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Host-Bacteria Interactions in Foreign Body Infections

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ABSTRACT

Persistent staphylococcal infections are a major medical problem, especially when they occur on implanted materials or intravascular catheters. This review describes some of the recently discovered molecular mechanisms of *Staphylococcus aureus* attachment to host proteins coating biomedical implants. These interactions involve specific surface proteins, called bacterial adhesins, that recognize specific domains of host proteins deposited on indwelling devices, such as fibronectin, fibrinogen, or fibrin. Elucidation of molecular mechanisms of *S aureus* adhesion to the different host proteins may lead to the development of specific inhibitors blocking attachment of *S aureus,* which may decrease the risk of bacterial colonization of indwelling devices (*Infect Control Hosp Epidemiol* 1996;17:514-520).

INTRODUCTION

Despite the continuing development of potent antimicrobial agents, acute septic and chronic persistent infections due to *Staphylococcus aureus*[1] and coagulase-negative staphylococci (CNS) have increased in recent years.[2-4] Major infections due to *S aureus* are either non–device-related, such as surgical wound infections, or device-related. The clinical significance of CNS in human infections was recognized only in the past 2 decades.[2-4] This recognition was delayed by the fact that these organisms were found to be less virulent than *S aureus* in animal models of experimental infection and frequently were considered to be contaminants of blood cultures. Coagulase-negative staphylococci now are considered as the leading pathogens of indwelling catheter and prosthetic device infections, thus contributing to the majority of hospital-acquired bacteremias.[2-4]

Irrespective of their different virulence and persistence characteristics, over the last decades, both *S aureus* and CNS have accumulated multiple, unrelated resistance determinants. Methicillin-resistant strains of *S aureus* or *Staphylococcus epidermidis,* which frequently harbor several additional resistance determinants, represent a high risk for severely ill patients. Control of such infections requires expensive surveillance programs.

ROLE OF IMPLANTED FOREIGN BODIES ON SUSCEPTIBILITY TO PERSISTENT STAPHYLOCOCCAL INFECTION

The growing number of staphylococcal nosocomial infections is due to the constant increase in transient or permanent medical devices.[5,6] Independently of their physical and chemical composition, and whatever their anatomical location, all artificial devices (eg, cerebrospinal fluid shunts, intraocular lenses, pacemaker wires and electrodes, prosthetic cardiac valves, vascular grafts, prosthetic joints, intravascular catheters) exhibit high susceptibility to microorganism infection. The predominant pathogens are *S aureus*[1] and *S epidermidis* or other CNS species.[2,3] Both the presence of implanted materials and the growing proportion of multiply antibiotic-resistant strains of staphylococci complicate the therapy of such infections, which are persistent and difficult to cure without implant removal and replacement.[7]

DEVELOPMENT OF EXPERIMENTAL MODELS OF FOREIGN BODY INFECTIONS

The development of an animal model that could reproduce some major features of clinically encountered

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foreign body infections was essential for studying various aspects of bacterial colonization and the blunted host response to a low microbial challenge. Another useful application of animal models was to evaluate the most effective antibiotic regimens for prophylaxis or therapy of implant-associated infections. The tissue cage model that we have used in the past 15 years is composed of polymeric multiperforated cylinders (called tissue cages) that are implanted subcutaneously in guinea pigs[8,9] or rats[10,11] for several weeks. The perforations in tissue cages allow repeated sampling of fluids for analysis of proteins, host cells, and microbial organisms during infection. In addition, tissue cages may be implanted with inserted polymethylmethacrylate (PMMA) coverslips, which are useful tools for studying the reactive extracellular matrix deposited during implantation and for evaluating its impact on microbial adhesion and colonization.

