrophobicities<sup>14</sup>. Although chemical composition is undoubtedly important surface texture and roughness are also factors. Scher *et al.* have questioned the role of monofilament structure of sutures to its infection resistance when compared to multifilament sutures<sup>28</sup>. Masini *et al.*, stated that absorbable braided suture should not be used in closer of contaminated wounds due to risk of developing infection<sup>29</sup>. We have found that monofilament sutures allow fewer bacteria to bind as compared to multifilament sutures. One possible explanation is the larger surface area of multifilament sutures which may promote the persistence of bacteria. Although some multifilament sutures are easier to handle and provide secure surgical knots, bacterial adhesion to such sutures should be considered in suture selection. Many reports have described the use of coated sutures with antibacterial agents to minimize the risk of infection<sup>4,30</sup>. Although this approach is useful, it does have two problems, antibiotics toxicity and the development of resistance to such antibiotic by bacteria. Silver-doped bioactive glass has been shown to reduce the adherence of *S. epidermidis* to sutures<sup>31</sup>. An alternative approach is the development of materials that reduce or even prevent bacterial adherence to sutures. For example as described in a recent report on surfactant polymers designed to suppress *S. epidermidis* adhesion to biomaterials<sup>32</sup>.

Very few *S. epidermidis* virulence factors have been identified and reported in the literature. However a number of adhesins which are believed to be important to the virulence of this organism have been described including the fibrinogen binding protein *SdrG*<sup>18</sup>, polysaccharide intercellular adhesin

<sup>20</sup>, lipases <sup>23</sup> and the autolysins AtlE <sup>20</sup>. The involvement of these factors in adhesion of this organism to sutures has not been investigated. By using *S. epidermidis* strains with deletion or disruption in the gene for these virulence determinants, we have examined their role in the adhesion of this bacterium to sutures. Examination of a *S. epidermidis* mutant deficient in the fibrinogen binding protein *SdrG*, showed the involvement of this protein in adhesion of *S. epidermidis* to suture materials. We found that polysaccharide intercellular adhesin (PIA) is not involved in adhesion of *S. epidermidis* to suture materials. In 1998 Higashi *et al.* found that slime (PIA) does not enhance the adhesion of *S. epidermidis* to polyethylene <sup>33</sup>. Although we have found that PIA is not involved in attachment to sutures it does not rule out its possible importance in cell to cell adhesion and biofilm formation in suture related infections. On the other hand, the *S. epidermidis* autolysin AtlE seems to play an important role in adhesion to the surgical sutures examined in this study. Rupp *et al.* have demonstrated the importance of both PIA and AtlE in a model of catheter related infection <sup>20</sup>. We found that the *S. epidermidis* autolysin AtlE was the most important virulence factor in adhesion to sutures. Finally we investigated the role of two *S. epidermidis* lipases in its adhesion to sutures. The results show that the *GehD* is involved in adhesion of *S. epidermidis* to sutures. The *GehD* lipase has been found to be a *S. epidermidis* collagen adhesin which enhances adhesion of *S. epidermidis* to immobilized collagen <sup>22</sup>. Adhesion of *S. epidermidis* to sutures

could be enhanced if such sutures are covered with host proteins such as collagen. In our study we have found coating sutures overnight with human plasma significantly increased *S. epidermidis* adhesion to suture materials. This increase in adhesion capacity of *S. epidermidis* in the presence of plasma can affect wound infection rate.

## CONCLUSIONS

This study demonstrates the ability of *S. epidermidis* to adhere to different surgical suture materials. *S. epidermidis* virulence determinants such as *GehD* lipase, *SdrG* protein and the autolysin AtlE are involved in the adhesion process. *S. epidermidis* autolysin AtlE was found to be the most important adhesin in adhesion of this organism to suture materials. Bacterial adhesion to sutures should be considered when selecting suture materials to reduce the risk of wound infection and subsequent complications. *S. epidermidis* autolysin AtlE inhibitors may be useful coating agents to prevent bacterial adhesion to sutures. The adherence of bacteria to suture materials seems to be affected by its physical properties, which favor the use of monofilament materials.

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