The tissue cage model has been used in two different animals for two separate applications: in guinea pigs, implanted tissue cages are very sensitive to a low bacterial challenge and are most appropriate for virulence[8,9] and prophylactic studies[12,13]; in rats, implanted tissue cages are infected in a more chronic mode (by *S aureus* only). These animals are more tolerant to prolonged antibiotic courses, thus allowing therapeutic trials to be extended for periods of 1 to 3 weeks.[10,11,13]

PHAGOCYTIC DEFECTS

Polymorphonuclear neutrophils collected from tissue cage fluid of guinea pigs were found to be markedly defective in their content of granule-associated bactericidal enzymes and in their oxidative burst-dependent bactericidal activity against *S aureus,*[9,14] compared to those of blood[9,14] or peritoneal[15] neutrophils. These defects were reproduced partly in vitro by exposure to artificial surfaces in suspension and suggest mechanisms of frustrated phagocytosis.[14] Additional studies were performed of polymorphonuclear neutrophil functions in relationship with phagocytosis of *S aureus* colonizing implants in order to analyze surface phagocytosis of bacteria colonizing artificial surfaces. In vitro coating of polymer surfaces by native plasma or matrix proteins markedly improved the phagocytic killing of surface-attached *S aureus.*[16] These contrasting in vitro versus in vivo observations suggest that chronically implanted materials may contain regions where plasma and extracellular matrix proteins have been degraded locally by released proteolytic enzymes, which may impair phagocytic recognition and killing of surface-attached bacteria and lead to their improved survival.

Partial restoration of locally deficient neutrophils in tissue cage fluid and increased resistance to a bacterial challenge can be achieved not only by local transfusion of fresh neutrophils[14] but also by local injection of particulate immunomodulators (ie, cell-wall components of *S aureus)* that can increase the concentrations of local cytokines,[8] in particular, of tumor necrosis factor. A causal relationship was found between the locally increased tissue cage fluid levels of tumor necrosis factor, which is known to promote neutrophil functions, and the prevention of foreign body infections.[8]

ROLE OF PLASMA AND EXTRACELLULAR MATRIX PROTEINS FOR PROMOTING STAPHYLOCOCCAL ADHESION TO FOREIGN IMPLANT SURFACES

Microbial adhesion is a key step for the colonization of indwelling devices. On their surface, staphylococci, in particular *S aureus,* express several specific receptors or adhesins[17-20] for interacting with a number of host proteins such as fibrinogen,[21-24] fibronectin,[22,25-28] collagen,[29-32] vitronectin,[33,34] laminin,[22,35] thrombospondin,[36] bone sialoprotein,[37,38] elastin,[39] and a recently described extracellular matrix-binding protein with broad specificity.[40] Several in vitro studies have demonstrated that these adhesins promoted *S aureus* attachment to each of the mentioned plasma or extracellular matrix proteins individually adsorbed onto polymeric or metallic surfaces. In contrast to *S aureus,* interaction of *S epidermidis* and other CNS species with plasma and extracellular matrix proteins has been characterized less well.[17] Most in vitro studies of CNS attachment and colonization of artificial surfaces were carried out in the absence of any protein coating and have focused on either slime production or describing a capsular surface polysaccharide that promotes adhesion to uncoated plastic.[41,42]

During the past 15 years, our group studied the role of plasma or extracellular matrix proteins, in particular, fibronectin, fibrinogen, or fibrin, in promoting *S aureus* (and to some extent *S epidermidis)* adhesion to implanted or inserted foreign materials.[25] For in vivo studies, our group used PMMA coverslips that were inserted in subcutaneously implanted tissue cages as described above. Coverslips explanted 4 weeks after surgery are coated with a complex network of matrix proteins and cellular elements: among them, fibronectin plays an important role in promoting *S aureus* adhesion to those explanted coverslips.[25] Adhesion of a protein A-defective strain of *S aureus* to fibronectin deposited in vivo was inhibited by antibodies to fibronectin.[27]

In a simplified in vitro assay, fibronectin[22] strongly promoted adhesion of all bacteremic isolates of *S aureus* and *S epidermidis,* as opposed to fibrinogen and laminin, which promoted *S aureus,* but rarely *S epidermidis* adhesion.[22] Thrombospondin,[36] a glycoprotein present in alpha-granules of platelets, also showed more binding activity and promotion of bacterial attachment with clinical isolates of *S aureus* than of *S epidermidis.* Activated platelets bound to plastic surfaces also may promote attachment to *S aureus* cells by interacting with fibrinogen or fibrin.[23]

Further bacterial adhesion studies, relevant to clinical situations of orthopedic infections of implanted metallic devices and performed in collaboration with the Clinique d'Orthopédie (University Hospital, Geneva, Switzerland) also demonstrated that fibronectin was an important determinant of *S aureus* and *S epidermidis* adhesion to either stainless steel, pure titanium, or titanium-aluminum-niobium–alloy coverslips.[43] Bacterial adhesion to each category of metallic surfaces coated in vitro with fibronectin and to coverslips explanted from the subcutaneous space of

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guinea pigs was promoted strongly over albumin-coated controls and was sensitive to inhibition by antifibronectin antibodies.[43]

The clinical relevance of our experimental observations also was evaluated on a large number of peripheral or central intravenous cannulas removed from hospitalized patients.[27] Compared to uninserted catheters, which allowed only minimal adhesion, previously inserted catheters promoted significant adhesion of staphylococcal isolates.[27] To define the respective contribution of fibrinogen or fibrin and fibronectin in promoting *S aureus* adhesion to central venous catheters, the amount, chemical integrity, and biologic activity of these proteins adsorbed on intravenous lines inserted in hospitalized patients were studied prospectively.[44] Polyurethane catheters promoted a significantly lower adhesion of *S aureus* than polyvinyl chloride or Hickman cannulas and contained the lowest amount of immunologically assayed fibronectin, but not of fibrinogen or fibrin.[44] Fibrinogen showed an extensive loss of adhesion-promoting activity on inserted cannulas, which was related to its proteolytic breakdown, as detected by SDS-PAGE and immunoblots with antifibrinogen antibodies[25] and confirmed by in vitro studies with purified protein fragments.[44] In contrast, either intact or fragmented fibronectin, although present in much lower amounts than fibrinogen or fibrin, could actively promote *S aureus* adhesion onto intravenous catheters.[44]

MOLECULAR AND FUNCTIONAL CHARACTERIZATION OF *S AUREUS* ADHESINS

Significant progress recently was made in the molecular identification, cloning, and sequencing of bacterial genes coding for bacterial adhesins.[17-20] These molecular studies allowed structural and functional characterization of the genes for a collagen adhesin[29,30,45] and two distinct but related fibronectin-binding proteins (FBP).[46,47] Putative adhesins of fibrinogen, whose molecular structure was related closely to that of staphylococcal coagulase, also were described.[48,49]

To either identify novel bacterial adhesins, such as the fibrinogen-binding protein (also called clumping factor, see below), or to confirm the functional significance of already described adhesins, a combined molecular and functional approach was necessary. These studies were promoted by the production of site-specific mutants of *S aureus* specifically defective in adhesion to a single host protein such as fibrinogen[24] or fibronectin.[50,51] Some of these mutants were instrumental in allowing the cloning and sequencing of a structural gene coding for a major fibrinogen adhesin.[24] Other mutants defective for the production of fibronectin adhesins demonstrated their role in bacterial attachment to the host protein.

In addition, the function of adhesin(s)-defective mutants could be restored by complementation with functional genes located either on multicopy plasmids or integrated into the bacterial chromosome.[24,51] Some of these restored mutants were useful for identification of host proteins specifically contributing to bacterial attachment in vivo.[52]

Fibrinogen-Binding Protein (Clumping Factor)

This recently discovered 92 kDa surface protein[24] now is considered the major fibrinogen adhesin and mediator of *S aureus* clumping.[17,20,24,53] This discovery was prompted by the isolation of four transposon-generated mutants of *S aureus* strain Newman, which were defective in the fibrinogen receptor (clumping factor) and mapped in the same locus (*clf*A). All the mutants failed to form clumps in soluble fibrinogen and lost attachment to PMMA coverslips coated in vitro with fibrinogen.[24] The transposon-generated mutants defective in fibrinogen binding were very helpful for the cloning of the wild-type clumping factor locus (*clf*A).[24] The *clf*A gene is predicted to encode a cell surface-associated fibrinogen-binding protein of 896 residues with a predicted molecular mass of 92 kDa (Figure 1). The *clf*A protein has in its C-terminal region features found in many cell surface-associated proteins in gram-positive bacteria, namely an LPXTG motif, a hydrophobic putative transmembrane domain and positively charged residues at the extreme C-terminus (Figure 1).[17,20]

A single copy of the *clf*A gene, when introduced into the chromosome of the mutant strains, fully complemented the clumping deficiency of these strains and restored the ability of these mutants to adhere to fibrinogen-coated PMMA. In addition, the cloned *clf*A gene introduced on a shuttle plasmid into a weakly fibrinogen-adherent strain of *S aureus* transformed it into a strain of strong affinity for surface-bound fibrinogen.[24]

The 520-residue N-terminal region A contains the fibrinogen-binding domain.[54] Studies with recombinant truncated derivatives of region A localized the fibrinogen-binding domain to a 218-residue segment (residues 332-550). One truncate (220-550) retained the ability to bind fibrinogen, to block the attachment of bacteria to solid phase fibrinogen (Figure 2), and to prevent bacterial clumping in a solution of fibrinogen.[54] Antibodies raised against truncate 220-550 strongly inhibited both bacterial adhesion to fibrinogen-coated surfaces (Figure 2) and cell clumping. All the smaller truncates lost the ability to interact with fibrinogen. One truncate (332-550) neutralized the ability of polyclonal antibodies raised against truncate 220-550 to block bacterial binding to fibrinogen. Antibodies raised against the smaller protein also blocked bacterial interactions with fibrinogen. This suggests that the ligand-binding domain is located between residues 330-550 and that residues 220-330 are required to promote correct folding of the fibrinogen-binding domain.

*Clf*A contains an unusual 308-residue region comprising 154 mainly Ser-Asp dipeptide repeats. A recombinant protein comprising region R did not bind fibrinogen and failed to block bacterial attachment to fibrinogen-coated surfaces,[54] and antiserum raised against region R did not block bacterial attachment to fibrinogen-coated surfaces (Figure 2). A deletion mutant lacking region R failed to bind fibrinogen, suggesting that the function of this region is to display the ligand-binding domain region A correctly on the cell surface (O.M. Hartford, PhD, unpublished data, August 1995).

To evaluate the in vivo contribution of fibrinogen or fibrin to *S aureus* attachment during brief exposure of

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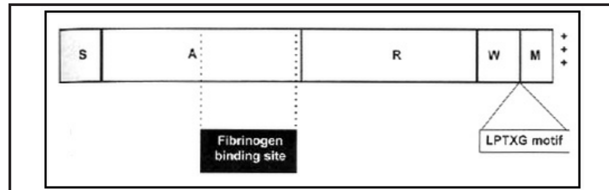

FIGURE 1. Schematic drawing showing the domain organization of *Staphylococcus aureus* fibrinogen-binding clfA protein. S, signal sequence; A, nonrepeat domain; R, repeat domain; W, wall region; M, membrane-spanning domain; +, positively charged residues. The black box indicates the fibrinogen-binding region.

intravascular devices to flowing blood, we tested the *clf*A-defective mutants or their complemented derivatives in an ex vivo canine arteriovenous shunt model.[52] After exposure of polymer tubings to circulating canine blood for 5 to 60 minutes, segments of blood-exposed tubings were tested for promotion of bacterial adhesion. *S aureus* mutants lacking the fibrinogen adhesin were more defective in attachment to the blood-exposed tubings than those lacking the fibronectin adhesin(s), compared to their respective parental strains.[52] In contrast, a highly adhesive derivative strain of *S aureus* 8325-4, produced by complementation with the plasmid pCF4 expressing multiple copies of the *clf*A gene, exhibited a strong increase over the parental strain in bacterial adhesion to blood-exposed tubing segments.[52] These findings indicate that fibrinogen and fibrin are the most active components for initially promoting in vivo adhesion of *S aureus,* whereas fibronectin and fibronectin proteolytic fragment are more active in central venous catheters inserted for >24 hours.[44]

In a collaborative work with Philippe Moreillon, MD (Infectious Diseases, University Hospital, Lausanne, Switzerland), the contribution of the *clf*A protein to the initial attachment and virulence of *S aureus* recently was evaluated in a rat model of endocarditis.[55] In this animal model of endocarditis with catheter-induced aortic vegetations, the virulence of various single or combined *clf*A- and coagulase-defective mutants was tested. A significant reduction in the ability of the *clf*A-defective mutant of *S aureus* to colonize rat valves was observed. In contrast, the coagulase-defective mutant showed no significant difference with the parental strain. Thus, the clumping factor also may contribute to *S aureus* attachment to damaged heart valves leading to bacterial endocarditis.[55]

Fibronectin-binding proteins. Molecular analysis of the genetic locus encoding fibronectin-binding surface component(s) of the laboratory strain 8325-4 of *S aureus* revealed two related genes, called *fnbA* and *fnbB,* located 682 base pairs apart.[19,46,47,56] Both *fnb* genes cloned in *Escherichia coli* could express functional FBPs, called FnBPA and FnBPB.[18,19,46,47]

Closely related ligand-binding domains have been identified in both FnBPs using truncated protein fragments and synthetic peptides in binding and inhibition studies. This common binding domain is composed of a 38-amino-acid unit that is repeated three times and partially a fourth, which is called the D-repeat unit or D1-D4[17,19,56] (Figure 3). The functional role of the D-repeat region has been confirmed by blocking studies with recombinant and synthetic peptides, which produce a very strong dose-dependent inhibition of *S aureus* binding to either fluid-phase or solid-phase fibronectin.[19,56-59] These peptides exhibit a stronger blocking activity than that of any polyclonal antibodies thus far developed against the fibronectin adhesins.[60]

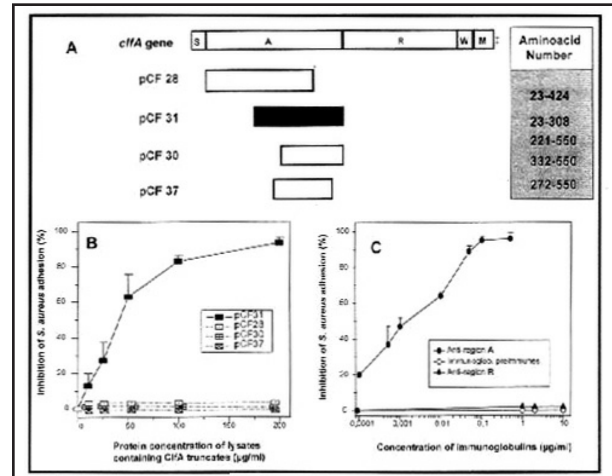

FIGURE 2. (A) Schematic diagram showing the location of the *clf*A fragments and the amino-acid numbers represented. (B) Inhibition of *Staphylococcus aureus* adhesion to fibrinogen-coated polymethylmethacrylate (PMMA) coverslips by lysates containing *clf*A truncates. (C) Inhibition of *S aureus* adhesion to fibrinogen-coated PMMA coverslips by immunoglobulins purified from anti-*clf*A sera and preimmune sera. Modified from reference 54 with permission from *Molecular Microbiology* (1995;16:895-906).

To evaluate the role of each of the fibronectin adhesins in vitro and in vivo, mutants of strain 8325-4 defective in the production of FnBPA, FnBPB, or both proteins were produced by inserting DNA fragments encoding antibiotic resistance into the *fnb* genes (a tetracycline resistance marker into *fnbA* and an erythromycin resistance marker into *fnbB*).[51] Adhesion properties of either *fnbA* or *fnbB* single mutants were not altered markedly compared to those of the parental strain.[51] In contrast, the double *fnbAfnbB* mutant was completely defective for attachment to either PMMA coverslips coated in vitro with fibronectin or to coverslips explanted from the subcutaneous space of guinea pigs.[51] The parallelism between in vitro and in vivo observations indicate an important role for FBPs in staphylococcal attachment, colonization, and infection of biomaterial implants.

Another category of bacterial mutants defective in FnBP production was generated by Kuypers and Proctor in strain 879R4S of *S aureus* by transposon insertion.[50] One fibronectin-adhesin-defective mutant showed a markedly reduced ability to adhere to traumatized heart valves and to induce bacterial endocarditis in rats.[50] A recently discovered characteristic of the parental and mutant strains of *S aureus* 879R4S is that it contains a single *fnb* gene closely related to the *fnbA* of strain 8325-4.[61] Recent molecular studies of the fibronectin-adhesin-defective mutant strain 879R4S/1536 and its spectinomycin-derivative R4SSp/1536

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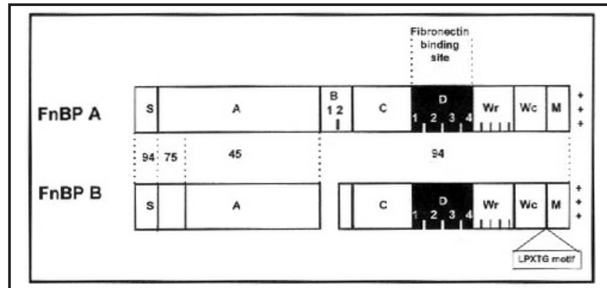

FIGURE 3. Schematic drawing comparing the domain organization of the two fibronectin-binding proteins of *Staphylococcus aureus* 8324-5. The percentage residue identity between different regions of FnBPA and FnBPB is indicated. S, signal peptide; A and C, nonrepeated regions of unknown function; B and D, repeat regions outside the cell-wall domain; Wr, repetitive region in the cell-wall binding domain; Wc, nonrepeat region in the cell-wall binding domain; M, membrane-spanning domain; +, positively charged residues. The black boxes indicate the fibronectin-binding domain.

demonstrated that the Tn*918* transposon was inserted between the promoter and coding sequence of the single *fnb* gene,[61] thus leading to its decreased expression.[61]

The mutant strain 879R4S/1536 showed interesting adhesion defects in a novel animal model of orthopedic colonization developed in the orthopedic clinic of our hospital.[62] In this model, which mimics conditions of internal fixation devices, titanium miniplates were fixed onto the iliac bones of guinea pigs or implanted into their subcutaneous space as controls for a period of 5 to 6 weeks. A significant reduction in adhesion of the fibronectin adhesin-defective mutant compared to its isogenic parent occurred on the metallic plates explanted from either the subcutaneous space or the iliac bone. These data suggest that fibronectin also may be present on bone-implanted metallic devices and promote attachment of *S aureus* to their surface.[62]

STRATEGIES FOR DECREASING HOST BACTERIA INTERACTIONS ON FOREIGN BODIES

The combined development of molecular techniques and experimental models of bacterial adhesion should help to elucidate some of the most important clinically and epidemiologically relevant mechanisms of *S aureus* attachment to major categories of biomaterial implants or indwelling devices.

The ligand-binding domains of both fibronectin and fibrinogen adhesins have been identified using truncated protein fragments and synthetic peptides in binding and inhibition studies. The binding domain of both fibronectin adhesins is the D-repeat unit or D1-D4 (Figure 3).[17,19,56] Synthetic peptides based on this fibronectin-binding domain exhibit a stronger blocking activity on *S aureus* binding to fibronectin[19,56-59] than any polyclonal antibodies thus far developed against the fibronectin adhesins.[60] In contrast, polyclonal antibodies raised against the fibrinogen-binding domain of the *clf*A protein, which is located within a 218-residue segment of its amino-terminal region A (Figure 2), have shown a more potent activity against bacterial clumping and adhesion to fibrinogen-coated polymeric surfaces than truncated peptides encompassing the ligand-binding domain of *clf*A.[54]

The important advances in the molecular characterization of the fibrinogen-binding protein *clf*A[24,54] and of both FBPs A and B[46,47,56] in *S aureus,* and the functional demonstration[24,51,52,54] that they contribute to attachment to the purified host proteins, offer interesting perspectives for the development of a novel category of specific antiadhesive agents.[17,56] Such agents would offer a useful alternative to antibiotic prophylaxis in circumventing the emergence of multiple resistance determinants in nosocomial strains of staphylococci.

In addition to the fluid-phase specific antiadhesive agents mentioned above, surface-bound molecules changing the chemical or physical properties of indwelling devices also should be evaluated carefully. We recently have described the impact of a surface coating procedure on the physical and biological properties of a polyurethane catheter.[63] Coating of this polyurethane catheter with a hydrogel based on cross-linked polyvinyl pyrrolidone led to a dramatic increase in its surface smoothness and hydrophilic properties.[63] The hydrophilic polyurethane catheter showed a strong reduction in the in vitro adsorption of either fibrinogen or fibronectin, leading to a proportional reduction in protein-mediated adhesion of either *S aureus* or *S epidermidis.*[63]

In conclusion, the combined development of specific fluid-phase antiadhesive agents and improved surface treatments of indwelling devices may lead to a significant reduction in bacterial colonization of the foreign bodies. Further studies are needed to evaluate the clinical significance of these in vitro observations.

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Bartonella quintana Infection Among Homeless

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Medical News Editors

Bartonella quintana first was identified as an important human pathogen during World War I, when it caused epidemics of louse-borne trench fever that affected an estimated 1 million troops in Europe. *B quintana* infections rarely were recognized from the end of the war until the 1980s, when the organism re-emerged as an opportunistic pathogen among HIV-infected persons.

B quintana has emerged among homeless persons in North America and Europe. In 1993, the organism first was isolated from the blood specimens of 10 patients at a single hospital in Seattle, Washington, within a 6-month period. These patients had illnesses characterized by fever and persistent bacteremia. Endocarditis developed in two patients, one of whom required a heart valve replacement. All 10 patients had chronic alcoholism, eight were homeless, and the six who were tested for HIV were HIV negative. These six were the first cases of invasive *B quintana* infection among HIV-negative persons reported in the United States.

As a follow up to this Seattle outbreak, Dr. Lisa Jackson and Dr. David Spach, from the University of Washington in Seattle, conducted a seroprevalence study of anti-*Bartonella* antibodies among 192 patients at a community clinic in the "skid row" section of Seattle, which serves a primarily homeless and indigent population. *B quintana* IgG titers $\geqslant$64 were detected among 39 (20%) of the 192 clinic patients.

The researchers note that multiple factors likely have contributed to the emergence of *B quintana* among the homeless, including those related to disease transmission, host susceptibility, and ability to detect the organisms. For example, transmission of *B quintana* from human to human by the body louse has been documented experimentally.

As with other emerging infectious diseases, further efforts to identify, evaluate, and control these infections will require coordinated effort of clinicians, microbiologists, and public health officials.

FROM: Jackson LA, Spach DH. Emergence of *Bartonella quintana* infection among homeless persons. *Emerg Infect* 1996;2(2):141-143.

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